IMPAACT 2005

A Phase I/II Open-label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected Children with MDR-TB

IND #: 134,732
DAIDS ES #20721

This file contains the current IMPAACT 2005 protocol comprised of the following documents, presented in reverse chronological order:

- Letter of Amendment #2, dated 30 April 2018
- Letter of Amendment #1, dated 2 November 2017
- IMPAACT 2005 Protocol Signature Page for protocol Version 1.0, with CM #1
- Clarification Memorandum #1, dated 4 August 2017
- Protocol Version 1.0, dated 9 March 2017
Letter of Amendment # 2 for:

IMPAACT 2005
A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

Version 1.0, dated 9 March 2017

IND#: 134,732
DAIDS Study ID 20721

Letter of Amendment Date: 30 April 2018

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT 2005 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 2005. If the IMPAACT 2005 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
IMPAACT 2005

A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

Version 1.0, dated 9 March 2017

IND#: 134,732
DAIDS Study ID #20721

Version 1.0, Letter of Amendment #2
dated 30 April 2018

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

The following modifications are included in this LoA:

1. Clarify in protocol Section 1.1 that the World Health Organization (WHO) shortened MDR-TB treatment regimen may be used.
2. Clarify that ECG assessments are based on the mean QTcF of triplicate ECG readings at each time point.
3. Clarify the exclusionary types of TB for study participation for consistency with inclusion criterion 4.1.5.
4. Update the allowable storage temperatures and storage instructions for DLM tablets for consistency with the Investigator’s Brochure.
5. Add bedaquiline as a prohibited medication due to concerns regarding potential QTc prolongation, when taken in combination with delamanid.
6. Clarify the classification of TB treatment outcomes in protocol Section 8.5, for consistency with the definitions provided in the study Manual of Procedures.
7. Add required language regarding regulatory entities that may review study records. 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.
8. Clarify and expand upon clinical management guidelines for confirmed Grade 1 and Grade 2 ECG-determined or clinical cardiac toxicity, specifically to include consultation with the CMC.
9. Provide other minor administrative updates, clarifications, and corrections.

Implementation

The modifications included in this LoA are listed below by modification. Additions to the text are indicated in bold; deletions are indicated by strikethrough.

1. Use of WHO shortened regimen

   Section 1.1 Background, sixth paragraph:

   For moxifloxacin, also a key component of the regimen, there is limited pediatric pharmacokinetic data and no child friendly formulation; the guidelines stipulate that levofloxacin should not be substituted for moxifloxacin in the shortened regimen. Because it is prohibited to use moxifloxacin together with DLM, the shortened regimen could not be used in the IMPAACT 2005 study. The shortened regimen may be used in IMPAACT 2005, in accordance with protocol Section 5.6. […]

2. QTcF calculation for ECG assessments

   a) Section 4.2, Exclusion Criterion 4.2.4:

   Abnormal ECG (including QTcF [mean value of QT interval, corrected using Fredericia correction, on ECG performed in triplicate] ≥ 450 ms, atrioventricular block, or prolonged QRS ≥ 120 ms) at screening
b) **Section 8.7 ECG Monitoring and Reading, second paragraph:**

ECGs will be performed as described in the Schedule of Evaluations. At Day 0, Week 2 and Week 8 visits (semi-intensive PK visit), ECGs will be performed pre-dose and at 4 hours after DLM administration. On-site clinicians will review **real-time** ECGs and assess for clinical relevance and identification of AEs, as specified in Section 8.1. This will include an assessment of QT (QTcF) interval. In accordance with accepted WHO guidance for the use of DLM, levofloxacin will replace moxifloxacin as the fluoroquinolone of choice based on a lower risk of potential QTc prolongation with levofloxacin.

ECGs will be interpreted based on age-specific criteria. **Mean QT interval will be calculated based on triplicate ECG readings (three consecutive ECGs) at each time point. Refer to the study-specific MOP for further information.** In addition, there will be a centralized review of all ECGs within three to five 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. […]

3. **Exclusionary types of TB**

**Section 4.2 Exclusion Criterion 4.2.8:**

Disseminated TB (including miliary TB, **Tuberculous meningitis** (TBM) Stage 2 or 3, abdominal TB, and/or osteoarticular TB, at screening

4. **Bedaquiline (BDQ) as a prohibited medication**

**Section 5.6.2 Prohibited medications during administration of DLM because of potential for QTc prolongation, bulleted list:**

The CMC must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. The following medications are prohibited during administration of DLM:

- Bedaquiline
- […]

5. **DLM tablet storage instructions**

**Section 5.2.3 Storage Instructions:**

DLM tablets must be stored at **20-25°C (68-77°F)** with excursions permitted at-between 15-30°C (59-86°F). **Do not refrigerate or freeze. Tablets must be dispensed in the original blister-pack in order to protect from moisture.**

6. **Definition of TB treatment outcomes**

**Section 8.5 TB Treatment Outcome, second paragraph:**

Treatment outcomes in children will be defined as bacteriological cure, probable cure, death, treatment failure, **TB recurrence**, and loss to follow-up (5). […]
7. Required Regulatory Authority Language

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, OHRP, and other U.S., local, and international applicable regulatory entities. […]

b) Appendix IIA, Sample Informed Consent Form, item #22:

Your child’s study records may be reviewed by study staff and groups that oversee the study. Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site IBC]
- [insert name of national Drug Regulatory Authority]
- [insert name of other local regulatory authorities]
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- Other U.S., local, and international regulatory entities
- The United States Food and Drug Administration (FDA)
- The IMPAACT Network that is coordinating the study

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

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

<table>
<thead>
<tr>
<th>ECG-determined or clinical cardiac toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEVERITY</strong></td>
</tr>
<tr>
<td>Grade 1</td>
</tr>
<tr>
<td>Grade 2</td>
</tr>
</tbody>
</table>

9. Other minor updates, clarifications, and corrections:

a) The following have been updated to reflect current protocol team membership:

- **Protocol Pharmacists**
  - Nayri Khairalla, PharmD
- **Pharmaceuticals Affairs Branch**
  - OCSO, DAIDS, NIAID, NIH
- **Senior Clinical Advisor Pharmacist**
  - 5601 Fishers Lane
- **Rockville, MD 20852**
b) Section 5.1.2 Study Treatment Administration, first paragraph, has been updated to clarify the upper weight limit for participants in Cohorts 1 and 2 to be at least 35kg (≥35kg):

Participants’ weight ≥35kg: […]
Letter of Amendment #1 for:

IMPAACT 2005

A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

Version 1.0, dated 9 March 2017

IND#: 134,732
DAIDS Study ID 20721

Letter of Amendment Date: 2 November 2017

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the IMPAACT 2005 study, including the study informed consent form (ICF), and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (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. This LoA increases blood draw volumes to accommodate sites that require larger volumes to perform protocol-specified laboratory tests.

- For sites that can perform protocol-specified tests within the blood volumes specified in protocol Version 1.0, approval of this LoA is not required prior to study initiation. However, after the LoA is approved, enrolled participants should be re-consented using the site-specific informed consent form corresponding to this LoA, and all newly enrolled participants should provide informed consent using the site-specific informed consent form corresponding to this LoA.

- For sites that cannot perform protocol-specified tests within the blood volumes specified in protocol Version 1.0, approval of this LoA is required prior to study initiation. All participants enrolled at these sites, after this LoA is approved, should provide informed consent using the site-specific informed consent form corresponding to this LoA.

Upon obtaining IRB/EC approval and any other applicable regulatory entity approvals, study sites must submit an LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete. This notification must be received prior to implementation of 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 2005. If the IMPAACT 2005 protocol is amended in the future, the contents of this LoA will be incorporated into the next version of the protocol.
IMPAACT 2005

A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

DAIDS Study ID #20721

Version 1.0, Letter of Amendment #1
dated 2 November 2017

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

The following modifications are included in this LoA:

- The prioritization of specimens for testing, in the event that the volume of blood collected is insufficient, has been updated.
- The blood volume required for chemistries and TSH testing and the total maximum blood volumes are corrected in Appendix I to ensure that enough blood is collected for these clinical safety tests. In addition, the corresponding maximum blood volume for collection at a given visit has been updated in the sample ICF (Appendix IIA). This increase in blood volume does not exceed the NIH recommendations for pediatric blood collection specified in protocol Section 6.26.1.

Implementation

Detailed modifications of the protocol text are shown below in the order they appear in the protocol. Deletions in the protocol text are indicated by strikethrough and additions are indicated in **bold**.

1. **Section 6.26.1, Specimen Collection, third paragraph:**

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

   1. Safety (in the following order: LFT, chemistry, hematology, TSH/fT4)
   2. Pharmacokinetics
   3. Virology
   4. Immunology
   5. Storage for future use

   **Note: At PK visits, pharmacokinetic specimens should take priority over TSH/fT4 specimens.**

2. **Appendix I, Schedule of Evaluation for All Cohorts, rows for Chemistries and TSH Sample Volume and corresponding maximum total blood volumes are modified in the attached SoE**

3. **Appendix IIA, Sample Informed Consent Form:**

   **FINDING OUT IF YOUR CHILD CAN JOIN THE STUDY, #4, item #11:**

   11. Take a little more than ½ a teaspoon of blood (about 5.0 mL 3.0 mL) in order to check:

   - How well your child’s thyroid, liver and kidneys are working.

   **ON THE STUDY, #5, third bullet, first and second sentences:**

   - **Blood:** The study staff will draw approximately one to two teaspoons a little more than ½ a teaspoon (about 5-10.0 mL 3.0 mL) of blood at most visits. The test will check how well your child’s liver, thyroid, and kidneys are working. These tests are routine, so you will be informed of the results. Some of the blood will be used to check the amount of DLM and other anti-TB medications in your child’s blood (see item #6 below).
## Appendix I, Schedule of Evaluation for All Cohorts, Rows for Chemistries and TSH Sample Volume, and Total Blood Volumes

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Day 0/ Start DLM</th>
<th>On treatment visits</th>
<th>Unsched Visit</th>
<th>Early DLM D/C only or Early DLM &amp; Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wk 2</td>
<td>Wk 4</td>
<td>Wk 8</td>
<td>Wk 12</td>
</tr>
<tr>
<td>Visit window</td>
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<td>±3 days</td>
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<td>±7 days</td>
<td>±7 days</td>
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</table>

### LABORATORY EVALUATIONS

#### Chemistries

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24 (End DLM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2.0mL</td>
<td>3.0mL</td>
<td>2.0mL</td>
<td>3.0mL</td>
<td>2.0mL</td>
<td>3.0mL</td>
<td>2.0mL</td>
</tr>
</tbody>
</table>

#### TSH, ft4 if TSH is elevated

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Wk 2</th>
<th>Wk 4</th>
<th>Wk 8</th>
<th>Wk 12</th>
<th>Wk 16</th>
<th>Wk 20</th>
<th>Wk 24 (End DLM)</th>
</tr>
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<td>3.0mL</td>
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</tr>
</tbody>
</table>

### MAXIMUM TOTAL BLOOD VOLUMES

#### Cohort 1, 2 & 3 (higher volumes for HIV+)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Week 28 and/or 4 wks post DLM</th>
<th>Week 32 and/or 8 wks post DLM</th>
<th>Week 36 and/or 12 wks post DLM</th>
<th>Week 40 and/or 16 wks post DLM</th>
<th>Week 48 and/or 36 wks post DLM</th>
<th>Week 60 and/or 48 wks post DLM</th>
<th>Week 72 and/or 72 wks post DLM</th>
<th>Week 96 and/or 96 wks post DLM</th>
<th>Unsched Visit</th>
<th>Off DLM Early Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>3.0-9.0mL</td>
<td>2.9-10.0mL</td>
<td>3.9-11.0mL</td>
<td>4.9-11.0mL</td>
<td>5.9-11.0mL</td>
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<td>5.0-11.0mL</td>
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<td>4.0-8.0mL</td>
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<td>5.0-11.0mL</td>
<td>6.0-11.0mL</td>
<td>7.0-11.0mL</td>
<td>8.0-11.0mL</td>
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<td>5.0-9.0mL</td>
<td>4.5-8.5mL</td>
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</table>

#### Cohort 4 (higher volumes for HIV+)

<table>
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<th>Study Visit</th>
<th>Screening</th>
<th>Week 28 and/or 4 wks post DLM</th>
<th>Week 32 and/or 8 wks post DLM</th>
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<th>Week 96 and/or 96 wks post DLM</th>
<th>Unsched Visit</th>
<th>Off DLM Early Study D/C</th>
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</thead>
<tbody>
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<td>4.0-10.0mL</td>
<td>5.0-10.0mL</td>
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<td>7.0-10.0mL</td>
<td>8.0-10.0mL</td>
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<td>10.0-10.0mL</td>
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### LABORATORY EVALUATIONS

#### Chemistries

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>Off treatment visits</th>
<th>Unsched Visit</th>
<th>Off DLM Early Study D/C</th>
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<tbody>
<tr>
<td></td>
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<td>Wk 2</td>
<td>Wk 4</td>
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#### TSH, ft4 if TSH is elevated

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### MAXIMUM TOTAL BLOOD VOLUMES

#### Cohorts 1, 2 & 3 (higher volumes for HIV+)

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#### Cohort 4 (higher volumes for HIV+)

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
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DAIDS Study ID # 20721

Version 1.0
dated 9 March 2017

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 #1 for:

IMPAACT 2005
A Phase I/II Open-label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-infected and HIV-uninfected Children with MDR-TB

Version 1.0, dated 9 March 2017
IND #134,732
DAIDS ES # 20721

Clarification Memorandum Date: 4 August 2017

Summary of Clarifications and Rationale

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

1. To indicate the IND number 134,732 was assigned following the FDA review of IMPAACT 2005 Version 1.0 and has been included in the protocol document.
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 2005 (instead of Version 2.0).
3. To incorporate minor corrections for accuracy and internal consistency and update the Protocol Team Roster to reflect current membership.

Implementation

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 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 2005. 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 2005 protocol.

Detailed modifications of the protocol text are shown below. Deletions in the protocol text are indicated by strikethrough and additions shown in bold text.
1. **Addition of the IND number to the title page**

   IND **#XX.XXXX 134,732** Held By DAIDS

2. **Updated protocol Section 7.3.3. to specify the use of Version 2.1 of the DAIDS Table for grading severity of adverse events**

   The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, dated November 2014 **Corrected Version 2.1, dated July 2017**, will be used to grade the severity of most adverse events in this study. This table is available on the RSC website at: [http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8](http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8).

3. **The following sections have been updated**

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   - Section 5.2.3, Storage Instructions

     DLM tablets must be stored at 25°C (77°F) with excursions permitted at 15-30°C (33 59-86°F).
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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

Pharmaceutical Support Provided by:
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ABBREVIATIONS AND ACRONYMS

ADE  Adverse drug effect
AE   Adverse event
AIDS Acquired Immunodeficiency Syndrome
ALT  Alanine transaminase
ART  Antiretroviral therapy
AUC0-24 Area under the curve during 24 hours
BID Twice a day
BMI  Body mass index
CBC  Complete blood count
CFR  Code of Federal Regulations
cfu  Colony-forming unit
CMP  Comprehensive Metabolic Panel
CNS  Central nervous system
CRF  Case report form
DAIDS Division of AIDS
DAERS DAIDS Adverse Experience Reporting System
DDI  Drug-drug-interaction
DLM  Delamanid
DMC  Data Management Center
DOT  Directly observed therapy
DST  Drug susceptibility testing
EBA  Early Bactericidal Activity
EC  Ethics committee
ECG  Electrocardiogram
eCRF Electronic case report form
EFV  Efavirenz
EMA  European Medicines Agency
FDA  Food and Drug Administration
FSTRF Frontier Science and Technology Research Foundation
GCP  Good clinical practices
GI  Gastrointestinal
HCG  Human chorionic gonadotropin
HIV  Human Immunodeficiency Virus
IATA International Air Transport Association
ICF  Informed consent form
IPD  Individual patient data
IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network
INH  Isoniazid
IoR Investigator of Record
IRB  Institutional review board
IND  Investigational new drug
INR  International Normalized Ratio
INSTI Integrase strand transfer inhibitor
LDMS Laboratory Data Management System
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SCHEMA

Purpose: To determine the age-appropriate dose of delamanid (DLM) to be added to optimized multidrug background regimens (OBR) for children with MDR-TB.

Design: Phase I/II open-label, single-arm, multisite study

Study Population: HIV-infected and HIV-uninfected infants, children, and adolescents less than 18 years of age with confirmed or probable MDR-TB enrolled in four age cohorts as shown in the table below.

Sample Size: Up to 48 participants to achieve at least 36 evaluable (9-12 evaluable in each age cohort). Within each age cohort at least six participants will be HIV-infected and at least three participants will be HIV-uninfected.

Study Treatment: DLM administered for 24 weeks, in addition to OBR, as follows:

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age in Years</th>
<th>DLM Formulation</th>
<th>DLM Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12 to &lt;18</td>
<td>Adult</td>
<td>At least 35 kg: 100 mg twice daily 15 to &lt;35 kg: 50 mg twice daily</td>
</tr>
<tr>
<td>2</td>
<td>6 to &lt;12</td>
<td>Adult</td>
<td>&gt;12 kg: 25 mg twice daily &gt;10 to 12kg: 10 mg twice daily</td>
</tr>
<tr>
<td>3</td>
<td>3 to &lt;6</td>
<td>Pediatric</td>
<td>&gt;8 to 10kg: 5 mg twice daily 5.5 to 8 kg: 5 mg once daily</td>
</tr>
<tr>
<td>4</td>
<td>0 to &lt;3</td>
<td>Pediatric</td>
<td></td>
</tr>
</tbody>
</table>

Study Duration: Approximately 168 weeks total. Accrual is expected to require approximately 72 weeks from the date of first enrollment and each participant will be followed for approximately 96 weeks.

Primary Objectives
- To evaluate the PK of DLM, when added to OBR in HIV-infected and HIV-uninfected children at doses determined to most likely achieve exposures similar to those achieved in adults with 100 mg twice-daily
- To evaluate the safety of DLM, when added to OBR over 24 weeks of treatment

Secondary Objectives
- To assess the contribution of dose, age, HIV co-infection and/or co-treatment to the variability in DLM drug disposition, using population PK modeling
- To evaluate the acceptability and tolerability of DLM over 24 weeks of treatment
- To assess the long-term safety of DLM over 72 weeks following treatment initiation
- To characterize the TB treatment outcomes among enrolled participants
For all cohorts, DLM will be continued through Week 24. After Week 24, participants will continue OBR to complete MDR-TB treatment. (HIV-infected participants will remain on routine ART treatment.)

Cohorts 3 and 4 (ages 0 to <6 years): open to accrual and dosing dependent on weight of participant:
- >12 kg: 25 mg twice daily
- >10 to 12 kg: 10 mg twice daily
- >8 to 10 kg: 5 mg twice daily
- 5.5 to 8 kg: 5 mg once daily

Criteria met to open Cohort (See Section 3.1)

Enrollment of (HIV - and HIV +) participants into IMPAACT 2005 commences.

Cohorts 1 and 2 (ages 6 to < 18 years): dosing is dependent on weight of participant:
- Weight >35 kg: 100 mg PO BID
- Weight >15 kg and <35 kg: 50 mg PO BID

For all cohorts, DLM will be continued through Week 24. After Week 24, participants will continue OBR to complete MDR-TB treatment. (HIV-infected participants will remain on routine ART treatment.)

Cohorts will remain open even after the within-cohort minimum of nine evaluable participants has been enrolled until one of the following occurs:
- Across all cohorts, at least eight evaluable children who are taking efavirenz (EFV)-based ART and eight evaluable children who are taking protease inhibitor (PI)-based ART are enrolled;
- or
- 12 participants have been enrolled to the cohort.

Note: An interim analysis will be conducted when Week 8 PK and safety data are available for at least six participants with HIV-infection taking LPV/r. Interim analysis will include all available PK and safety data for all participants at the time of the interim analysis.
1 INTRODUCTION

1.1 Background

Multidrug-resistant (MDR) tuberculosis (TB), defined as TB resistant to both isoniazid (INH) and rifampicin (rifampicin), is a growing global health emergency. The World Health Organization (WHO) estimated there were 480,000 new MDR-TB cases globally in 2014, with an estimated 9.7% of these being extensively drug-resistant (XDR)-TB, defined as MDR-TB with additional resistance to both a fluoroquinolone and a second-line injectable anti-TB drug (1).

Pediatric MDR-TB

WHO estimates that approximately one million children developed incident TB in 2014, with 140,000 deaths (1). Published data about MDR- and XDR-TB in children are limited, however, the risk of infection by MDR-TB is equivalent in adults and children in the same setting (2, 3) and model-based estimates suggest there were as many as 32,000 pediatric MDR-TB cases in 2010 (3). Although there were considerable gains in recent years in controlling global TB incidence, MDR-TB threatens those gains because it is hard to treat, with disease outcomes akin to those from the era before effective anti-tubercular drugs were available.

Pediatric TB is different from adult TB in many important ways (4). The risk of progression to TB disease after exposure and infection is highly variable, and closely related to age, with a bimodal risk which is highest in young children (<3-5 years) and rises again in early adolescence (>10 years). The disease spectrum is also quite wide and similarly related to age. Children <10 years of age most commonly develop intrathoracic lymph node TB, which is usually paucibacillary; however, children <2 years of age are also at high risk of developing severe forms of disease such as disseminated TB and TB meningitis. The paucibacillary nature of most childhood TB has important implications for diagnosis and treatment. The low organism burden complicates the microbiologic confirmation of TB in children, and among children treated for TB, only 10-15% are acid-fast bacilli smear positive, and a mere 30-40% are culture positive at diagnosis for Mycobacterium tuberculosis. As only 40% of children treated for MDR-TB would be expected to have bacteriologic confirmation, the majority will have probable MDR-TB, meaning clinical symptoms and radiologic signs consistent with TB and exposure to a source case with MDR-TB (5). Fewer organisms also means that the risk of treatment failure is much lower in children than in adults with cavitary disease, who frequently have high organism burdens and “persister” organisms that are recalcitrant to therapy. In fact, it is recommended that children with non-severe intrathoracic TB receive an intensive phase with three rather than the usual four drugs (5). Because TB in children is most often paucibacillary, the risk of acquired resistance during inadequate treatment is much less than in adults. Drug-resistant TB in children is much more likely to be primary (i.e., transmitted) rather than the result of one or more insufficiently treated cases of TB, so lung damage is less common at presentation. If children are going to progress to disease after TB infection, the majority (>90%) will do so within 12 months, so a history of recent exposure to an adult with infectious TB is critically important in pediatric MDR-TB.

Treatment of MDR-TB, in adults and children

Drug treatment for MDR-TB has not been fully optimized for adults, and the pharmacokinetics (PK), pharmacodynamics (PD), and safety of second-line anti-tuberculosis drugs in children are only beginning to be characterized.
In 2016, WHO released new guidelines for the treatment of MDR-TB in adults and in children. WHO recommends that standard regimens for MDR-TB or XDR-TB contain at least five drugs—pyrazinamide, plus at least four core second-line drugs (a fluoroquinolone, an injectable agent, and two of the following: ethionamide, clofazimine, linezolid, and cycloserine) (6). In children with “mild forms of disease”, WHO guidelines now say that injectable agents can be spared. For patients infected with a strain that is known to be sensitive to fluoroquinolones and injectables, a “shortened” 9-12 month regimen can be used that includes gatifloxacin (or moxifloxacin), kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol. This regimen is not recommended in persons who are infected with a strain that is resistant to any of the component drugs, as the regimen’s performance in this situation is not sure. Children were generally not included in the studies assessing this regimen, but there is no biological reason this regimen would not work in children. However, the dose of clofazimine in children is not established, there is no pediatric formulation, and the capsule cannot be divided.

For moxifloxacin, also a key component of the regimen, there is limited pediatric pharmacokinetic data and no child friendly formulation; the guidelines stipulate that levofloxacin should not be substituted for moxifloxacin in the shortened regimen. Because it is prohibited to use moxifloxacin together with DLM, the shortened regimen could not be used in the IMPAACT 2005 study. The 2016 WHO guidelines also give a higher priority to the use of linezolid and clofazimine in building an MDR-TB treatment regimen. The increasing use of linezolid does not have important implications for DLM use. Co-treatment with clofazimine has the potential for additive effects on QT prolongation, however it is not clear how clinically significant this is. Clofazimine is not a disallowed medication in the Otsuka 232/233 trials, and has been frequently used in combination with DLM in compassionate use programs without reported problems. Additionally, it is quite likely that clofazimine and DLM will be used together outside of the research context in an increasing number of routine MDR-TB regimens, and it will be important to study them together to inform their safe use. QT prolongation will be carefully monitored in the study so we will be able to identify if there are problems that weren’t suspected.

MDR-TB treatment regimens are poorly tolerated and have significant toxicities. A common standard regimen, for example, may include a fluoroquinolone (the best-tolerated and most effective drug in the regimen), kanamycin or amikacin (ototoxicity, which can be irreversible; poor bactericidal activity), ethionamide or prothionamide (dose-limiting gastrointestinal [GI] toxicity), pyrazinamide (risk of resistance, as this drug is a standard part of first-line regimens), cycloserine/terizidone (central nervous system [CNS] toxicity), and ethambutol (ophthalmologic toxicity risk and risk of resistance, as this drug is a standard part of first-line regimens). Having effective new anti-TB drugs and regimens is, thus, not only important to improve cure rates and reduce risk of acquired resistance but also to reduce suffering related to the common and severe side effects of standard MDR-TB regimens.

The physical and emotional suffering related to MDR-TB and its prolonged and toxic treatment cannot be understated and is particularly acute among patients co-infected with HIV (7, 8). The daily intramuscular injections required for use of kanamycin, amikacin, and capreomycin are an especially important source of pain for children and of prolonged distress for children and their caregivers. As new drugs are evaluated and registered, rigorous testing of these drugs to ensure that they can be used safely and effectively in all populations will be required to build the evidence base needed to develop shorter, effective, injectable-sparing regimens or regimens that do not include highly toxic drugs. It is important that these new, less-toxic, more effective regimens be available for all patients, including children and individuals with HIV co-infection.
Fortunately, treatment outcomes for MDR-TB are generally better in children than in adults. Outcomes can be quite good in children given individually optimized treatment regimens (80 to >90% favorable outcome), but standard regimens are long (typically 18 months), toxic, frequently require hospital admission, and tend to have poorer treatment outcomes in HIV co-infected children, who have higher mortality than HIV-uninfected children (9-12). In particular, irreversible toxicities, such as hearing loss or vestibular damage, occur in at least 25% of children who receive injectable agents (13). These toxicities may be particularly damaging to children, who have developing brains, as impaired hearing can adversely affect neurocognitive development, psychosocial functioning, and school performance (8, 13). The toxicities of the injectable drugs also introduce substantial programmatic challenges to the delivery of MDR-TB treatment in children. Audiologic monitoring for ototoxicity is more challenging in young children, requiring specialized equipment (different from that needed for monitoring in adults) and expertise, which may not be available in many settings. Additionally, many health care workers are uncomfortable providing daily injections for prolonged durations to young children, with the result that children with MDR-TB often must receive the intensive phase of their treatment in specialized hospitals or centers.

There is an urgent need for more efficacious, well-tolerated, safe, and palatable drug combinations for MDR-TB in oral formulations for all children, not just those children with minimal disease.

**Fluoroquinolones and injectable agents as components of OBR for MDR-TB**

In their 2016 guidance for treatment of MDR-TB, the WHO “strongly recommended” use of a fluoroquinolone and ethionamide (14). They provided further “conditional” recommendations based on “very low quality evidence,” about other drugs in the regimen. Bedaquiline and delamanid are recommended as possible “add-on” drugs if a regimen cannot be built with standard second-line drugs. At the time of the publication, neither bedaquiline nor delamanid was registered in any country. Up to now, bedaquiline has not been tested in children.

In the WHO analysis that informed the guidelines, fluoroquinolones were significantly associated with cure and this effect was more pronounced with later-generation fluoroquinolones (14, 15). The evidence that fluoroquinolones have potent bactericidal activity and benefit patients with MDR-TB is strong and consistent.

However, no evidence was provided to support the recommendation for use of injectable agents for adults or for children without minimal disease in the WHO guidelines. The evidence that injectables provide meaningful microbiologic activity to MDR-TB treatment regimens is mixed. In mouse models, human-equivalent doses of amikacin provide weak bactericidal activity and similar kanamycin doses are bacteriostatic (16). In vitro and mouse studies suggest the drug provides little sterilizing activity. In clinical early bactericidal activity (EBA) studies involving amikacin in which patients with pulmonary TB received amikacin monotherapy at doses of 5-15 mg/kg/day, there was no measurable effect of amikacin on sputum bacterial load with treatment, in contrast to all other TB drugs currently in use (17, 18). In a careful review of early studies carried out by the British Medical Research Council, streptomycin appeared to have limited sterilizing activity as measured by relapse rates in some studies, but which never reached statistical significance (19).

The clinical outcomes data also provides little conclusive evidence of benefit from the addition of injectables. Among patients with MDR-TB, only observational cohort data are available, as there have not been randomized controlled trials of injectable-containing versus injectable-sparing.
regimens (20). In one meta-analysis, pre-existing susceptibility to any of the recommended drugs for MDR-TB (fluoroquinolones, pyrazinamide, injectables, ethambutol, ethionamide, cycloserine, and p-aminosalicylic acid) was associated with increased unadjusted odds of treatment success associated with use of that drug (21). In another meta-analysis including patients with MDR-TB, treatment was successful in 64% of patients with MDR-TB, 56% of patients with MDR-TB with additional resistance to injectable agents (MDR-TB+INJr), 48% in patients with MDR-TB with resistance to fluoroquinolones (MDR-TB+FQr), and 40% among patients with XDR-TB. Resistance to additional second-line drugs was more common among patients with MDR-TB+INJr than MDR-TB alone, making it challenging to assess the individual contribution of injectable agents (22). In another study, among 337 patients with MDR-TB receiving a regimen that included a fluoroquinolone plus an injectable, baseline resistance to fluoroquinolones was associated with a 4-fold higher odds of unfavorable outcome whereas baseline resistance to injectable agents was not associated with higher risk of unfavorable outcome (23). In a large individual patient data (IPD) meta-analysis that helped inform WHO 2011 guidance and included data from 9,153 patients from 32 observational cohorts, the use of kanamycin, amikacin or capreomycin versus no injectable was not associated with successful treatment outcome, although that analysis was limited due to the small number of patients who did not receive an injectable agent (20). In a recently completed systematic review and IPD meta-analysis of children with multidrug-resistant tuberculosis, 119 of 842 children were treated without a second-line injectable medication; this included children from 14 of 27 included cohorts. Of these 119 treated without a second-line injectable, 41 of 57 (71.9%) of those with culture-confirmed MDR-TB had successful outcomes, and 58 of 62 (93.5%) children with probable MDR-TB had successful outcomes (6). Overall, in cohort studies, patients with MDR-TB with additional resistance to the injectables seem to do modestly less well than patients with MDR-TB that is susceptible to injectable agents. It is unclear if this is due to the microbiologic activity of the injectable, higher rates of resistance to companion drugs, strengthened DOT when injectables are part of a regimen, or patient factors that were associated with both higher risk of drug resistance and poor outcomes (poor absorption, malnutrition, adherence challenges, etc.).

Clinical practice and expert guidance reflect this ambiguity about the cost/benefit ratio of injectables in the treatment of pediatric MDR-TB. Because children tend to have paucibacillary TB and are less likely to have cavitary lung disease, mycobacterial burden in children is typically lower than in adults, and treatment outcomes are better in children than adults. Given this, and because of the high risk of irreversible and life-altering toxicity related to injectable agents and limited efficacy data for these drugs, many clinicians and programs are using injectable-sparing regimens to treat children with minimal disease or who develop toxicities to injectables, with good effect. In one cohort, 45% of patients with minimal disease and 95% of patients with extensive disease were treated with injectables; results were highly favourable, even with only one bactericidal agent in the regimen (the fluoroquinolone) (13). Although to date, children with severe MDR-TB have generally received injectables in routine care, there has not previously been access to other bactericidal and well-tolerated medications that could replace the injectable. The availability of another bactericidal drug, like delamanid, substantially changes the risk-benefit ratio for injectable use, making it much harder to justify its use given the known serious adverse effects. Injectable-sparing regimens that include a fluoroquinolone plus a second bactericidal drug (such as bedaquiline or delamanid) plus standard bacteriostatic second-line drugs have not been tested specifically in children. However, a regimen that included a nitroimidazole antibiotic (pretomanid) plus a fluoroquinolone and pyrazinamide alone (with no additional first- or second-line drugs) had higher microbiologic activity over the first eight weeks of treatment than standard first-line drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) among patients with drug-sensitive TB, prompting a Phase 3 trial of this regimen. The three-drug nitroimidazole-moxifloxacin-pyrazinamide regimen also had promising activity in patients with MDR-TB,
though numbers were small (24, 25). In addition, in a post-hoc analysis among patients with XDR-TB (in whom injectables and fluoroquinolones would not have been expected to contribute to the regimen’s efficacy), use of DLM added to background treatment for six months increased two-month culture conversion from 44 to 77% and successful treatment from 44 to 65%, though numbers were small (26).

**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 pediatric 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 posttreatment 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 IMPAACT 2005 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 the most promising TB emerging biomarkers. 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 measure tuberculosis treatment response in children with MDR-TB objectively (27, 28).

**Delamanid, a New Medicine for the Treatment of MDR-TB**

Delamanid is a new nitroimidazole that inhibits the synthesis of mycolic acids, a crucial component of the cell wall of *Mycobacterium tuberculosis*. It represents a promising new weapon in the arsenal for treatment of MDR-TB. Details regarding the preclinical and clinical testing of DLM can be found in Section 1.2 below. Based on the Phase II trial results described below showing highly favorable microbiologic outcomes (29, 30), DLM has received regulatory approvals in several countries.

In 2014, the WHO issued interim guidance on the use of DLM for the treatment of MDR-TB (31). They recommended that the following five conditions be met in order to use DLM in adults:

1. Inclusion of pyrazinamide as well as four effective second-line drugs against MDR-TB in any treatment regimen which includes DLM;
2. Close monitoring of safety and efficacy while DLM treatment is ongoing;
3. Use of active pharmacovigilance measures to detect and manage both drug-drug-interactions (DDIs) and AEs;
4. Provision of informed consent by the patient before treatment begins; and
5. Use of special caution when giving the medication to people over the age of 65, or people with chronic illnesses such as HIV and diabetes given that the paucity of data in these groups.

The interim policy guidance from 2014 did not recommend DLM for the treatment of MDR-TB in children or pregnant or lactating women, largely based on the lack of dosing and safety information that would be required for its use in these populations. The guidance underlined the
critical need to strengthen understanding of use of DLM in both HIV-uninfected and HIV-TB co-infected populations, especially children (31).

In 2016, WHO issued a new interim guidance entitled “The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents”(32). In the guidance, WHO described the use of delamanid in children and adolescents 6-17 years of age with MDR- or rifampin-monoresistant TB receiving standard-duration MDR-TB treatment. Delamanid is now being used for children with MDR- and XDR-TB in many global settings.

1.2 Prior Research

Delamanid has shown potent anti-TB activity in vitro in pre-clinical studies (33).

Delamanid and MDR-TB in Adults: Background Studies

Drug interactions and use in patients with HIV-TB co-infection: Because DLM has no known major interactions with antiretroviral agents in adult drug interaction studies (34) (35), it is of particular interest in the treatment of children co-infected with HIV and MDR-TB. More specifically, coadministration of DLM and EFV in adults had no effects on the PK of either drug. Lopinavir/ritonavir was associated with a 20% increase in DLM exposures, but DLM did not affect tenofovir, lopinavir, or ritonavir concentrations. The effects of HIV infection itself or of ART drugs on DLM PK among patients with HIV/MDR-TB co-infection have not been investigated; Phase 3 trial results will shed some light on this in the near future.

Clinical efficacy: A treatment trial in which adults with smear-positive pulmonary TB were randomized to receive one of four doses of DLM demonstrated that the average EBA of all dosages combined was 0.040 ± 0.056 log10 cfu/ml sputum/day, which was significant from day two onward. There were higher rates of meaningful reductions in sputum bacterial burden, defined as a response of ≥0.9 log10 cfu/ml sputum decline over 14 days, in patients receiving 200 mg (70%) and 300 mg (80%) of DLM per day than those receiving 100 mg (45%), demonstrating a dose response; of note, exposures were less than dose-proportional (36). A 2-month trial of DLM plus optimized background regimen (OBR) compared to WHO-approved OBR alone for HIV-uninfected adults with pulmonary MDR-TB (Trial 204) showed 45.4% sputum-culture conversion in liquid broth at two months among patients receiving OBR plus 100 mg of DLM twice daily and 41.9% among those receiving 200 mg twice daily. In comparison, patients receiving OBR plus placebo had a 29.6% culture conversion at two months (p=0.008) (29). In this trial, rates of severe treatment-emergent adverse events were similar in the DLM 100mg BID (5.6%) and 200mg BID (6.3%) groups to rates in the placebo group (5.0%). With pairwise comparisons of the frequency of adverse events among groups, only QT prolongation was found to be significant (P=0.048 for the rate of QT prolongation in the 100mg DLM group as compared to placebo, and P=0.005 for the comparison of the 200mg DLM group to placebo.) Dose-response trend in adverse events incidence, as measured by the Cochran-Armitage trend test, was observed only for QT prolongation, with a P value of 0.004 (27). It is worth noting that overall adverse events were high in this trial in all groups, likely attributable to the other components of participants’ multidrug background regimens.

In a follow-up, non-randomized 24-month observational study of DLM, patients who received >6 months of the drug had lower mortality (1.0%) than patients who received the drug for <2 months (8.3%; p<0.001). Overall, out of 192 patients who received DLM for ≥6 months, 142 (74.5%) had favorable outcomes (cure or treatment completion), compared to 126 (55%) of 229 patients who received DLM for ≤2 months (30). In this follow-up observational study, adverse events were not
formally reported; rather, treatment outcomes classified as either favorable or unfavorable were reported. As noted above, among patients enrolled in the Phase 2 studies of DLM who were later discovered to have XDR-TB (in whom injectables and fluoroquinolones would not be expected to have activity), use of DLM added to background treatment for at least six months increased two-month culture conversion from 44 to 77% and successful treatment from 44 to 65% compared to 0-2 months’ use of DLM, though numbers were small (26).

A Phase 3 multicenter randomized controlled trial (RCT) (Trial 242-09-213) evaluating the safety and efficacy of DLM at a dose of 100 mg twice daily for two months followed by 200 mg once daily for four months together with OBR versus placebo plus OBR, is nearing completion, with results expected soon. This trial enrolled adult participants with MDR-TB, and in addition, involved a sub-study of participants co-infected with MDR-TB and HIV taking antiretrovirals at a limited number of sites designated as having a sufficient population of co-infected patients for enrollment. Results from this sub-study are not yet available. Based on the Phase 2 trials data, the European Medicines Agency (EMA) licensed DLM in April 2014 at a dose of 100 mg twice daily for six months. The drug is also licensed in the European Union, Japan, and Korea. Submission to the U.S. Food and Drug Administration (FDA) is anticipated in 2016.

**Delamanid Pharmacokinetics**

In adults, DLM reaches a peak concentration (Tmax) four hours post-dose, and the apparent terminal elimination half-life (T1/2) is 30-38 hours. DLM bioavailability is increased 2- to 4-fold when it is taken with food. The T1/2 of its main metabolites is approximately 150-600 hours. The PK profile of DLM is similar for healthy volunteers and for patients with TB. Among adult patients with MDR-TB, a dose of 100 mg twice daily achieves an AUC0-24h of 7234 (CV% 32) at two weeks and a n AUC0-24h of 7925 (CV% 38) at two months (29).

**Delamanid and Safety in Adults: Background Studies**

Twelve phase I trials of DLM in healthy adults have shown a favorable side effect profile, with the most commonly reported side effects emerging while on treatment being dizziness, nausea, and headache. The total number of adult individuals exposed to DLM in these safety trials has been 949, and overall the side effects were similar in the groups receiving DLM plus OBR and the groups receiving placebo plus OBR (37).

**QTc Prolongation with Delamanid**

There was one exception to the report of equal safety among arms in the two-month RCT in adults mentioned above. There was a slightly higher frequency of QTc prolongation in the DLM 100mg BID + OBR group (4.3%; 7/161) and DLM 200mg BID + OBR (5.6%; 9/160) than in the placebo + OBR group (1.9%; 3/160) (29). The mean placebo QTc interval increases in another RCT among adults receiving DLM 100mg twice daily were 7.6ms at one month and 12.1ms at two months; 3% of patients exhibited a QTc increase of 60ms or greater. Only one of 161 patients receiving 100 mg twice daily exhibited a QTcF interval at any time in the study that was greater than 500ms. Torsades de Pointes was never observed in this trial, and there were no events suggestive of arrhythmias.

The QTc prolongation seen in patients treated with DLM is characterized by a slow increase over the first 6-10 weeks of treatment followed by stability thereafter, appearing to correlate with plasma concentrations of the major metabolite, DM-6705. Both hypoalbuminemia (<2.8 g/dL) and hypokalemia have been found to be risk factors for DLM associated QTc prolongation (35).
To mitigate risk of prolonged QTc related to the use of two or more drugs that prolong QT in the Phase 2 trials, levofloxacin was used instead of moxifloxacin in the Phase 2 trials, as levofloxacin carries less QT prolongation risk; in the Phase 3 trial, though, moxifloxacin has been used together with DLM in some patients in a closely monitored setting.

Safety data from children who have received DLM are described below.

**Drug-Drug Interactions (DDIs) with Delamanid**

Albumin in serum primarily regulates the metabolism of DLM, with the cytochrome P450 3A4 enzyme also contributing modestly, so concurrent administration with medications known to inhibit or induce this enzyme may modestly alter drug levels (38, 39). In addition, administration of DLM to patients with albumin levels <2.8 is not recommended. Therefore, this trial will monitor concomitant medications, electrolytes, and serum albumin levels at regular intervals.

DLM and its major metabolites do not show meaningful inhibition of CYP isoenzyme activity, including CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4. DLM is not an inducer of CYP1A2, CYP2C9, CYP3A4/5. In DDI studies of DLM used in healthy volunteers in combination with tenofovir, EFV, and/or lopinavir-ritonavir, no significant drug-drug-interactions were seen; when given with lopinavir/ritonavir, a modest increase in DLM area under the concentration-time curve of 20% was observed (31). No drug interaction studies of DLM together with integrase strand transfer inhibitors (INSTIs) have been performed. Based on knowledge of metabolic pathways, risk of metabolic drug interaction is low.

**Pharmacokinetics in Children**

Drug disposition is significantly different at different points along the age continuum, and both the structure and function of various metabolizing and clearance organ systems change with increasing body weight. Among infants, intestinal transit is slowed, and oral absorption may be decreased by lower acidity in the GI tract of infants. In addition, the ontogeny of hepatic clearance in infants and young children is such that they may lack fully functional enteral metabolizing enzymes or transporters. Renal clearance is deficient at birth, and does not reach adult levels of glomerulotubular function until at least one year of age, drastically affecting drug dosing (40, 41). Theory-based allometry predicts that a child’s volume of distribution is linearly proportional to the child’s body weight. However, children’s body composition shifts with maturation, and for example, changes in the overall water content of the body can alter the volume of distribution dramatically (42). For these reasons, it is critical to gather empirical PK data for children taking DLM, particularly young children and children for whom comorbidities might affect drug disposition, such as HIV infection.

**Drug acceptability in Children**

Acceptability is a broad term referring to the overall suitability of a dosage formulation, and includes factors such as palatability, dose volume or size, dosing frequency, dosing device for liquid medications, and directions for use (43). Palatability is defined as the overall acceptance of the taste, smell, volume or size, and texture of a medication to be taken orally, and is a key determinant of medication acceptability in children. Age has been shown to impact taste preferences, and palatability is best assessed in children rather than via extrapolation from adult data. Acceptability of medications is an important factor influencing adherence and thus treatment success (44, 45). Children may refuse, spit, or vomit poorly palatable medications (46). The administration of medication to young children can be challenging for caregivers, particularly for chronic medications for conditions such as TB and HIV, and any factors that
make administration more complicated or difficult may adversely affect adherence and treatment outcomes. Understanding the acceptability and palatability of TB drugs in children is important for anticipating potential adherence challenges.

**Delamanid and MDR-TB in Children: Ongoing Trials**

The data on PK, safety, and tolerability of DLM among infants, children, and adolescents treated for MDR-TB, particularly among children with HIV co-infection, remain limited. Otsuka Trial 232 is a Phase 1 trial among HIV-uninfected children with MDR-TB evaluating a dose of 100 mg twice daily for ten days in children ages 12-17 and a dose of 50 mg twice daily for ten days in children ages 6-11 years (six children per age cohort). Completion of trial 232 is required for participation in trial 233. Children in 233 receive the same DLM dose as they received in 232, but for six months. Enrollment of the two oldest cohorts into 232 and 233 is complete. Trials 232 and 233 are enrolling children in the two youngest age cohorts (age 0 to 5 years). These participants are receiving DPF (DLM pediatric formulation), at doses that are expected to produce DLM plasma concentrations equivalent to those from the adult DLM tablets (25 mg twice daily for children ages 3-5 and weight-based dosing for children less than 3 years old). A dose of 125mg DPF reaches similar Cmax and AUC as 100mg of the adult formulation and is, thus, bioequivalent [Ref: personal correspondence with Otsuka]. The DLM adult formulation is available in unscored, 50mg tablets, whereas the DLM pediatric formulation will be available in dispersible tablets in two strengths (25 mg and 5 mg).

**Pharmacokinetics**

Alignment with Otsuka studies (for dose determination and optional increased power) will guide timing and dosing for this IMPAACT trial. Data analysis for Otsuka Trial 232 is complete for the three oldest cohorts of children, from 3-17 years old. In the oldest age group, the 12-17 year-olds, 100mg of DLM was given twice daily. In the second age group, 6-11 years, 50mg of DLM was given twice daily. The third group, which includes children 3-5 years of age, received the pediatric DLM formulation at a dose of 25 mg twice daily. For all three groups, the achieved median DLM and DM-6705 exposures at the doses provided were contained within the range of exposures seen in adults. Exposures to DLM were generally slightly higher in the pediatric population compared to adults (please see tables below; references are Hafkin et al., ICAAC 2015 for Group 1 and 2, direct communication with Dr. Jeff Hafkin, Otsuka for Group 3). Exposures to DM-6705, on the other hand, were generally somewhat lower in the pediatric populations, especially in Group 3. Moreover, the drug was well-tolerated, no participants discontinued DLM or study participation prior to trial completion, and there were no safety concerns attributable to DLM.

**Safety**

Overall, among 21 children who have received DLM in clinical trials to date, there have been no serious adverse events. In trial 233, one participant was diagnosed with non-Hodgkin’s lymphoma which was not considered to be related to DLM. There were no serious adverse events (death, hospitalization, AE that leads to congenital defect, or other medically significant events per the FDA definitions). There were 0 AEs among the youngest group, Group 3. In Group 2, there was one case of arthralgia, one of headache, and one of dizziness. In Group 1, there was one case of dizziness. All these children were also receiving optimized background regimens [Ref: personal correspondence with Otsuka].
Table 1. Median Delamanid Plasma Pharmacokinetic Parameters in Children in Otsuka Trial 232 compared with values in adults

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (Age 12-17 yrs)</th>
<th>Group 2 (Age 6-11 yrs)</th>
<th>Group 3 (Age 3-5 yrs)</th>
<th>Adults</th>
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<td>10*</td>
</tr>
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<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
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<td>4.00 [0.0-24.0]</td>
<td>12.00 [2.0-24.0]</td>
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</table>

Adapted with permission from: Hafkin J et al, ICAAC 2015 (47); also personal communication with Jeff Hafkin.

Table 2. Median DM-6705 Plasma Pharmacokinetic Parameters in Children in Otsuka Trial 232 compared with values in adults

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (Age 12-17 yrs)</th>
<th>Group 2 (Age 6-11 yrs)</th>
<th>Group 3 (Age 3-5 yrs)</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>10*</td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>8.60 [8.6-15.5]</td>
<td>81.7 [52.9-93.2]</td>
<td>7.68 [6.07-23.1]</td>
<td>90.0 [62.4-112]</td>
</tr>
<tr>
<td>T&lt;sub&gt;1/2,z&lt;/sub&gt; (h)</td>
<td>ND</td>
<td>216</td>
<td>ND</td>
<td>257</td>
</tr>
</tbody>
</table>

Adapted with permission from Hafkin J et al, ICAAC poster A-960 2015 (47); also personal communication with Jeff Hafkin.

* For DM-6705, which has a much longer half-life than the parent drug, we would expect additional accumulation between Days 10 and 14. For that reason, we have estimated Day 10 values for adults for comparison reasons. The Day 10 values for adults are estimated here based on the half-life of the metabolite of 150-600 hours. Approximations include: assuming 1-compartment kinetics for the metabolite, and that the formation is not limiting the accumulation. Based on these assumptions and half-life of 150-600 hours, Day 10 DM-6705 concentrations are estimated at 24% to 67% of steady state concentrations and Day 14 DM-6705 concentrations are estimated at 32% TO 79% of steady state concentrations. For comparability with the pediatric data, Day 10 exposures can therefore be adjusted downward, to be about 15-25% lower than Day 14 exposures. [ND= No Data]
Table 3. Summary of Pharmacokinetic Parameters of DLM and DM-6705 at Day 56 Among Adults Who Received DLM 100mg PO BID (Trial 204)

<table>
<thead>
<tr>
<th></th>
<th>Delamanid (Day 56)</th>
<th>DM-6705 (Day 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>AUC0-24h (h•ng/mL)</td>
</tr>
<tr>
<td>N</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td>Median</td>
<td>391</td>
<td>7654</td>
</tr>
<tr>
<td>Mean</td>
<td>414</td>
<td>7925</td>
</tr>
<tr>
<td>SD</td>
<td>165</td>
<td>2973</td>
</tr>
<tr>
<td>%CV</td>
<td>39.9</td>
<td>37.5</td>
</tr>
<tr>
<td>Min</td>
<td>79.5</td>
<td>635</td>
</tr>
<tr>
<td>Max</td>
<td>961</td>
<td>17400</td>
</tr>
</tbody>
</table>

Building on existing PK data in children, the team has developed pharmacometric models that take into account the developmental pharmacology of DLM and incorporate existing PK data from both adults and children. The team will evaluate doses that are anticipated to achieve exposures that fall into the range of exposures seen in adults with the currently registered dose, a dose that in adults has been shown to be safe and effective. Moreover, reassuringly, exposures of the metabolite are not expected to exceed exposures of the metabolite seen in adults (Table 3). Details about these models and how they informed the design of this study can be found in Appendix III.

**QTc Prolongation**

In children, the data on QTc prolongation while on DLM has been very reassuring. In the below table, QTc effects among the 13 children in the two older age cohorts of the Otsuka 232 and 233 trials among children with MDR-TB are summarized (of note, in the 233 trial, study drug was discontinued after six months, or on Day 182, while in the 232 trial it was discontinued on Day 10.) Details regarding these trials can be found below. These trials are still enrolling for the two youngest age groups, so no data are currently available for the youngest children (age 0 to <3). In the 233 trial, among the 21 children from age 3 to 17 who received DLM, 0 had a QTcF greater than 480 ms, and only one of 21 (4.7%) had a QTc elevation of >60 msec above baseline. Overall, among 21 children who have received DLM in clinical trials to date, there were no events of QTcF greater than 480 ms. Similarly, although data are limited, among children with MDR-TB receiving OBR that included a fluoroquinolone (regimens that did not include DLM), there have been no reports of QT interval prolongation (48, 49).
Table 4. Summary of QT effects Among Children on Delamanid Ages 6-17 in Otsuka Trials
(personal communication: Otsuka, Feb 2016)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Visit</th>
<th>Mean QTc (Fridericia; ms)</th>
<th>Mean Change from Baseline (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-17 years:</td>
<td>Baseline</td>
<td>407.0</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>423.4</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>Day 56</td>
<td>417.1</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>Day 84</td>
<td>427.9</td>
<td>20.9</td>
</tr>
<tr>
<td></td>
<td>Day 126</td>
<td>428.6</td>
<td>21.6</td>
</tr>
<tr>
<td></td>
<td>Day 154</td>
<td>423.6</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>Day 182</td>
<td>420.8</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>Day 210</td>
<td>414.2</td>
<td>8.5</td>
</tr>
<tr>
<td>6-11 years:</td>
<td>Baseline</td>
<td>411.8</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>421.1</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Day 56</td>
<td>420.0</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>Day 84</td>
<td>416.7</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Day 126</td>
<td>424.4</td>
<td>12.6</td>
</tr>
<tr>
<td></td>
<td>Day 154</td>
<td>421.0</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Day 182</td>
<td>420.9</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Day 210</td>
<td>407.8</td>
<td>-4.0</td>
</tr>
<tr>
<td>3-5 years:</td>
<td>Baseline</td>
<td>400.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 28</td>
<td>413.3</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>Day 56</td>
<td>407.4</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Day 84</td>
<td>396.2</td>
<td>-5.2</td>
</tr>
<tr>
<td></td>
<td>Day 126</td>
<td>393.8</td>
<td>-10.7</td>
</tr>
<tr>
<td></td>
<td>Day 154</td>
<td>399.3</td>
<td>-5.2</td>
</tr>
<tr>
<td></td>
<td>Day 182</td>
<td>392.0</td>
<td>-27.0</td>
</tr>
</tbody>
</table>

*note that the Day 210 visit is following treatment completion.

1.3 Rationale

This study aims to characterize the safety and PK of DLM in children with MDR-TB. It will further assess DLM among children without HIV infection, using weight-based, rather than age-based dosing. While a dose of 100 mg BID for children aged 12-17 years and 50 mg BID for children aged 6-11 years was recommended in the WHO interim guidance for use of DLM in children and adolescents because those were the only doses tested in children up to now, simulations with our model developed on the observed PK data from children in the 232 and 233 trials demonstrates that age- and weight-based dosing is more likely to result in adult target concentrations than dosing based on age alone. This is the rationale for the weight bands that will be used in this protocol. In this study, more information will be generated to inform dose recommendations for children without HIV infection. This is important because the majority of children with MDR-TB do not have HIV co-infection and initial dosing studies included only a small number of children and did not use weight-based dosing. This study will also assess DLM safety and pharmacokinetics among children with HIV co-infection. This is important because we want to be sure that DLM absorption is not impacted by HIV co-infection and also confirm that medications commonly used to treat HIV in children do not meaningfully impact DLM or metabolite exposures. Information from this trial plus the ongoing Otsuka-sponsored trials among HIV-uninfected children will inform the potential use of DLM for treatment of pediatric MDR-TB. This is an essential public health concern given the paucity of effective agents available on the market to treat MDR-TB in children, the unacceptable toxicity profile of current regimens,
and the poor outcomes of children co-infected with MDR-TB and HIV. Of note, DLM is particularly attractive as a drug to treat MDR-TB in children co-infected with MDR-TB and HIV, as it is one of the few new TB drugs that does not appear to have significant drug interactions with first-line antiretroviral agents such as efavirenz and protease inhibitors in adults. The effects of HIV co-infection and co-administration of ART on drug absorption and PK, though, are as-yet unknown (11, 13). Given the high burden of HIV-TB co-infection in many international settings, even in the era of widespread rollouts of Prevention-of-Mother-to-Child Transmission (PMTCT) of HIV, it is necessary to study the safety and tolerability of this drug when co-administered with antiretroviral regimens for HIV.

In addition, DLM is likely to be a backbone drug for shortened, injectable-sparing MDR-TB treatment regimens going forward, and its toxicity profile is excellent especially compared to OBR drugs that commonly cause serious toxicities such as hearing loss, neuropathy, severe nausea, and CNS disturbance.

There are several lines of evidence to support the substitution of DLM for the injectable in this study, from an efficacy standpoint. Drug activity against various subsets and populations of bacilli is the most important consideration in determining which drugs in any TB regimen can be substituted for others. For example, the basis for rifampicin’s potent sterilizing activity (i.e. its ability to eradicate the last remaining persister mycobacteria, leading to cure) and its ability to shorten therapy from 18 to 6 months is related to its mechanism of action and ability to kill metabolically inactive or metabolically slightly-active organisms (the state many mycobacteria assume when they are being assaulted with anti-TB treatment). The nitroimidazoles (e.g. DLM) appear to have similar activity against “persisters”. In sharp contrast, the injectables have poor activity against slowly multiplying mycobacteria (50, 51). In addition, they do not have measurable early bactericidal activity in patients with pulmonary TB, whether given as standard or liposomal formulation (17). While it is true that the injectables may contribute something to a multidrug regimen, there is no study that quantitatively demonstrates the individual contribution of injectables to TB treatment in an unbiased way, the activity of the injectables is not unique, and there is no convincing reason to use them when a good regimen can be constructed that does not include them. In sum, DLM has strong and noteworthy effects on persister organisms, with sterilizing activity similar to rifampicin’s effects on drug-sensitive TB, and it and other nitroimidazoles have demonstrated microbiologic activity in Phase II trials (25, 26, 29, 30). It is thus reasonable to substitute it for an injectable in an MDR-TB regimen given the evidence suggesting its better sterilizing and bactericidal activity. New 2016 WHO guidelines (6) currently recommend excluding injectables in some children with MDR-TB, particularly in those with mild or clinically-diagnosed disease given that its harms may outweigh benefits and injectable-sparing regimens are highly effective in this setting (94% success rate); in addition, as noted in Table 2 above, children in IMPAACT 2005 are expected to be at the higher end of DLM exposures observed in adults, but without higher metabolite exposures (Table 3), according to data from Trials 232 and 233, which could imply higher efficacy without the concomitant toxicity.

The main risk to substituting one drug for another in TB treatment (in this case, DLM for the injectable) would be a poor treatment response. However, to date, treatment failure and relapse are very uncommon in children with MDR-TB, and DLM has better bactericidal and sterilizing activity than injectables, so this risk would be expected to be quite low. Given the uncertainty contributed by HIV infection and its treatment, aggressive measures will be undertaken in this protocol to minimize risk, including the interim analysis (See Section 10.4), which examines QTc and safety and assesses PK endpoints. The PK data will feed back to inform dose in subsequent participants if for some reason the observed exposures are outside of the expected target range. In addition, with the goal of characterizing the safety, efficacy, and microbiological activity as well
as possible, we will perform stringent repeated assessments of microbiological and clinical response as detailed, consistent with the efficacy and safety outcomes being reported in other recent and ongoing MDR-TB trials in children. In order to further minimize the risk of treatment failure, a positive smear or culture eight weeks after starting DLM will trigger a review by the protocol team and clinical team to assess the participant’s clinical course to date and to consider whether or not the participant might benefit from the addition of the injectable or another TB medication, based on the participant’s clinical course and all laboratory data up to then.

The most serious risk of including the injectable as a standard component in all regimens is that of permanent sensorineural hearing loss, which has been clearly demonstrated to occur in 20-25% of children treated with these agents long-term. The risk-benefit ratio has been considered to be in favor of using the injectables in children with MDR-TB to date because of the seriousness of the disease and the limited treatment options; however, with the availability of an effective drug like DLM, that risk-benefit ratio is substantially altered and strongly argues against their use. As participants in the trial will have access to DLM, we feel it is not in the participants’ best interest to be exposed to the high risk of permanent hearing loss from the injectables when they are likely not to gain clinically meaningful benefit.

Thus, children with MDR-TB in this trial will receive an injectable-sparing regimen that includes DLM, a fluoroquinolone, pyrazinamide, plus at least three other active second-line drugs. In this way, children will receive two drugs with demonstrated bactericidal activity (fluoroquinolone and DLM) plus several bacteriostatic agents (companion standard second-line drugs) and pyrazinamide. An injectable will only be included if an appropriate regimen cannot be constructed based on local drug availability and the resistance pattern of that individual’s infecting M. tuberculosis strain (for example, participants with pre-XDR TB with demonstrated resistance to fluoroquinolones but susceptibility to injectables). Compared with adults, children with MDR-TB have a lower burden of disease, better treatment outcomes and higher risk of long-term sequelae related to ototoxicity of injectables; with injectables, 20-30% of children suffer deafness that is often irreversible. DLM has bactericidal and sterilizing activity, is well-tolerated, and improves long-term outcomes in MDR-TB in Phase II trials. Further, regimens containing a nitroimidazole plus fluoroquinolone plus pyrazinamide have demonstrated potency in other trials and there are promising, albeit limited, data suggesting DLM-based regimens are active in patients with injectable-resistant disease, underscoring the potentially high efficacy of a DLM-fluoroquinolone-based multidrug regimen.

Data from this trial will build on and enrich existing knowledge about DLM drug disposition in HIV-uninfected children derived from ongoing Otsuka trials and will help quantify the effects of HIV co-infection and use of ART (specifically efavirenz and lopinavir/ritonavir) on drug disposition. In addition, it will provide early safety, tolerability, and efficacy data for a DLM-containing, injectable-sparing regimen in all children with MDR-TB (not just those with minimal disease). Children constitute a population that stands to benefit most from an all-oral regimen that does not include irreversibly toxic injectable agents. The WHO recommendations contain a call for further research of MDR-TB regimens, given that the quality of evidence for current recommendations is of low quality. They specifically call for research that establishes conditions under which injectable-sparing regimens can be used in adults and children.
1.4 Hypotheses

1) Using population PK modeling, and using combined pediatric PK data from this study and Otsuka trials 232-233, doses of DLM that achieve target exposures associated with favorable treatment outcomes in HIV-uninfected adults can be predicted in children ages 0-17 years with MDR-TB with or without HIV co-infection with adequate precision.

2) DLM will be safe and well-tolerated when given together with OBR for MDR-TB among children with and without HIV co-infection.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

2.1.1 Evaluate the PK of DLM, when added to OBR, in HIV-uninfected and HIV-infected children at doses determined to most likely achieve exposures similar to those achieved in adults with 100 mg twice-daily.

2.1.2 Evaluate the safety of DLM, when added to OBR, over 24 weeks of treatment.

2.2 Secondary Objectives

The secondary objectives of this study are to:

2.2.1 Assess the contribution of dose, age, HIV co-infection and/or co-treatment to the variability in DLM drug disposition, using population PK modeling.

2.2.2 Evaluate the acceptability and tolerability of DLM over the 24 weeks of treatment.

2.2.3 Assess the long-term safety of DLM over 72 weeks following treatment initiation.

2.2.4 Characterize the TB treatment outcomes among enrolled participants.

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

2.3.1 Characterize HIV treatment outcomes among enrolled participants.

2.3.2 Describe the overall safety and tolerability of injectable-sparing, DLM-containing regimens in the treatment of MDR-TB.

2.3.3 Characterize the TB treatment outcomes with injectable-sparing, DLM-containing regimens.
2.3.4 Evaluate the risk of QT prolongation and its association with DLM (and DM6705 metabolite) exposures among children taking DLM plus OBR.

2.3.5 Explore longitudinal biomarkers of tuberculosis treatment responses in children for MDR-TB.

3 STUDY DESIGN

3.1 Identification of Study Design

This is a Phase I/II open-label, single-arm, PK and safety study to determine the appropriate dose of DLM, by age group, for infants, children, and adolescents less than 18 years with MDR-TB, with and without HIV co-infection.

The study will involve four age cohorts (based on age at enrollment):

1) Cohort 1: Ages 12 to <18 years: adult formulation
2) Cohort 2: Ages 6 to <12 years: adult formulation
3) Cohort 3: Ages 3 to <6 years: pediatric formulation
4) Cohort 4: Ages 0 to <3 years: pediatric formulation

Each cohort will enroll a minimum of nine evaluable children (six HIV-infected, three HIV-uninfected). Cohorts 1 and 2 will open immediately upon study start. Cohort 3 will open to enrollment following review of safety data from children in that age group enrolled in Otsuka trials 232 and 233. Safety data reviewed must include data from at least six children who have received 24 weeks of DLM plus all other safety data available from 232/233. Cohort 4 will open to enrollment following review of safety data among participants in Group 4 in 232/233 (similar to the process for Cohort 3) as well as review of PK data (to confirm the appropriateness of dose selection).

If a child crosses an age limit during treatment (e.g., two years old at enrollment and then turns three a few months later), the dose will continue at the next study visit based on the updated weight-band of the child, rather than on an age-based dose.

In addition, to ensure that the effects of HIV infection and treatment with ART (EFV-based or PI-based, as these are the most widely used and available options worldwide) on DLM PK are fully characterized, each cohort will remain open after the minimum of nine evaluable participants has been enrolled until one of the following occurs:

1) The study has enrolled at least eight evaluable children across all the age cohorts who are taking EFV-based ART and eight evaluable children who are taking PI-based ART; or,
2) 12 participants have enrolled into the cohort.

Participants are considered ‘evaluable’ if they have completed PK visits up to Week 8 and have PK data sufficient to estimate drug exposures using a model-based approach.

Participants will be assessed for evaluability in real time once PK data at week 8 are available. Non-evaluable participants will be immediately replaced unless the maximum of 12 participants per cohort is already achieved.
An interim analysis will be conducted when Week 8 PK and safety data are available for at least six participants with HIV-infection taking LPV/r. The main purpose of the interim analysis is to assess interaction between DLM and LPV/r. Interim analysis will include all available PK and safety data for all participants at the time of the interim analysis. Refer to Section 10.4 for additional details.

DLM will be given for a total duration of 24 weeks, during which time the participants will also be receiving OBR for MDR-TB. Children with HIV co-infection will receive routine ART treatment regimens. It is anticipated that most children less than three years of age will be receiving PI-based ART while the majority of older children will be receiving EFV-based ART. Thus, drug interaction data (including PK and safety findings) from older cohorts are not expected to be informative for younger cohorts. Major drug interactions or overlapping toxicities are not expected given the metabolic profiles and currently known toxicity profiles of the drugs. Following study treatment, children will continue OBR to complete MDR-TB treatment (typically for a total treatment duration of 12-18 months, depending on the severity of disease). Children will be followed until 72 weeks after DLM treatment initiation (Please See Schedule of Evaluations (Appendix I), for a schedule of PK sampling and other clinical procedures).

Participants will undergo semi-intensive PK sampling at Day 0 (three samples), Week 2 (four samples) and Week 8 (three samples). The Day 56 sampling will capture concentrations of parent and metabolite at steady state, to quantify accumulation of the metabolite over time. Additionally, sparse sampling will be performed. Trough concentrations (one sample per occasion) will be collected at Weeks 4, 12, 16, 24 and 28. Pharmacometric modelling was used to identify the most efficient sampling approach to obtain sufficient data for PK parameter estimation while minimizing blood draws. A previously developed population model based on data from Study 232 and data from adult trials was made available by Otsuka to the Uppsala University pharmacometrics team, led by Dr. Mats Karlsson. Existing raw pediatric PK data were also shared. Multiple sampling schedules were evaluated, starting from the schedule used in Otsuka pediatric studies to date. The simulations and re-estimations demonstrated that reducing the schedule from 18 to 15 samples per child was feasible and sufficient to meet study aims. These clinical trials simulations are described in detail in Appendix III.

4 STUDY POPULATION

This study will be conducted among up to 48 HIV-infected and HIV-uninfected infants, children, and adolescents less than 18 years of age with confirmed or probable MDR-TB who will be enrolled in age-based cohorts as described in Figure 1 and Section 3.0.

Participants will be selected for the study according to the criteria in Sections 4.1-4.3. 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 Sections 4.6 and 4.7, respectively.
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 (or legal guardian) is willing and able to provide written informed consent for child study participation. Additionally, for children whose assent is required per site IRB/EC policies and procedures, child is willing and able to provide written assent for his or her study participation.

4.1.2 Age < 18 years at enrollment

4.1.3 HIV-uninfected, or HIV-infected (as defined in Section 4.3)

4.1.4 If HIV-infected: Initiated the standard of care ART regimen at least two weeks prior to enrollment (note: regimens including EFV, NVP, a boosted PI, or INSTI are allowed)

4.1.5 Confirmed or probable MDR-TB classified as follows:

**Confirmed MDR-TB (or RMR-TB, pre-XDR or XDR-TB):**
- Intra-thoracic (pulmonary) TB based on chest radiograph consistent with TB, with or without one of the following forms of extrathoracic TB:
  1) Peripheral TB lymphadenitis
  2) Pleural effusion or fibrotic pleural lesions
  3) Stage 1 TB meningitis
  4) Miliary and abdominal TB,
  5) Other non-disseminated forms of TB disease

AND

- Microbiological confirmation of *Mycobacterium tuberculosis* from any clinical specimen by either culture or molecular methods (including Xpert MTB/RIF)

AND

- Drug-resistance demonstrated by genotypic (molecular) or phenotypic methods, with any of the following resistance patterns:
  - MDR-TB (resistance to both rifampicin and isoniazid)
  - Rifampicin mono-resistant TB (RMR-TB) or where additional INH resistance has not been confirmed (i.e., isolated Xpert MTB/RIF rifampicin resistance)
  - Pre-XDR-TB (MDR-TB plus resistance to either a fluoroquinolone or a second-line injectable agent)
  - XDR-TB (MDR-TB plus resistance to both a fluoroquinolone and a second-line injectable)
  - Note: RMR-TB, MDR-TB, pre-XDR-TB and XDR-TB are therefore collectively referred to as “MDR-TB” for the purposes of the protocol
Probable MDR-TB (or RMR, pre-XDR or XDR-TB)

- A presumptive diagnosis of intrathoracic (pulmonary) TB based on well-documented clinical symptoms or signs of TB AND chest radiograph consistent with 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

AND

- One of the following:
  - Exposure to a confirmed MDR-TB source case* (RMR-TB, pre-XDR-TB, XDR-TB)
  - Documented failure to respond to a first-line regimen, and where adherence was well documented.

AND

- The clinical decision has been made to treat for MDR-TB

* Confirmed MDR-TB source cases defined as a case with intrathoracic TB with or without extrathoracic TB, with microbiological confirmation of Mycobacterium tuberculosis from any clinical specimen by either culture or molecular methods (including Xpert MTB/RIF), and with drug-resistance demonstrated by genotypic (molecular) or phenotypic methods, with any of the resistance patterns described above.

4.1.6 Albumin level > 2.8 g/dL within 30 days prior to enrollment

4.1.7 Potassium > 3.4 and < 5.6 mmol/L; magnesium > 0.59 mmol/L within 30 days prior to enrollment

Note: Electrolytes can be repeated and a recheck may performed to meet eligibility criteria.

4.1.8 BMI Z-score greater than -3 for children > 5 years of age; weight for length/height Z-score greater than -3 for children < 5 years of age (using latest World Health Organization scores), at screening

4.1.9 For Cohorts 1 and 2, weight > 15 kg at screening
4.1.10 Has initiated an appropriate OBR MDR-TB treatment regimen as per routine treatment decision, at least two weeks but not more than eight weeks prior to enrollment, and in the opinion of the site investigator, is tolerating the regimen well at enrollment.

*Note: An appropriate OBR MDR-TB treatment regimen is defined as including components based on the sensitivities of the infecting isolate, if known, and past treatment history, if known. This regimen should also follow the OBR MBR-TB treatment guidelines as described in Section 8.2.*

4.1.11 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 DLM).

4.1.12 If female and of reproductive potential, defined as having reached menarche and not having undergone a documented sterilization procedure (hysterectomy, bilateral oophorectomy, or salpingectomy): Negative pregnancy test at screening within 14 days prior to enrollment.

4.1.13 If female, of reproductive potential (as defined in Section 4.1.12), and engaging in sexual activity that could lead to pregnancy: Agrees to avoid pregnancy and to use one of the following forms of birth control while receiving DLM and for one month after stopping DLM: condoms, diaphragm or cervical cap, intrauterine device (IUD), hormonal-based contraception. The selected method must be initiated prior to enrollment.

4.2 Exclusion Criteria

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

4.2.1 Known allergy to any nitroimidazoles or nitroimidazole derivatives

4.2.2 Active use of prohibited medications listed in Section 5.6.2, within 3 days of enrollment

4.2.3 Participant has a history of any of the following, as determined by the site investigator or designee based on maternal report and available medical records:
   - 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
   - Significant GI, metabolic, neuropsychiatric, kidney or endocrine disease at screening that would, in the investigator’s opinion, preclude safe participation in the trial and/or assessment of primary endpoints
   - Previous DLM or pretomanid exposure

4.2.4 Abnormal ECG (including QTcF $\geq 450$ ms), atrioventricular block, prolonged QRS $\geq 120$ ms at screening

4.2.5 Karnofsky score $< 30\%$ for participants $\geq 16$ years of age or Lansky play score $< 30\%$ for participants $< 16$ years of age, at screening

4.2.6 Alcohol intake that in the opinion of the study investigator could potentially interfere with study participation and/or introduce safety concerns with use of DLM
4.2.7 Lactating with plans to breastfeed, at enrollment

4.2.8 Disseminated TB (including miliary TB, TBM Stage 2 or 3, abdominal TB, and osteoarticular TB), at screening

4.2.9 Co-enrolled in any other trial involving pharmacologic regimens, at screening

4.2.10 If HIV-exposed and < 2 years of age: Breastfeeding at enrollment

4.3 Documentation of HIV Status

At the time of study enrollment HIV status must 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

Participants will be considered HIV-infected based on 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. As this study is being conducted under an IND, all test methods should be FDA-approved, if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT Laboratory Center.

4.3.1.1 Participants less than two years of age

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 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.

4.3.1.2 Participants two years of age and older

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

Participants will be considered HIV-uninfected based on one or two negative results, as described below in Sections 4.3.2.1-4.3.2.4. All samples tested must be whole blood, serum or plasma using methods approved by the IMPAACT Laboratory Center. As this study is being conducted under an IND, all test methods should be FDA-approved, if available. If FDA-approved methods are not available, test methods should be verified according to GCLP and approved by the IMPAACT Laboratory Center. As noted in exclusion criterion 4.2.10, above, participants who are HIV-exposed and less than two years of age may not be breastfeeding at enrollment.

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 HIV-exposed participants in Cohort 4 at Week 48 (20 weeks post DLM) and the Week 72 (48 weeks post DLM) visit are required.

Any participant considered HIV-uninfected at study entry who subsequently has a positive HIV test should be informed of the result as soon as possible and referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that these participants should be followed as HIV-infected.

4.3.2.1 HIV-exposed or HIV-unexposed participants two years of age and older

For participants who are at least two years of age and have not had any exposure to breast milk for at least 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, Sample #1, will suffice as documentation a participant is HIV-uninfected. As described in Section 4.3.1.2, Sample #1, if rapid testing only is done, two negative rapid tests would be required from different manufacturers or based on different principles or epitopes.
For participants who are at least two years of age and have had any exposure to breast milk in the eight weeks prior to the time of HIV testing, a single negative result from any one of the testing methods listed in Section 4.3.1.1 will suffice as documentation a participant is HIV-uninfected.

4.3.2.2 HIV-exposed participants less than two years of age

For participants who were exposed to potential HIV transmission in utero, and who are less than two years of age: a single negative result from any one of the testing methods listed in Section 4.3.1.1 will suffice as documentation a participant is HIV-uninfected. The sample must be tested in the site’s designated VQA-certified laboratory. In addition, the specimen must be drawn when the infant is four weeks of age or older. If an infant has received single ARV prophylaxis, specimens must be drawn after the infant has been off ARVs for at least two weeks; if an infant has received double or triple ARV prophylaxis, specimens must be drawn after the infant has been off ARVs for at least four weeks.

For participants who have any reported exposure to breast milk:

- They may not have had any exposure to breast milk for at least eight weeks prior to the time of HIV testing.
- 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.

4.3.2.3 HIV-unexposed participants less than two years of age

For participants who are less than two years of age with no documented HIV exposure: one negative test result from the testing methods listed in Section 4.3.1.1 will suffice as documentation a participant is HIV-uninfected. The test must be performed in the site’s designated VQA-certified laboratory. If the test is positive, the infant should be referred to non-study sources for HIV care and treatment as soon as possible. The infant may be considered HIV-exposed or HIV-infected (depending on subsequent results) and may be re-evaluated per the applicable criteria above.

4.4 Co-Enrollment Considerations

Co-enrollment in other trials involving pharmacologic agents will not occur, given the complexity of the pharmacologic regimens in this trial.

For all participants, co-enrollment in other studies is not precluded, although careful consideration must be given to visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment must be approved in advance by the Protocol Teams of both studies. Requests for such approval should be emailed to the Clinical Management Committee (CMC; refer to Sections 7.1.2 and 9.5.1 for more information regarding the role of the CMC for this study).

4.5 Recruitment, Screening, and Enrollment Process

Recruitment methods for this study may vary across sites. Generally, children with MDR-TB in non-U.S. settings, where this protocol will be implemented, are 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.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the participant and their parent/guardian. As described in greater detail in the study-specific Manual of Procedures (MOP), the informed consent process will include detailed review of the study informed consent form (ICF), and will allow time to address any questions or concerns each participant/parent (or legal guardian) may have, and an assessment of each participant’s/parent’s understanding will be performed before proceeding to the informed consent decision. The process will be fully documented and only participants/parents (or legal guardians) 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. 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. Screening evaluations may be repeated during the 30-day screening period, with the latest outcome used for eligibility determination. In the event that the 30-day screening period is exceeded, the screening process may be repeated; in this case, most but not all screening evaluations must be repeated, as specified in Section 6.1.

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 for the study, a participant identification number PID 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, an electronic case report form (eCRF) will be completed to record the screening outcome. Refer to Section 9.5 for more information on monitoring participant accrual in this 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 maximizing statistical power and minimizing potential biases associated with loss to follow-up. Each site must establish and implement SOPs that target retention rates that are sufficient to allow the primary study outcomes to be reliably estimated (a maximum 10% loss to follow-up is assumed in the determination of the allowed enrollment of 36-48 participants in this study). Refer to Section 9.5 for more information on monitoring participant retention in this study.

4.7 Participant Withdrawal or Termination from the Study

Regardless of the participant retention procedures referenced above, participants may voluntarily withdraw from the study. Participants may also be terminated from the study by the site investigator or designee under the following circumstances:

- Participant re-locates away from the study site and cannot be transferred to another site or is otherwise determined to be lost-to-follow-up
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, after consultation with the CMC
- The study is stopped or canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs or IBCs
- Participant (or parent/legal guardian) elects to enroll in another clinical research trial involving pharmacologic agents

Participants who discontinue use of study drug for any reason will not be withdrawn from the study; any such participants should ideally be retained through the scheduled duration of follow-up.

Should the consenting parent/guardian of an enrolled participant die or no longer be available for any reason, all applicable IRB/EC policies and procedures should be followed; however, no further study-specific evaluations should be performed until informed consent for continued study participation is obtained from the participant’s authorized guardian, as defined locally. If an authorized guardian cannot be identified, or if the authorized guardian does not consent to continued study participation, the participant must be withdrawn from the study. Refer to Section 13.3 for further guidance on informed consent procedures.

For any participant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff will document the reason for the withdrawal or termination in detail and will make every effort complete final evaluations as described in Section 6.17. In the event that the circumstances that led to a participant’s withdrawal or termination change (e.g., he or she returns to the study site area after having re-located previously), the site investigator or designee should contact the CMC to discuss options for resumption of follow-up.

5 STUDY TREATMENT

Study treatment is defined as delamanid tablets.

5.1 Study Treatment Regimens, Administration, and Duration

In each cohort, DLM will be administered for 24 weeks as shown in Table 5.

<table>
<thead>
<tr>
<th>Table 5. DLM administration by Age Cohort</th>
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<tbody>
<tr>
<td><strong>Cohort</strong></td>
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<tr>
<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
</tr>
</tbody>
</table>

In all cohorts, DLM will be administered with high-fat food by mouth twice daily, with DLM dosing separated in time from other drugs by at least one hour.
If an enrolled child crosses his or her cohort age limit during the 24-week treatment period (e.g., a 2-year-old at enrollment has his or her third birthday a few months later), dosing will continue as specified for the cohort in which the child was enrolled (with weight-based dose adjustments as needed).

The doses and weight banding selected for Cohort 3 are based on observed exposures in all children who have participated in Otsuka study 232, including the first 6 participants in Cohort 3. The doses and weight banding selected for Cohort 4 are aligned with doses that Otsuka plans to use in their youngest cohort and are based on modeling of PK data from study 232 Cohorts 1-3. The doses and weight banding in IMPAACT 2005 Cohorts 3 and 4 will be reassessed prior to opening these cohorts, as per Section 3.1.

Figure 2. Illustration of information used for dose selection for Cohorts 1 and 2

![Graph illustrating dose selection criteria for Cohorts 1 and 2.](image)

Smaller black dots – model predicted typical exposure given 100 mg BID in children >=35kg and 50 mg BID in children <35kg, larger symbols – individual exposures observed at Day 10 (steady state expected to be reached) in Study 232 (Open triangles: Group 1: 100 mg BID, black crosses: Group 2, 50 mg BID), grey lines – min, median and max exposure observed in adults at Day 14 (steady state expected to be reached).
5.1.2 Study Treatment Administration

Cohorts 1 and 2:

*Participants’ weight >35kg:* DLM will be administered with high-fat food as two 50 mg tablets (100mg) by mouth BID. DLM dosing should be separated in time from other drugs by at least one hour.

*Participants’ weight > 15kg and <35kg:* DLM will be administered with high-fat food as one 50 mg tablets (50mg) by mouth BID. DLM dosing should be separated in time from other drugs by at least one hour.

Cohorts 3 and 4:

DLM will be administered with high-fat food as pediatric formulation by mouth QD or BID. DLM dosing should be separated in time from other drugs by at least one hour. Exact dose to be determined from PK modeling.

5.2 Study Product Formulation, Preparation and Storage

5.2.1 Description of Formulation

DLM will be supplied in adult and pediatric formulations:

*Adult formulation:* DLM 50 mg film-coated tablets, in blister packs, for oral administration.

*Pediatric formulation:* DLM 5 mg dispersible tablets and 25 mg dispersible tablets, in blister packs, for oral administration.

5.2.2 Study Drug Preparation (for pediatric population)

The adult formulation of DLM required no additional preparation/

For administration of the pediatric formulation via medication cup, DLM should be prepared and given as follows:
- Place tablet(s) into the medication cup and add 15 mL of water
- Let stand for 30 seconds to allow tablet to dissolve
- Shake gently to make a uniform suspension
- After the tablet has been fully suspended, administer the contents promptly
- Pour another 15 mL of water and shake gently, and administer any remaining contents

For administration of the pediatric formulation via oral syringe, DLM should be prepared and given as follows:
- Place tablet(s) in oral syringe and draw up 15 mL of water
- Cap the syringe and shake five times to suspend the tablet
- Confirm the suspension is consistent throughout. If necessary, shake the syringe a few more times in order to suspend the tablet evenly
- After the tablet has been fully suspended, administer the contents promptly
- Refill the syringe with 15 ml of water, shake gently, and administer any remaining contents
Competency of the parent or caregiver to both properly prepare and administer the doses to the participants must be documented by site staff.

5.2.3 Storage Instructions

DLM tablets must be stored at 25°C (77°F) with excursions permitted at 15-30°C (33-86°F).

5.3 Pharmacy: Drug Supply, Distribution and Accountability

5.3.1 Study Drug Acquisition/Distribution

DLM is the only study-provided product. DLM will be provided by Otsuka Pharmaceutical Company, Ltd.

DLM will be available to study sites through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain supplies of DLM by following the instructions in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. Cups and oral syringes will also be available through the CRPMC.

5.3.2 Study Drug Accountability

The site pharmacist is required to maintain complete records of all study drug 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 must be returned to the CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. Procedures and relevant forms are provided in the manual Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks in the Study Product Management Responsibilities section.

5.4 Study Drug Adherence Assessment and Counseling

With the exception of PK sampling days, DLM, OBR and ART may be administered by routine personnel or caregivers on all other occasions. Persons responsible for administering DLM will be trained on appropriate administration. OBR adherence will be supervised as per routine care-usually supported through clinic-based, community-based (trained family member or community health worker) or hospital-based DOT(S), depending on local practice. DOT is standard of care for the treatment of MDR-TB, and young children with MDR-TB are frequently hospitalized for the duration of the intensive phase of treatment, which typically lasts for 4-6 months. Therefore, the administration of DOT for OBR is not expected to be prohibitively challenging. Spot checks for OBR or DLM adherence will be considered if there are adherence concerns.

5.4.1 Adherence in-hospital

During the intensive phase of MDR-TB therapy, hospitalization is frequently routine practice and therefore adherence is more likely to be well-controlled. Adherence to study drug and background routine MDR-TB and ART, where relevant, will be documented with ward dispensing charts while the participant is admitted in hospital. Adherence to DLM will also be documented with pill counts. DLM and all routine TB drugs and ART will be administered by the research team on the day of PK sampling. The time of the two preceding doses of DLM, OBR and ART, where relevant, will also be documented. DLM, OBR and ART may be administered by routine personnel or caregivers on all other occasions.
5.4.2 Adherence out-patient

Following hospital discharge or instead of hospitalization, children may be treated on an ambulatory basis and adherence assessment will be done using TB dispensing card (TB treatment card) and ARV treatment card (if relevant). Adherence to DLM will also be documented with pill counts. Local models of care (e.g. community-based treatment supporter or other health care worker) may be used for adherence support. DLM and all routine TB drugs and ART will be administered by the research team on the day of PK sampling. The time of the two preceding doses of DLM, OBR and ART, where relevant, will also be documented. DLM, OBR and ART may be administered by routine personnel or caregivers on all other occasions.

5.5 Concomitant Medications

All concomitant medications received by participants throughout the duration of study participation must be source documented as part of the medical and medication histories obtained at each study visit (see Section 6.23). This includes prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; contraceptives; vitamins and other nutritional supplements; co-trimoxazole (TMP/SMX) and other antibiotics; antifungals; and alternative, complementary, and traditional medications and preparations.

ARVs and background standard MDR-TB treatment medications will not be provided through the study and must be obtained locally by the site as a standard of care. They will be prescribed by the health care provider according to local national and/or international guidelines for treatment of children with MDR-TB or HIV/MDR-TB and supplied via non-study prescription. Following study treatment, children will continue OBR to complete MDR-TB treatment provided by local TB programs for 12-18 months, depending on the severity of disease. Requirements for entering concomitant medications into eCRFs are specified in Section 6.23.

5.6 Prohibited and Precautionary Medications

5.6.1 Precautionary medications during administration of DLM

Systemic use of moderate and strong CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, voriconazole, itraconazole, ketolides such as telithromycin; and macrolide antibiotics other than azithromycin) for more than two weeks is discouraged. However, for individual participants with a clinical need for a strong inducer or inhibitor for greater than two weeks, these drugs may be allowed in consultation with the CMC and attending clinicians.

5.6.2 Prohibited medications during administration of DLM because of potential for QTc prolongation:

The CMC must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered. The following medications are prohibited during administration of DLM:

- Neuroleptics – phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole, and pimozide
- Quinolone antimalarials (e.g. chloroquine and quinacrine)
- Moxifloxacin, gatifloxacin, and sparfloxacin
- Tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, and clomipramine
- Anti-arrhythmic medications – quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, digitalis
- Clarithromycin

Note: In accordance with accepted WHO guidance for the use of DLM, levofloxacin will replace moxifloxacin as the fluoroquinolone of choice based on a lower risk of potential QTc prolongation with levofloxacin. Children willing to participate in the study who were on moxifloxacin as part of the OBR would be permitted to change from moxifloxacin to levofloxacin at the time of consent for the study, given that there is not convincing evidence in children that moxifloxacin results in better clinical outcomes than levofloxacin.

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 is additional information on visit-specific study procedures.

All visits and procedures must be performed at the clinical research site or associated facilities as approved by the study sponsor. The expectation is that many of the participants may be hospitalized during at least part of the study, as per the local standard of care for treatment of child with MDR-TB. Unless otherwise specified, visits may be split, with required procedures performed on more than one day within the allowable visit window if necessary. Regardless of whether the child is being treated on an in- or out-patient basis, all study visits and procedures must be documented in accordance with the NIAID Division of AIDS (DAIDS) policies for source documentation; refer to Section 11.2 for more information on documentation requirements and completion of eCRFs. Refer to Section 7.3 for information on expedited adverse event (EAE) reporting, which may be required at any time during follow-up.

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 reminders; and following up on missed visits. All such tasks should be documented consistent with site SOPs. Study staff should inform participants (or other authorized guardians if applicable) of clinically meaningful physical exam findings and laboratory test results when available.

6.1 Screening Visit

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

Screening may be initiated after written informed consent is obtained. Screening procedures may be performed on multiple days, including on the date of enrollment (see Section 6.2). For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined (enter the relevant eCRF to record the screening outcome).
### Screening Visit Procedures (up to 30 days prior to enrollment)

#### Administrative and Regulatory

- Obtain written informed consent (and assent in accordance with local guidelines)
- Assign participant identification number (PID)
- Obtain screening number from SES
- Assess eligibility thus far

#### Clinical

- Obtain available medical records and medications history.
- Perform complete physical examination,
- Perform assessment of concomitant medications.
- Document HIV Status. 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.
- Record *M. tuberculosis* infection status through TST or IGRA, depending on what is available at the site, if done as part of standard of care.
- Classify TB disease spectrum and severity
- 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.

#### Laboratory

<table>
<thead>
<tr>
<th>Blood</th>
<th>Collect blood for:</th>
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<tbody>
<tr>
<td></td>
<td>- Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td></td>
<td>- Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), AST, alkaline phosphatase,</td>
</tr>
<tr>
<td></td>
<td>- Liver Function Tests (LFT): ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
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<tr>
<td></td>
<td>- TSH (and fT4 if TSH is elevated)</td>
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<tr>
<td></td>
<td>- HIV testing as needed per Section 4.3</td>
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<tr>
<td></td>
<td>- <em>If female and of reproductive potential</em>, pregnancy test (blood or urine test may be performed)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Specimen</th>
<th>Collect respiratory specimen for TB testing*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear</td>
<td>- Smear, Xpert MTB/Rif, culture, DST</td>
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</table>

<table>
<thead>
<tr>
<th>Urine</th>
<th>*If female and of reproductive potential, collect urine for:</th>
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<tbody>
<tr>
<td></td>
<td>- Pregnancy testing (urine or blood test may be performed)</td>
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</tbody>
</table>

#### Other

<table>
<thead>
<tr>
<th>ECG</th>
<th>Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXR</td>
<td>Obtain chest X-ray, and interpret based on standard clinical approach</td>
</tr>
<tr>
<td>Audiology</td>
<td>Obtain available medical records documenting all previous audiology assessments.</td>
</tr>
<tr>
<td></td>
<td>Perform age appropriate audiology assessment</td>
</tr>
</tbody>
</table>

* At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate as appropriate) will be collected on all individuals at screening and sent for concentrated fluorescent smear, Xpert MTB/RIF and TB culture (solid media and MGIT culture). Collection of other respiratory specimens and other specimens (e.g. fine needle aspiration of cervical lymphadenopathy) will be performed if clinically indicated; further specimens can be collected at enrollment. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens. The choice of procedure will be according to local practice, with the same technique used for each child for the duration of the study.
All screening procedures are expected to be performed within 30 days prior to enrollment. In the event that the 30-day screening period is exceeded, the screening process may be repeated. In this case, all of the screening procedures listed above must be repeated, with the exception that:

- New PIDs should not be assigned
- Previously documented medical and medications history information should be reviewed and updated through the date of re-screening (it is not necessary to re-record history information that was previously documented)

6.2 Enrollment Visit

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. In the event that a participant is found to be ineligible on the day of enrollment, enrollment must not occur.

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

- Final eligibility determination and confirmation must precede enrollment
- Enrollment must precede prescribing of DLM
- Prescribing must precede dispensing and administering of DLM
- Pre-dose PK blood collection must precede administration of DLM
- ECGs must be performed prior to administration of DLM (around the time of pre-dose PK sampling) and approximately four hours after DLM administration
## Enrollment Visit Procedures (Day 0)

### Administrative and Regulatory
- Complete final eligibility determination and confirmation*
- Complete paper-based eligibility checklist*, enter checklist data into SES to enroll the participant, print and file a copy of the confirmation file

### Clinical
- Obtain interval medical/medications history
- Perform complete physical examination*
- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)
- Record dosing times of DLM, OBR and ARVs for this date and the two days prior

### Laboratory

#### Blood
- **Collect blood for:**
  - Semi-intensive PK: pre-dose, and 4 and 8 hours post dose
  - Hematology: complete blood count with cell differential and platelet count (only if enrollment is >2 weeks post screening visit)
  - Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase, (only if enrollment is >2 weeks post screening visit)
  - Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)
  - If female and of reproductive potential, pregnancy test (blood or urine test may be performed)*
  - Biomarkers (storage for future use)
  
  **If participant is HIV-infected, collect additional blood for:**
  - CD4 cell count
  - HIV RNA

#### Urine
- If female and of reproductive potential, collect urine for:
  - Pregnancy testing (urine or blood test may be performed)*
- Urine biomarkers (storage for future use)

#### Respiratory Specimen
- **Collect respiratory specimen for TB testing:**
  - Smear, culture, DST***

### Other

#### ECG
- Perform ECGs (pre-dose and at approximately four hours post dose) on study-specific ECG machine and interpret based on age-specific criteria

### Study Drug
- Prescribe, dispense, and administer DLM (directly observed dosing)

---

*Perform prior to enrollment

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study), and then on subsequent isolates only when necessary, per Section 8.4.
6.3 Week 2 Visit

The Week 2 Visit is targeted to take place between Days 10 and 14, counted from the date of Enrollment. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM
- ECGs must be performed prior to DLM administration (around the time of pre-dose PK sampling) and approximately four hours after DLM administration.

<table>
<thead>
<tr>
<th>Week 2 Visit Procedures (Days 10-14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>• Record dosing times of DLM, OBR and ARVs for this date and the two days prior</td>
</tr>
<tr>
<td>• Administer Acceptability Questionnaire</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Semi-intensive PK: pre-dose, and 2, 4, and 8 hours post dose</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count with differential</td>
</tr>
<tr>
<td>• Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td><strong>Other ECG</strong></td>
</tr>
<tr>
<td>• Perform ECGs (pre-dose and approximately four hours post dose) on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
</tr>
<tr>
<td>• Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td>• Assess adherence to DLM</td>
</tr>
</tbody>
</table>
6.4 Week 4 Visit

The Week 4 Visit is targeted to take place on Day 28, counted from the date of Enrollment as Day 0, with an allowable window of ±3 days. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM.
- ECG must be performed prior to DLM administration (around the time of pre-dose PK sampling).

<table>
<thead>
<tr>
<th>Week 4 Visit Procedures (Week 4 ± 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>• Record dosing times of DLM, OBR and ARVs for this date and the two days prior</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 only (store residual plasma)</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td>• If female and of reproductive potential, pregnancy test (blood or urine test may be performed)</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood test may be performed)</td>
</tr>
<tr>
<td><strong>Respiratory Specimen</strong></td>
</tr>
<tr>
<td>Collect respiratory specimen for TB testing:**</td>
</tr>
<tr>
<td>• Smear, culture, DST***</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td><strong>ECG</strong></td>
</tr>
<tr>
<td>• Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
</tr>
<tr>
<td>• Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td>• Assess adherence to DLM</td>
</tr>
</tbody>
</table>

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
### 6.5 Week 8 Visit

The Week 8 Visit is targeted to take place on Day 56, counted from the date of Enrollment as Day 0, with an allowable window of ±3 days. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM
- ECGs must be performed prior to DLM administration (around the time of pre-dose PK sampling) and approximately four hours after DLM administration.

<table>
<thead>
<tr>
<th>Week 8 Visit Procedures (Week 8 ± 3 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>- Obtain interval medical/medications history</td>
</tr>
<tr>
<td>- Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>- Perform targeted physical examination</td>
</tr>
<tr>
<td>- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>- Record dosing times of DLM, OBR and ARVs for this date and the two days prior</td>
</tr>
<tr>
<td>- Administer Acceptability Questionnaire</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>- Collect blood for:</td>
</tr>
<tr>
<td>- Semi-intensive PK: pre-dose, and 4 and 8 hours post dose</td>
</tr>
<tr>
<td>- Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>- Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>- TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>- Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries).</td>
</tr>
<tr>
<td>- If female and of reproductive potential, pregnancy test (blood or urine test may be performed)</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>- If female and of reproductive potential, collect urine for:</td>
</tr>
</tbody>
</table>
|   - Pregnancy testing (urine or blood test may be performed) *
| **Respiratory Specimen**                 |
| - Collect respiratory specimen for TB testing:** |
|   - Smear, culture, DST** |
| *If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).* |
| **Other**                                |
| - ECG                                     |
|   - Perform ECGs (pre-dose and approximately four hours post dose) on study-specific ECG machine and interpret based on age-specific criteria |
| **Study Drug**                           |
| - Dispense and administer DLM (directly observed dosing) |
| - Assess adherence to DLM |

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.6 Week 12 Visit

The Week 12 Visit is targeted to take place on Day 84, counted from the date of Enrollment as Day 0, with an allowable window of ±7 days. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM
- ECG must be performed prior to DLM administration (around the time of pre-dose PK sampling)

### Week 12 Visit Procedures (Week 12 ± 7 days)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Blood</th>
<th>Respiratory Specimen</th>
<th>Other</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain interval medical/medications history</td>
<td>Collect blood for:</td>
<td>Collect respiratory specimen for TB testing:**</td>
<td>Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
<td>Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td>Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
<td>Sparse PK: pre-dose only (store residual plasma)</td>
<td>Smear, culture, DST***</td>
<td></td>
<td>Assess adherence to DLM</td>
</tr>
<tr>
<td>Perform targeted physical examination</td>
<td>Hematology: complete blood count with cell differential and platelet count</td>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
<td>Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record dosing times of DLM, OBR and ARVs for this date and the two days prior</td>
<td>Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
### 6.7 Week 16 Visit

The Week 16 Visit on Day 112, counted from the date of Enrollment as Day 0, with an allowable window of ±7 days. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM
- ECG must be performed prior to DLM administration (around the time of pre-dose PK sampling).

#### Week 16 Visit Procedures (Week 16 ± 7 days)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Blood</th>
<th>Laboratory</th>
<th>Respiratory Specimen</th>
<th>Other</th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obtain interval medical/medications history</td>
<td>Collect blood for:</td>
<td>Collect blood for:</td>
<td>Collect respiratory specimen for TB testing:**</td>
<td>Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
<td>Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td>Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
<td>Sparse PK: pre-dose only (store residual plasma)</td>
<td>Hematology: complete blood count with cell differential and platelet count</td>
<td>Smear, culture, DST***</td>
<td>Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
<td>Assess adherence to DLM</td>
</tr>
<tr>
<td>Perform targeted physical examination</td>
<td>Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
<td>TSH (and fT4 if TSH is elevated)</td>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
<td>If female and of reproductive potential, pregnancy test (blood or urine test may be performed) *</td>
<td>If female and of reproductive potential, collect urine for:</td>
<td>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Record dosing times of DLM, OBR and ARVs for this date and the two days prior</td>
<td></td>
<td>Pregnancy testing (urine or blood test may be performed)*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.8 Week 20 Visit

The Week 20 Visit on Day 140, counted from the date of Enrollment as Day 0, with an allowable window of ±7 days. Additional requirements for sequencing of procedures at this visit are as follows:

- ECG must be performed prior to DLM administration (around the time of pre-dose PK sampling).

<table>
<thead>
<tr>
<th>Week 20 Visit Procedures (Week 20 ± 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination. Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td><strong>Laboratory Respiratory Specimen</strong></td>
</tr>
<tr>
<td>Collect respiratory specimen for TB testing:*</td>
</tr>
<tr>
<td>• Smear, culture, DST**</td>
</tr>
<tr>
<td><em>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</em></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>• Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
</tr>
<tr>
<td>• Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td>• Assess adherence to DLM</td>
</tr>
</tbody>
</table>

* Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

**DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.9 Week 24 Visit

The Week 24 Visit on Day 168, counted from the date of Enrollment as Day 0, with an allowable window of ±7 days. Additional requirements for sequencing of procedures at this visit are as follows:

- Pre-dose PK blood collection must precede administration of DLM
- ECG must be performed prior to DLM administration (around the time of pre-dose PK sampling).

**Week 24 Visit Procedures (Week 24 ± 7 days)**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Laboratory Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Obtain interval medical/medications history</td>
<td>• Sparse PK: pre-dose only (store residual plasma)</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
<td>• Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
<td>• Chemistries: albumin, potassium, magnesium, calcium, creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td>• Record dosing times of DLM, OBR and ARVs for this date and the two days prior</td>
<td>• TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>• Administer Acceptability Questionnaire</td>
<td>• If female and of reproductive potential, pregnancy test (blood or urine test may be performed)*</td>
</tr>
</tbody>
</table>

*If participant is HIV-infected, collect additional blood for:*
- CD4 cell count
- HIV RNA

<table>
<thead>
<tr>
<th>Laboratory Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood test may be performed) *</td>
</tr>
<tr>
<td>• Biomarkers (future use)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Specimen</th>
<th>Collect respiratory specimen for TB testing: **</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Smear, culture, DST***</td>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
</tr>
</tbody>
</table>
### Week 24 Visit Procedures (Week 24 ± 7 days)

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>- Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td></td>
<td>CXR</td>
</tr>
<tr>
<td></td>
<td>- Obtain chest X-ray and interpret based on standard clinical approach</td>
</tr>
<tr>
<td></td>
<td>Audiology</td>
</tr>
<tr>
<td></td>
<td>- Obtain available medical records documenting all previous audiology assessments.</td>
</tr>
<tr>
<td></td>
<td>- Perform age appropriate audiology assessment</td>
</tr>
<tr>
<td>Study Drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dispense and administer DLM (directly observed dosing)</td>
</tr>
<tr>
<td></td>
<td>- Assess adherence to DLM</td>
</tr>
</tbody>
</table>

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.

### 6.10 Week 28 Visit

The Week 28 Visit on Day 196, counted from the date of Enrollment as Day 0, with an allowable window of ±7 days. Additional requirements for sequencing of procedures at this visit are as follows:

- ECGs must be performed prior to DLM administration (around the time of the PK sampling).

<table>
<thead>
<tr>
<th>Category</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Obtain interval medical/medications history</td>
</tr>
<tr>
<td></td>
<td>- Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td></td>
<td>- Perform targeted physical examination</td>
</tr>
<tr>
<td></td>
<td>- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>Laboratory Blood</td>
<td>Collect blood for:</td>
</tr>
<tr>
<td></td>
<td>- Sparse PK: may be collected at any time</td>
</tr>
<tr>
<td></td>
<td>- If female and of reproductive potential, pregnancy test (blood or urine test may be performed) *</td>
</tr>
<tr>
<td>Urine</td>
<td>If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td></td>
<td>- Pregnancy testing (urine or blood test may be performed) *</td>
</tr>
<tr>
<td>Respiratory Specimen</td>
<td>Collect respiratory specimen for TB testing:**</td>
</tr>
<tr>
<td></td>
<td>- Smear, culture, DST***</td>
</tr>
<tr>
<td></td>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
</tr>
<tr>
<td>Other</td>
<td>ECG</td>
</tr>
<tr>
<td></td>
<td>- Perform ECG on study-specific ECG machine and be interpret based on age-specific criteria</td>
</tr>
</tbody>
</table>

* The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation.
** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.

### 6.11 Week 32 Visit

The Week 32 Visit on Day 224, counted from the date of Enrollment as Day 0, with an allowable window of ± 28 days. There is no required sequencing of procedures at these visits.

| Clinical | • Obtain interval medical/medications history  
• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)  
• Perform targeted physical examination  
• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>**</td>
<td></td>
</tr>
</tbody>
</table>
| Laboratory | Blood | Collect blood for:  
• If female and of reproductive potential, pregnancy test (blood or urine test may be performed) * |
| | Urine | If female and of reproductive potential, collect urine for:  
• Pregnancy testing (urine or blood test may be performed) * |
| | Respiratory Specimen | Collect respiratory specimen for TB testing:  
• Smear, culture, DST***  
If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4). |

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
## 6.12 Week 36 Visit

The Week 36 Visit on Day 252, counted from the date of Enrollment as Day 0 with an allowable window of ± 28 days. There is no required sequencing of procedures at these visits.

<table>
<thead>
<tr>
<th>Week 36 Visit Procedures (Week 36 ± 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>• Collect blood for:</td>
</tr>
<tr>
<td>• Chemistries: albumin, potassium, magnesium, calcium creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td>• TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>• If female and of reproductive potential, pregnancy test (blood or urine test may be performed) *</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood test may be performed) *</td>
</tr>
<tr>
<td><strong>Respiratory Specimen</strong></td>
</tr>
<tr>
<td>• Smear, culture, DST***</td>
</tr>
<tr>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
</tr>
</tbody>
</table>

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.13 **Week 40 Visit**

The Week 40 Visit on Day 280, counted from the date of Enrollment as Day 0, with an allowable window of ± 28 days. There is no required sequencing of procedures at these visits.

<table>
<thead>
<tr>
<th>Week 40 Visit Procedures <strong>(Week 40 ± 28 days)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• <em>If female and of reproductive potential,</em> pregnancy test (blood or urine test may be performed)</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
</tbody>
</table>
| *If female and of reproductive potential, collect urine for:*
| • Pregnancy testing (urine or blood test may be performed) |
| **Respiratory Specimen**                      |
| *Collect respiratory specimen for TB testing:*
| • Smear, culture, DST***                      |
| *If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).* |

* The outcome of pregnancy must be recorded and may be obtained by participant contact and/or medical documentation.
** Note: *Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.***

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.

6.14 **Week 48 Visit**

The Week 48 Visit on Day 308, counted from the date of Enrollment as Day 0, with an allowable window of ± 28 days. There is no required sequencing of procedures at these visits.

Any bacteriology assessments done as clinically indicated between Weeks 24 and 48 should be included in source documentation and entered into eCRFs.
**Week 48 Visit Procedures (Week 48 ± 28 days)**

### Clinical
- Obtain interval medical/medications history
- Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)
- Perform targeted physical examination
- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)
- Document HIV Status, Cohort 4, HIV-exposed participants only. Refer to protocol Section 4.3 for acceptable documentation of HIV status *

### Laboratory

<table>
<thead>
<tr>
<th>Blood</th>
<th>Collect blood for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hematology: complete blood count with cell differential and platelet count Chemistries: albumin, potassium, magnesium, calcium creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td></td>
<td>• TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td></td>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td></td>
<td>• <em>If female and of reproductive potential</em>, pregnancy test (blood or urine test may be performed)**</td>
</tr>
</tbody>
</table>

*If participant is HIV-infected, collect additional blood for:*
- CD4 cell count
- HIV RNA

<table>
<thead>
<tr>
<th>Urine</th>
<th>If female and of reproductive potential, collect urine for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Pregnancy testing (urine or blood test may be performed) **</td>
</tr>
</tbody>
</table>

### Respiratory Specimen

<table>
<thead>
<tr>
<th>Collect respiratory specimen for TB testing:***</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Smear, culture, DST****</td>
</tr>
</tbody>
</table>

*If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).*

### Other

<table>
<thead>
<tr>
<th>CXR</th>
<th>Obtain chest X-ray and interpret based on standard clinical approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audiology</td>
<td><em>If participant had not been off injectables for at least 12 weeks as of the Week 24 Visit: Perform age appropriate audiology assessment.</em></td>
</tr>
</tbody>
</table>

* Any participant with a positive HIV test should be informed of the result as soon as possible and referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that these participants should be followed as HIV-infected.**

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

*** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

****DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.15 **Week 60 Visit**

The Week 60 Visit on Day 420, counted from the date of Enrollment as Day 0, with an allowable window of ± 42 days. There is no required sequencing of procedures at these visits.

<table>
<thead>
<tr>
<th>Week 60 Visit Procedures (Week 60 ± 42 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>- Obtain interval medical/medications history</td>
</tr>
<tr>
<td>- Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>- Perform targeted physical examination</td>
</tr>
<tr>
<td>- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collection for:</strong>*</td>
<td></td>
</tr>
<tr>
<td>- If female and of reproductive potential, pregnancy test (blood or urine test may be performed) *</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collection for:</strong>*</td>
<td></td>
</tr>
<tr>
<td>- If female and of reproductive potential, collect urine for:</td>
<td></td>
</tr>
<tr>
<td>- Pregnancy testing (urine or blood test may be performed) *</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Respiratory Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Collection for TB testing:</strong></td>
<td></td>
</tr>
<tr>
<td>- Smear, culture, DST***</td>
<td></td>
</tr>
<tr>
<td><strong>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</strong>*</td>
<td></td>
</tr>
</tbody>
</table>

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

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.16 Week 72 visit (Final Study Visit)

The Week 72 Visit on Day 504, counted from the date of Enrollment as Day 0, with an allowable window of ± 42 days. There is no required sequencing of procedures at these visits.

Any bacteriology assessments done as clinically indicated between Weeks 48 and 72 should be included in source documentation and entered into eCRFs.

<table>
<thead>
<tr>
<th>Week 72 Visit Procedures (Week 72 ± 42 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify review update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>• Document HIV Status, Cohort 4, HIV-exposed participants only. Refer to protocol Section 4.3 for acceptable documentation of HIV status*</td>
</tr>
<tr>
<td>• Final assessment of TB treatment outcome</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
</tr>
<tr>
<td><strong>Blood</strong> Collect blood for:</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>• Chemistries: albumin, potassium, magnesium, calcium creatinine, urea (BUN), alkaline phosphatase</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td>• TSH (and fT4 if TSH is elevated)</td>
</tr>
<tr>
<td>• If female and of reproductive potential, pregnancy test (blood or urine test may be performed) **</td>
</tr>
<tr>
<td>• Biomarkers (storage for future use)</td>
</tr>
<tr>
<td>If participant is HIV-infected, collect additional blood for:</td>
</tr>
<tr>
<td>• CD4 cell count</td>
</tr>
<tr>
<td>• HIV RNA</td>
</tr>
<tr>
<td><strong>Urine</strong> If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood test may be performed) **</td>
</tr>
<tr>
<td>• Biomarkers (future use)</td>
</tr>
<tr>
<td><strong>Respiratory Specimen</strong> Collect respiratory specimen for TB testing: ***</td>
</tr>
<tr>
<td>• Smear, culture, DST****</td>
</tr>
<tr>
<td>If the sample obtained at this visit is the third consecutive negative test, then no further microbiologic testing is necessary unless clinically indicated (see Section 8.4).</td>
</tr>
<tr>
<td><strong>Other</strong> CXR Obtain chest X-ray and interpret based on standard clinical approach</td>
</tr>
</tbody>
</table>

* Any participant with a positive HIV test should be informed of the result as soon as possible and referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that these participants should be followed as HIV-infected.

** The outcome of pregnancy must be recorded and may be obtained by participant contact at a study visit or via telephone if beyond the Week 72/End of Study and/or medical documentation.

*** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.
DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.

A participant is noted to have an ongoing AE of Grade 3 or higher at this visit should be followed closely until resolution and brought back to the clinic as needed prior to the final study contact at Week 96.

6.17 Week 96 (Final Study Contact)

At Week 96 (Day 672, counted from the date of Enrollment as Day 0, with an allowable window of ± 42 days), the participant’s parent/guardian will be contacted by phone to confirm vital status and see if the participant has experienced any hospitalizations or recurrence of TB since the Week 72 Visit. Parent/guardian report will be acceptable for documentation of vital status, hospitalization, or recurrence of TB. If there have been hospitalizations, recurrent TB, change in vital status or other concerns, study staff should make reasonable attempts to obtain medical records. If the participant was still on TB treatment at the time of the Week 72 visit, clinic records documenting the TB treatment outcome should be obtained.

6.18 Continued Participant Contact After End of Study: Pregnancy, Unresolved Adverse Event, Early Study Discontinuation

Participants may be contacted after Week 96 (Final Study Contact) or Early Study Discontinuation Visits:

- To document the outcome of a pregnancy
- To follow any unresolved AE to resolution/stabilization (see Section 8.1)
- To obtain interim history following early withdrawal from the study through 72 weeks after the last dose of DLM.

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.

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 4, 16, 36 and 48 weeks after last DLM 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 6.20.
6.19 Unscheduled Visits

Participants may be seen at unscheduled study visits for evaluation of acute issues or follow up of ongoing issues. 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 adverse events even if after the final visit.

6.20 Early Discontinuation of DLM Visit or Early Discontinuation from Study and of DLM

Refer to Section 8.9 for criteria for discontinuation of study drug. Refer to Section 8.10 for criteria for discontinuation of study.

If study drug is discontinued prior to Week 24 – regardless of whether the participant will be continuing on study/off study drug or exiting the study -- the participant should have a series of evaluations as close as possible to study drug discontinuation and within ± 7 days. This visit should follow the requirements as indicated in the SoE column for “Early DLM D/C only or Early DLM and Study D/C.” Sites should work closely with the participants to encourage continued follow up after early discontinuation of DLM.

<table>
<thead>
<tr>
<th>Premature Discontinuation of Study Drug Visit Procedures (+/- 7days)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td><strong>Laboratory Blood</strong></td>
</tr>
<tr>
<td>Collect blood for:</td>
</tr>
<tr>
<td>• Sparse PK: maybe collected at any time (store residual plasma)</td>
</tr>
<tr>
<td>• Hematology: complete blood count with cell differential and platelet count</td>
</tr>
<tr>
<td>• Chemistries: albumin, potassium, magnesium, calcium creatinine, urea (BUN), alkaline phosphatase,</td>
</tr>
<tr>
<td>• Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
</tr>
<tr>
<td>• If female and of reproductive potential, pregnancy test (blood or urine test may be performed)</td>
</tr>
<tr>
<td>If participant is HIV-infected, collect additional blood for:</td>
</tr>
<tr>
<td>• CD4 cell count</td>
</tr>
<tr>
<td>• HIV RNA</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Pregnancy testing (urine or blood test may be performed)</td>
</tr>
<tr>
<td><strong>Other ECG</strong></td>
</tr>
<tr>
<td>• Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td><strong>Study Drug</strong></td>
</tr>
<tr>
<td>• Retrieve any remaining study drug</td>
</tr>
</tbody>
</table>
6.21 Off Treatment Visit Procedures

Following the Early DLM D/C visit, participants should continue to be followed in the study, until 48 weeks after the last DLM dose. Note that this schedule aligns with the expected evaluations and frequency of visits following the full duration of DLM treatment. (See follow-up as per page two of Appendix I).

There are no requirements for the sequencing of evaluations at these visits.

### Off Treatment Visit Procedures: 4, 8, 12, 16, 20, 24, 36, and 48 weeks post DLM

**Visit window of +/- 14 days: 4 weeks post DLM**

**Visit window of +/- 28 days: 8, 12, 16, 20 and 24 weeks post DLM**

**Visit window of +/- 42 days: 36 and 48 weeks post DLM**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Laboratory</th>
<th>Blood</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Obtain interval medical/medications history</td>
<td></td>
<td>Collect blood for:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
<td></td>
<td>- 4 weeks post DLM only: Sparse PK (may be collected at any time; store residual plasma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Perform targeted physical examination</td>
<td></td>
<td>- 20 and 48 weeks post DLM only: Hematology: complete blood count with cell differential and platelet count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
<td></td>
<td>- 12, 20 and 48 weeks post DLM only: Chemistries: albumin, potassium, magnesium, calcium creatinine, urea (BUN), alkaline phosphatase, Liver Function Tests: ALT, AST, total bilirubin, direct bilirubin (may be done on the same sample collected for the chemistries)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 48 weeks post DLM only: TB treatment outcome</td>
<td></td>
<td>- 20 and 48 weeks post DLM only: If female and of reproductive potential, pregnancy test (blood or urine test may be performed) *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

20 and 48 weeks post DLM only: If participant is HIV-infected, collect additional blood for:

- CD4 cell count
- HIV RNA

<table>
<thead>
<tr>
<th>Urine</th>
<th>Other</th>
<th></th>
<th>Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>- If female and of reproductive potential, collect urine for: 20 and 48 weeks post DLM only: Pregnancy testing (urine or blood test may be performed) *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ECG</td>
<td>Retrieve any remaining study drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 4 weeks post DLM only: Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CXR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 20 and 48 weeks post DLM only: Obtain chest X-ray and interpret based on standard clinical approach</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Audiology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 20 weeks post DLM: Perform age appropriate audiology assessment</td>
<td></td>
</tr>
</tbody>
</table>

* The outcome of pregnancy must be recorded and may be obtained by participant contact at a study visit or via telephone if beyond the 48 weeks post DLM /End of Study and/or medical documentation.
6.22 Off DLM Early Study Discontinuation Visit

Refer to Section 4.7 for criteria for withdrawal from the study.

Whenever possible, final study evaluations should be conducted when a participant indicates that continued full participation in the study is no longer possible, according to the “Off Treatment Study D/C” column of the Schedule of Evaluations. There is no required sequencing of procedures at these visits.

As part of the informed consent process, participants will be asked to permit periodic telephone contact even if other study evaluations cannot be conducted. Those who agree will be contacted at 4, 16, 36 and 48 weeks after the last DLM 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.

<table>
<thead>
<tr>
<th>Premature Termination from Study Visit Procedures (+/- 28 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative and Regulatory</td>
</tr>
<tr>
<td>• Confirm that study participant provided consent for continued contact at 12, 24, 48 weeks after the last DLM dose.</td>
</tr>
<tr>
<td>Clinical</td>
</tr>
<tr>
<td>• Obtain interval medical/medications history</td>
</tr>
<tr>
<td>• Identify/review/update AEs (abnormal lab values, signs, symptoms, diagnoses)</td>
</tr>
<tr>
<td>• Perform targeted physical examination</td>
</tr>
<tr>
<td>• Only if study d/c is prior to Week 24: Assess adherence to routine TB drugs (all participants) and ARV drugs (HIV-infected participants only)</td>
</tr>
<tr>
<td>• Document HIV Status, Cohort 4, HIV-exposed participants only. Refer to protocol Section 4.3 for acceptable documentation of HIV status.*</td>
</tr>
<tr>
<td>• Classify final TB treatment outcome (if completed MDR treatment)</td>
</tr>
<tr>
<td>Laboratory</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>If participant is HIV-infected, collect blood for:</td>
</tr>
<tr>
<td>• CD4 cell count</td>
</tr>
<tr>
<td>• HIV RNA</td>
</tr>
<tr>
<td>Urine</td>
</tr>
<tr>
<td>If female and of reproductive potential, collect urine for:</td>
</tr>
<tr>
<td>• Only if study d/c is prior to Week 24: Pregnancy testing (urine or blood test may be performed)</td>
</tr>
<tr>
<td>Respiratory Specimen</td>
</tr>
<tr>
<td>Collect respiratory specimen for TB testing:**</td>
</tr>
<tr>
<td>• Smear, culture, DST***</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>• Only if study d/c is prior to Week 24: Perform ECG on study-specific ECG machine and interpret based on age-specific criteria</td>
</tr>
<tr>
<td>CXR</td>
</tr>
<tr>
<td>• Only if study d/c is prior to Week 24: Obtain chest X-ray and interpret based on standard clinical approach</td>
</tr>
</tbody>
</table>

* Any participant with a positive HIV test should be informed of the result as soon as possible and referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled with the exception that these participants should be followed as HIV-infected.

** Note: Only participants who had lab-confirmed MDR-TB at diagnosis will have bacteriology completed at this visit. However, if clinically indicated, specimens may be collected. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens.

***DST will be performed on first isolate only (generally this will occur at screening but in rare cases will occur later in the study) and then on subsequent isolates only when necessary, per Section 8.4.
6.23 Medical and Medication History

Collection of medical and medication history information is required at each scheduled visit. A baseline history is established at Screening and Enrollment, and interval (since the last visit) histories are obtained at subsequent follow-up visits. All history information may be obtained based on participant self-report (or parent/legal guardian report) but available medical records should be obtained when possible to supplement reported information.

Documented medical conditions will be assessed for severity as described in Section 7.3.3, and new conditions occurring during follow-up will also be assessed for relationship to study drug as described in Section 8.1. Relevant dates will be source documented for all conditions and medications; see Section 5.5 for more information on concomitant medications.

The following should be source documented and entered into associated eCRFs as part of the baseline medical and medication history:

- Date of birth
- MDR-TB diagnosis
- HIV status, WHO clinical staging, and treatment history (including all prior ARV use)
- Reproductive and obstetrical history (including date of last menstrual period prior to the current pregnancy and dates and outcomes of all prior pregnancies)
- TB exposure history
- TB treatment history
- History of allergy and/or hypersensitivity (including to ARVs)
- Medical conditions (signs, symptoms, illnesses, and other diagnoses) occurring during the 30 days prior to enrollment and/or ongoing at the time of enrollment
- Medications taken within the 30 days prior to enrollment and/or ongoing at the time of enrollment
- Any other information needed to determine eligibility for the study

The table below specifies the interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

<table>
<thead>
<tr>
<th>Assess for and Source Document</th>
<th>Enter into eCRFs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interval Medical and Medication History Elements</strong></td>
<td></td>
</tr>
<tr>
<td>Current status of conditions that were ongoing at the previous visit</td>
<td>Any updates of previous entries (e.g., resolution dates)</td>
</tr>
<tr>
<td>Occurrence of any new conditions (signs, symptoms, illnesses, and other diagnoses) since the last visit</td>
<td>Any newly identified adverse events that meet criteria in Section 7.2</td>
</tr>
<tr>
<td>Current status of medications that were ongoing at the previous visit</td>
<td>Any updates of previous entries (e.g., stop dates)</td>
</tr>
<tr>
<td>Use of any new medications since the last visit</td>
<td>All ARVs taken from time of enrollment through completion of follow-up</td>
</tr>
<tr>
<td></td>
<td>All medications taken as part of OBR from time of enrollment through completion of follow-up</td>
</tr>
<tr>
<td></td>
<td>All medications taken at onset of or in response to adverse events that are specified to be entered into eCRFs per Section 7.2</td>
</tr>
</tbody>
</table>
6.24 Physical Examinations

A physical examination is required at each scheduled visit. Complete exams are required at the Screening and Enrollment Visits; targeted exams are required at all other visits.

Complete exams should include the following:

- Height measurement
- Weight measurement
- Vital signs (temperature, blood pressure, pulse and respiratory rate)
- Assessment of Karnofsky or Lansky score (Screening only)
- Examination of:
  - Skin
  - Head
  - Mouth
  - Neck
  - Chest (heart and lung exam)
  - Abdomen
  - Extremities
  - Lymph nodes

Targeted exams should include the following:

- Height measurement
- Weight measurement
- Vital signs (temperature, blood pressure, pulse and respiratory rate)
- Examination of body systems driven by prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the examining clinician.

All exam findings should be source documented and the following should be entered into eCRFs: height and weight. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs. Abnormal findings identified after enrollment will be entered into adverse events eCRFs as specified in Section 7.2.

6.25 Nutritional Support

A study-specific meal will be provided on the intensive PK days (refer to the study MOP for additional information). Sites will be encouraged to provide participants with ongoing standardized nutritional supplementation, as locally relevant, given that proper absorption of DLM depends on being co-administered with food. Study sites will be provided with guidelines on acceptable but feasible forms of and administration of nutritional supplementation. Information on sites’ ability to provide nutritional support was solicited from each site in the Site Application and will be supported in the study budget.
6.26 Laboratory Assays

Safety laboratory assays will be collected as per the Schedule of Evaluations (Appendix I). Semi-intensive and sparse PK sampling for DLM and its DM-6705 metabolite will be performed, as described above. Also performed will be mycobacterial culture and DST; Xpert MTB/Rif; any testing for HIV documentation as described in Section 4.3.1, along with HIV RNA PCR and CD4 (absolute, percentile, and CD4:CD8 ratio). Plasma samples will be stored for possible future ART and second-line TB drug PK analysis, should this be of scientific interest (beyond the scope of this trial). Please see Section 8.4 for a detailed description of mycobacterial testing.

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: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

6.26.1 Specimen Collection

Specimens will be collected for this study as indicated in the Schedule of Evaluations and per detailed guidance provided in the Laboratory Processing Chart (LPC), which will be available on the IMPAACT web site: www.impaactnetwork.org. Further information on collection of sputum specimens will also be provided in the study-specific Manual of Procedures (MOP).

In accordance with U.S. 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 (in the following order: LFT, chemistry, hematology)
2. Pharmacokinetics
3. Virology
4. Immunology
5. Storage for future use

6.26.2 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 6.26 site and local laboratory SOPs, and the MOP, and in the LPC. The frequency of specimen collection and testing will be directed by 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, storage, and shipping as specified in the LPC.

Mycobacterial isolates collected from participants will be stored for further analysis.

HIV RNA/DNA PCR or HIV NAT 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.
6.26.3 Biohazard Containment

Respiratory pathogens such as *M.tbc* 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.

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 (IATA) 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.

7 SAFETY MONITORING, ASSESSMENT AND REPORTING

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of all study participants and for alerting the CMC if any concerns arise. Site investigators and their designees will enter safety-related data into eCRFs as indicated in Section 7.2 and complete expedited adverse event (EAE) reporting as indicated in Section 7.3. Site investigators are also responsible for prompt reporting to their IRBs/ECs and other applicable review bodies of any unanticipated problems involving risks to participants or others.

7.1.2 Clinical Management Committee (CMC)

The following Protocol Team members comprise the CMC: Chair and Vice Chairs, Medical Officers, Pharmacometricians and Protocol Pharmacologist, Statisticians, Data Managers, Clinical Trial Specialists, or their designees. The CMC will provide guidance as needed to site investigators regarding all aspects of participant management, including but not limited to questions of participant eligibility and management of adverse events, study product administration, cART regimens, and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the CMC will monitor participant safety through routine review of study data reports as described in Section 9.5.1.
7.1.3 Study Monitoring Committee (SMC)

An independent IMPAACT Study Monitoring Committee (SMC) will monitor participant safety through routine and as needed reviews of study data. Refer to Section 9.5.2 for more information on the composition and role of the SMC in monitoring of this study.

7.2 Safety-Related Data Collection

Note: This section describes eCRF data collection for pre-existing conditions and adverse events. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Sections 7.3.3 and 7.3.2, respectively, for detailed information on these topics.

The definition of the term adverse event provided in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual) will be used in this study. This definition will be applied to participants, beginning at the time of enrollment, regardless of subsequent administration of or exposure to study drug. Any untoward medical conditions (including abnormal laboratory test results, signs, symptoms, or diseases) identified prior to enrollment will be considered pre-existing conditions. Refer to Section 4.5 for more information on defining the effective point of enrollment in the study.

Pre-existing conditions and adverse events will be entered into eCRFs as specified in Section 7.2.1.

7.2.1 Data Collection

Pre-Existing Conditions

All pre-existing conditions identified among participants during the 30 days prior to study entry and/or present on the day of entry will be entered into medical history eCRFs.

Adverse Events

The following adverse events — inclusive of abnormal laboratory test results and clinical signs, symptoms, and diagnoses except as specified in the IMPAACT Do Not Report List — will be entered into adverse event eCRFs:

- All Grade 2 or higher adverse events
- All adverse events that lead to any change of study drug (i.e., any hold, discontinuation, dose or frequency modification)
- All serious adverse events (SAEs) as defined in Version 2.0 of the DAIDS EAE manual

In addition to the above specifications for entry into adverse event eCRFs, further detailed eCRFs will be entered for all ECG reports, including QT intervals (see Section 8.7).
**Laboratory Test Results**

In addition to the recording specified above, the following laboratory test results will be entered into the relevant laboratory eCRFs, regardless of whether the test was protocol-specified or ordered by the site investigator for clinical purposes:

- All Grade 2 or higher results
- All results that lead to any change of study drug

eCRFs used to record the above-listed safety outcomes must be entered into the study database within 48-72 hours of availability of the relevant clinical findings and laboratory test results at the site.

**7.3 Expedited Adverse Event (EAE) Reporting**

Data on all AEs will be collected and recorded on eCRFs in a standard manner. This section pertains specifically to those AEs that meet the threshold for reporting as Expedited Adverse Events to the study sponsor.

**7.3.1 Adverse Event (AE) Reporting to DAIDS**


The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE 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 the NIAID Clinical Research Management System (CRMS) CRMSsupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting. For questions about expedited reporting, please contact DAIDS RSC DAIDSRSCSafetyOffice@tech-res.com.
7.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

- In addition, all Grade 3 or higher QTcF and Grade 3 or higher cardiac arrhythmias will be reported as EAEs for this study.
- The study agent for which expedited reporting are required is delamanid (DLM).
- Reported EAEs will be assessed as related or not related to DLM, as defined in the DAIDS EAE Manual. With respect to the relationship categories specified for purposes of participant and toxicity management in Section 8.1, the categories of definitely related, probably related, and possibly related will correspond to an assessment of “related” for EAE reporting; the categories of probably not related and not related will correspond to an assessment of “not related” for EAE reporting.

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, dated November 2014, will be used to grade the severity of most adverse events in this study. This table is available on the RSC website at:


The exceptions are as follows: the Supplemental Toxicity Table for Grading ECG Changes and Possible Symptoms Related to Cardiac Conduction Abnormalities (Appendix VII), and the Table to Determine the Lower Level of Normal Heart Rate by Age (Appendix VIII), will be used for grading these events.

7.3.4 Expedited AE Reporting Period

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

After the protocol-defined AE reporting period, defined as the entire study duration, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS 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

All AEs identified in this study will be source documented in participant research records, consistent with the policies and procedures referenced in Section 11. 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 and definitions:

- **Definitely related**: The event and administration of study drug are related in time, and a direct association can be demonstrated.
- **Probably related**: The event and administration of study drug are reasonably related in time and the event is more likely explained by study drug than other causes.
- **Possibly related**: The event and administration of study drug are reasonably related in time and the event can be explained equally well by causes other than study drug.
- **Probably not related**: A potential relationship between the event and study drug could exist (i.e., the possibility cannot be excluded), but the event is most likely explained by causes other than study drug.
- **Not related**: The event is clearly explained by another cause not related to study drug.

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 (legal guardian) and self-reporting, where appropriate. Data will be collected on all AEs ranging from Grade 2 through 5; their potential relation to DLM, background TB drugs (OBR) and/or ART, as appropriate, will be described.

Appendix X provides general guidance for management of the study drug (DLM) in response to toxicities; Appendix IX provides guidance on DLM management for the following specific toxicities:

- ECG-determined or clinical cardiac toxicity
- Liver toxicity

Site investigators will consult with the CMC as directed in the Toxicity Management Tables in Appendices IX and X and otherwise at their discretion as needed. Clinical or laboratory adverse events (AEs) that are probably not related or not related to DLM need not result in study drug interruption, unless the site investigator deems interruption necessary due to the specific circumstances.

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

All AEs must be followed to resolution (return to baseline) or stabilization, with the frequency of repeat evaluations determined by the clinical significance of each event. Grade 3 or higher...
laboratory tests should be repeated as soon as possible (within three business days) and all Grade 3 or higher AEs should be re-evaluated at least weekly until improvement to Grade 1 or lower. Additional evaluations beyond those listed in Appendix IX and X may be performed at the discretion of the site investigator to determine the etiology of a given event and/or further assess its severity or relationship to study product. Clinical management of all AEs should be provided consistent with the best medical judgment of the site investigator and local clinical practice standards.

Participants with an ongoing AE at the time of the End of Study visit (Week 72 and/or 48 weeks post DLM) of Grade 3 or higher will continue to be followed as per the appropriate table in Appendix IX until resolution or stabilization of the event. The CMC 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 MDR-TB Optimized Background Regimen

Children with MDR-TB in this trial will receive an injectable-sparing regimen that includes DLM, a fluoroquinolone, pyrazinamide, plus at least three other active second-line drugs. This is in keeping with the interim guidance on use of DLM in children which states that children should receive pyrazinamide plus four second-line drugs and DLM may be added to bring the total to at least five drugs. An injectable will only be included if an appropriate regimen cannot be constructed based on local drug availability and the resistance pattern of that individual’s infecting M. tuberculosis strain (for example, participants with pre-XDR TB with demonstrated resistance to fluoroquinolones but susceptibility to injectables). Potential participants who may have been initiated on an MDR-TB regimen that includes an injectable are eligible for IMPAACT 2005 and, to the extent possible, will be transitioned to the injectable-sparing study regimen, following the protocol-defined strategy for building appropriate regimen.

If toxicities related to the OBR, such as ototoxicity or hypothyroidism, develop during study follow-up, participants will be immediately referred for appropriate non-study clinical care and treatment.

8.3 TB screening, diagnosis and disease classification

Routine screening for TB will follow standard local protocols in 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 (CXR), clinical history, standard symptom-based questionnaire (52), physical examination, and MDR-TB exposure history. CXR will be repeated as per schedule of evaluations in children with intrathoracic TB.

8.4 Mycobacterial culture, smear, and DST

It is expected that approximately 30-40% of children with MDR-TB will have bacteriological or molecular proof of MDR-TB at diagnosis, based on available data from non-U.S. sites. Given that severity of illness, drugs used in OBR and duration of OBR prior to enrollment are likely to vary significantly in this study, assessment of microbiologic outcomes will be purely exploratory. As children do not tend to develop acquired resistance and many participants will not have bacteriological confirmation at the start of the trial, acquired mycobacterial drug resistance will not be formally examined.
At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected from all participants at Screening, and at other visits as clinically indicated (see Section 6.0). Specimens collected at screening and enrollment will be sent for concentrated fluorescent smear and TB culture (solid media and MGIT culture). Xpert MTB/Rif will be performed at screening only. If culture is positive, phenotypic and genotypic drug susceptibility testing will be performed for first line and second line drugs (see LPC for details). Drugs tested should include, as a minimum, isoniazid, rifampicin, ofloxacin, amikacin OR kanamycin. 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. Other types of specimens should be collected only if routinely done by the clinical site, in addition to sputum or gastric aspirate specimens. It may be that children initially started on MDR-TB treatment because of probable TB disease and exposure to a source case with MDR-TB may not have final diagnostic culture results at the time of enrollment in the study. These children should have sampling until their pre-treatment (diagnostic) samples are all negative. Once pre-treatment/diagnostic samples are negative, further sampling is not required. Children with microbiologically confirmed MDR-TB should have monthly repeat sampling (with testing for acid fast bacilli (AFB) smear and TB culture) until they have at least three negative cultures. DST will only be repeated in patients with positive cultures six months or later following study treatment initiation.

A positive smear or culture eight weeks after starting DLM will trigger a review by the CMC and clinical team to assess the participant’s clinical course to date and to consider whether or not the participant might benefit from the addition of the injectable or another TB medication, based on the participant’s clinical course and all laboratory data up to then. 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. All isolates will be stored long-term (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.

8.5 TB Treatment Outcome

Participants will be assessed through serial CXR (in the case of intrathoracic TB), anthropometric measurements (height and weight), clinical evaluation of symptoms, and evaluation of smear and mycobacterial culture (MGIT, Becton-Dickinson with DST (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 dual pediatric pulmonologists/clinicians with expertise in pediatric TB, using a standard published CXR reading tool (54). Standard CXR reading and reporting tools (CRF) will be provided to capture radiological features and TB disease severity.

Treatment outcomes in children will be defined as bacteriological cure, probable cure, death, treatment failure, and loss to follow-up (5). In children with bacteriologically confirmed MDR-TB, cure is defined as follows: three consecutive MTB-negative respiratory cultures obtained at least one month apart with no bacteriological MTB-positive cultures after the MTB-first negative culture, with at least one MTB-negative culture in the last 12 months of treatment after initiation of therapy. ‘Probable cure’ (for all participants) is defined as follows: (a) completion of the
prescribed treatment; (b) attainment of clinical and radiological improvement (c) microbiological criteria, however, are not met (three consecutive MTB-negative respiratory cultures obtained at least one month apart with no bacteriological MTB-positive cultures after the MTB-first negative culture, with at least one MTB-negative culture in the last 12 months of treatment after initiation of therapy) (5, 11). (more information provided in the MOP). Treatment failure will be considered persistent culture positivity (positive culture at 8 months after starting treatment) (55) OR failure to meet criteria for both clinical and radiological improvement after more than 6 months on treatment. 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 HIV-Related Outcomes

HIV viral suppression and treatment response will be assessed at standard time points, though this study will not be formally powered for this purpose. Major DDIs between DLM and key ARVs (EFV, NVP, boosted PI, INSTI) are not anticipated based on the metabolic pathway of DLM and human hepatocyte studies that indicate that DLM is not an inducer or inhibitor of major metabolizing enzymes plus adult drug interaction trials data (see above). Specifically, DLM is not expected to have an impact on ART exposures and, thus, there are no DDIs that would be expected to reduce ART efficacy. Allowable antiretroviral regimens will include age-appropriate suppressive ART, and in addition to the regimens that have already been studied in adults given DLM (EFV-, PI-, and NVP-based ART), we will allow use of the newer regimens such as the INSTIs raltegravir and/or dolutegravir, depending on local approvals and/or availability. Of note, while EFV- and PI-based ART did not significantly affect DLM concentrations in adults, their effects in children have not been assessed, and we will assess these DDIs formally in this study. Given that ritonavir-boosted lopinavir increased DLM concentrations 20% in adults, it will be important to assess the magnitude of this interaction in children, with specific attention to DM-6705 concentrations, as this metabolite has been associated with effects on the QT interval.

8.7 ECG Monitoring and Reading

ECGs will be performed as described in the Schedule of Evaluations. At Day 0, Week 2 and Week 8 visits (semi-intensive PK visit), ECGs will be performed pre-dose and at 4 hours after DLM administration. On-site clinicians will review ECGs and assess for clinical relevance and identification of AEs, as specified in Section 8.1. This will include an assessment of QT (QTcF) interval. In accordance with accepted WHO guidance for the use of DLM, levofloxacin will replace moxifloxacin as the fluoroquinolone of choice based on a lower risk of potential QTc prolongation with levofloxacin.

ECGs will be interpreted based on age-specific criteria. In addition, there will be a centralized review of all ECGs within three to five 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 IX), which will include review and interpretation by the protocol cardiologist. Finally, the protocol cardiologist will review consolidated cardiac data at least annually. This will assist with interpretation of all ECG data analysis in relation to study hypotheses, including for SMC review, as required.
8.8 Management of Contraception and Pregnancy

As per eligibility criteria 4.1.11 and 4.1.13, participants must agree to contraceptive use throughout the first 28 weeks on study (i.e., until four weeks after discontinuation of DLM). Sites will be expected to monitor this closely. For participants engaging in sexual activity that could lead to pregnancy, self-reported confirmation of contraception use should be obtained at every visit through the first 28 weeks on study. In addition, throughout study participation (i.e., through Week 72), all participants should be provided with contraception counseling, as applicable. Sites should reinforce directions related to use of effective, medically accepted contraception methods. These discussions should be source documented in research records. 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 CMC 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 DLM must promptly discontinue further treatment with DLM, but can continue to take their OBR 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 DLM on pregnancy are 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. Every effort will be made to determine pregnancy outcomes, with the permission of the participant and the participant’s pregnant partner.

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 Criteria for Premature Discontinuation of Study Drug

- Treatment with disallowed medications.
- Drug toxicity that is related to DLM and that requires permanent discontinuation of DLM as specified in the Toxicity Management Tables in Appendices IX and X.
- Sustained non-adherence to DLM and/or OBR that, in the opinion of the investigator, warrants early DLM discontinuation.
- Participant diagnosis changed to drug-susceptible TB or a diagnosis other than TB, despite initial diagnosis of MDR-TB.
- Pregnancy. 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 U.S., Canada: 1-800-258-4263, international: 910-256-0238).

Note that in the event of early treatment discontinuation, participants will continue to be followed in the study, as per Section 6.20. Participants who prematurely discontinue study drug will be
referred to the local TB program for further management of their MDR-TB. Site staff will ensure the initial visit is made.

### 8.10 Criteria for Premature Discontinuation of Study Participation

- The participant or legal guardian refuses further treatment and/or follow-up evaluations (i.e., withdraws continued consent to participate).
- 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.

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 II.

### 9 STATISTICAL CONSIDERATIONS

#### 9.1 General Design Issues

This is a Phase I/II open-label, single-arm study with the primary aim of characterizing the PK and safety of DLM in combination with OBR for the treatment of MDR-TB in HIV-infected and uninfected infants, children and adolescents, at DLM doses prescribed in this study. These cohort-specific doses were hypothesized to most likely achieve exposures similar to those achieved in adults with a 100 mg twice-daily dose, based on modeling of available PK data from the previous Otsuka studies on DLM.

This statistical section describes the methodology and analyses for the primary safety objective and non-PK secondary objectives only. Please refer to Section 10.0 for methodology and analyses planned for the primary and secondary PK objectives.

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

Approximately 36-48 participants will be enrolled to obtain a minimum of nine evaluable participants in each of Cohorts 1, 2, 3 and 4, with a minimum target of six HIV-infected and three HIV-uninfected participants in each cohort. Analyses planned for the PK objectives in this study will use the combined PK data from the pediatric Otsuka trials 232, 233, and PK data from this study (IMPAACT 2005). The safety analyses will include the safety data from all participants in IMPAACT 2005 only, across all study follow-up.

Accrual is expected to be completed within 72 weeks after the first participant is enrolled, and each participant will be followed for up to 96 weeks. Hence, the expected duration of the study is 168 weeks after the first participant is enrolled. These expectations are contingent on the timing of availability of data from Otsuka trials 232/233 that will inform the dosing for Cohorts 3 and 4, as well as the duration of the approval process necessary for opening of these cohorts.
Each age cohort will open to accrual pending the availability of PK data from HIV-uninfected children from the same age cohort in Otsuka trials 232 and 233, as well as availability of the corresponding appropriate formulation. Since safety and PK data from HIV-infected participants in the older cohort are not expected to provide critical information for dosing decisions or safety issues among HIV-infected participants in the younger cohort, we will allow enrollment in younger age cohorts regardless of availability of PK and safety data from HIV-infected participants in the older age cohorts in this study. In making dosing decisions for each age cohort, the protocol team will review all available safety data from the Otsuka pediatric trials and this study, as well as the results of PK modeling.

9.2 Outcome Measures

9.2.1 Primary Outcome Measures

9.2.1.1 See Section 10 for Primary PK Outcome Measures

9.2.1.2 Primary Safety Outcome Measures (evaluated at 24 weeks from study enrollment)

- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses)
- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses) judged by the CMC to be related to DLM
- Permanent discontinuation of DLM due to a toxicity or adverse event
- QTcF interval >500 ms
- Death (Grade 5 event)

9.2.2 Secondary Outcome Measures

9.2.2.1 See Section 10 for Secondary PK Outcome Measures

9.2.2.2 Acceptability Outcome Measures

- Permanent discontinuation of DLM due to: (i) intolerance, or (ii) refusal to take medication due to number/volume of medication, mode of administration, timing of treatment, or dislike of taste of the medication
- Cumulative responses to items in an acceptability assessment, by Week 24

9.2.2.3 Secondary Safety Outcome Measures

The following will be evaluated over 72 weeks from DLM initiation:

- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses)
- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses) judged by the CMC to be related to DLM
- Permanent discontinuation of DLM due to a toxicity or adverse event
- QTcF interval >500 ms
- Death (Grade 5 event)
- Grade 2, 3 or 4 adverse events (labs, signs/symptoms, diagnoses)
- Grade 2, 3 or 4 adverse events (labs, signs/symptoms, diagnoses) judged by the CMC to be related to DLM
- Change in QTcF interval from baseline of >60 ms
9.2.2.4 TB treatment outcome as defined in Section 8.5 through Week 72

9.2.3 Exploratory Outcome Measures

9.2.3.1 Viral load suppression (HIV RNA levels < 200 copies/mL) at Weeks 24, Week 48 and Week 72

9.2.3.2 Exploratory Safety Outcome Measures

The following will be evaluated after 24 and 72 weeks from DLM initiation, among children who were on injectable sparing regimens:

- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses)
- Grade 3 or 4 adverse events (labs, signs/symptoms, diagnoses) judged by the CMC to be related to DLM
- Permanent discontinuation of DLM due to a toxicity or adverse event
- QTcF interval >500 ms
- Death (Grade 5 event)
- Grade 2, 3 or 4 adverse events (labs, signs/symptoms, diagnoses)
- Grade 2, 3 or 4 adverse events (labs, signs/symptoms, diagnoses) judged by the CMC to be related to DLM

9.2.3.3 QT prolongation represented as continuous or binary outcome

9.2.3.4 TB treatment outcome as defined in in Section 8.5, in participants who were given injectable-sparing regimen

9.3 Randomization and Stratification

There will be no randomization. Participants will be enrolled into one of the four age cohorts described in the “Study Design” section (Section 3.0), with minimum target enrollments for HIV-infected and for HIV-uninfected participants within each age cohort.

9.4 Sample Size and Accrual

Total accrual will depend on the number of participants who must be enrolled to achieve a minimum of nine participants with evaluable PK data within each of the four age cohorts. The following minimum limits are targeted:

- At least six HIV-infected and at least three HIV-uninfected evaluable participants within each age cohort
- At least eight evaluable participants on an EFV-based regimen and at least eight evaluable participants on PI-based regimen across all age cohorts

Participants are considered ‘evaluable’ if they have completed PK visits up to Week 8 and have PK data sufficient to estimate drug exposures using a model-based approach.

Participants will be assessed for evaluability in real time once PK data at Week 8 are available. Non-evaluable participants will be immediately replaced unless the maximum of 12 participants
per cohort is already achieved. It is possible for a cohort to enroll the maximum of 12 participants and not achieve the nine evaluable participants; however, the sample size has been inflated to 12 per cohort precisely to accommodate loss of participant data due to non-evaluability/loss to follow-up.

Maximum accrual is 48 across all cohorts and 12 for each cohort. The target sample size was primarily based on PK considerations. Clinical trial simulations were performed to ensure a sample size sufficient to provide parameter estimate precisions as specified by the FDA criteria for pediatric trials (56). The simulations also show that the FDA precision criteria are met for both the HIV-uninfected and the HIV-infected sub-groups. The methods and results of the simulations are described in Appendix III. A sample size of nine participants per cohort (six with concomitant HIV-infection and three without) was found to be sufficient.

Safety data from all participants who started DLM in this study will be included in all safety analyses. The primary analysis will also include a combined analysis of safety data among all participants across all age cohorts who received doses that are consistent with the final dosing recommendations.

Table 6 presents 95% confidence intervals around various potential rates of primary safety events that might be observed in a total sample of 36 participants who contribute to the primary safety analysis under the final dosing recommendations. Similar 95% confidence intervals are shown for a potential sample of 27 participants and a potential sample of 18 participants, to include as an example of the precision of safety event rates when some participants do not contribute data to the combined safety analysis. We also present precision of potentially observed rates for a sample of nine participants within any age stratum and a sample of six HIV-infected participants within any age stratum. Precision of safety event rates is low under most scenarios, with confidence intervals being shortest when all enrolled participants across cohorts are included. Moreover, under a given sample size, the confidence interval is wider for larger observed rates. With a sample size of six HIV-infected children and three HIV-uninfected children in each age cohort, any AE rates in this study will be reported with low precision, and there will be low power to detect safety differences by HIV status. There is very minimal safety information on HIV-uninfected children/youth within each age group that can be obtained, given only a sample size of three per cohort; consequently, no confidence intervals are provided.
Table 6. Percent of Participants Experiencing Primary Safety Events with Exact 95% Confidence Intervals

<table>
<thead>
<tr>
<th>N*</th>
<th>% With Primary Safety Event</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0%</td>
<td>(0%, 46%)</td>
</tr>
<tr>
<td>9</td>
<td>0%</td>
<td>(0%, 34%)</td>
</tr>
<tr>
<td>18</td>
<td>0%</td>
<td>(0%, 19%)</td>
</tr>
<tr>
<td>27</td>
<td>0%</td>
<td>(0%, 13%)</td>
</tr>
<tr>
<td>36</td>
<td>0%</td>
<td>(0%, 10%)</td>
</tr>
<tr>
<td>6</td>
<td>20%</td>
<td>(1%, 67%)</td>
</tr>
<tr>
<td>9</td>
<td>20%</td>
<td>(2%, 58%)</td>
</tr>
<tr>
<td>18</td>
<td>20%</td>
<td>(5%, 45%)</td>
</tr>
<tr>
<td>27</td>
<td>20%</td>
<td>(7%, 40%)</td>
</tr>
<tr>
<td>36</td>
<td>20%</td>
<td>(9%, 37%)</td>
</tr>
<tr>
<td>6</td>
<td>40%</td>
<td>(7%, 82%)</td>
</tr>
<tr>
<td>9</td>
<td>40%</td>
<td>(11%, 76%)</td>
</tr>
<tr>
<td>18</td>
<td>40%</td>
<td>(18%, 65%)</td>
</tr>
<tr>
<td>27</td>
<td>40%</td>
<td>(22%, 61%)</td>
</tr>
<tr>
<td>36</td>
<td>40%</td>
<td>(24%, 58%)</td>
</tr>
</tbody>
</table>

* Note: N refers to total sample size of combined analysis across cohorts or possible sub-group analysis

9.5 Monitoring

Implementation of this study will be monitored at multiple levels, consistent with standard IMPAACT procedures. A study monitoring plan that details monitoring roles and responsibilities and data to be reviewed at each level will be prepared before the study opens to accrual. Sections 11 and 12 provide for more information on on-site monitoring and quality management at the site level. Further information on monitoring of study progress, quality of study conduct, and participant safety across sites is provided below.

9.5.1 Monitoring by the Protocol Team

**Study Progress and Quality of Study Conduct**

The Protocol Team is responsible for continuous monitoring of study progress, including timely achievement of key milestones, 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 twice per year, first based on site activation and then on accrual. Initially, the team will monitor site activation monthly to ensure that an adequate number of sites have registered to complete the protocol. If relatively few of the eligible sites have registered after the protocol has been approved for six 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.
Once accrual into the study begins, the team will begin to monitor accrual. If accrual is not proceeding as rapidly as expected, the team will identify the reasons for lack of accrual and will possibly 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 48 participants will be enrolled to achieve a minimum of 36 evaluable participants, and assuming Cohorts 3 and 4 will open within a year after study opening, enrollment is projected to be completed within 18 months after the first participant is enrolled. It should be noted that this expectation is contingent on the timing of availability of data from Otsuka trials 232/233 that will inform dosing for Cohorts 3 and 4, as well as the duration of the approval process necessary for opening of the two youngest age cohorts. Each site must establish and implement an SOP to achieve the projected rates of enrollment specified in the accrual plan. Should accrual rates falls below projections, the protocol team will work with study sites to take action as needed and may consider inclusion of additional sites. This information will also be included in the SMC reviews that will be held twice a year.

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 evaluability, 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.

**Participant Safety**

The study will be monitored intensely in real time by the CMC, which will review safety data regularly, for purposes of assessing treatment attribution and monitoring patient safety in general.

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

As noted above, the safety of DLM will be monitored by means of adverse events reports and toxicity reports presenting laboratory and clinical events. It is required that the data required for the toxicity reports be entered into the database within 48-72 hours of the time at which the results of the laboratory tests or clinical examinations become available. Reports compiled by the DMC will be reviewed and discussed by the Protocol Team on conference calls held at least once a month. For Grade 2 and higher events that may affect administration of study product (as described in Section 7.2.1), relationship to study drug will also be assessed by the protocol chairs and medical officers.
Data on toxicity will be reviewed. Adverse events will be monitored from study enrollment onwards throughout the follow-up period. If the protocol team identifies any potentially 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 DLM treatment will be examined for long-term safety (although less frequently) for the next 48 weeks, unless a clinical trigger requires closer follow-up. A telephone visit will occur at Week 96 to assess vital status. Sites should refer to the Schedule of Evaluations in Appendix I.

9.5.2 Monitoring by the SMC

An independent IMPAACT Study Monitoring Committee (SMC) will review this study regularly, following policies described in the IMPAACT Manual of Procedures. The composition of the SMC will include the SMC Chair; IMPAACT Chair or Vice Chair; IMPAACT TB Scientific Committee Chair or Vice Chair; representatives of the IMPAACT Operations Center, Statistical and Data Management Center, and Laboratory Center; and representatives of NIAID and NICHD. The frequency of SMC review will be determined by the accrual rate, and is planned to occur twice per year, with the first review after at least five participants have enrolled. In addition, the SMC will participate in an Interim Review of PK and safety data, as described in Section 10.3. Also, the SMC will be presented with the proposed dosing and dosing rationale for Cohorts 3 and 4 prior to opening those cohorts. The SMC will determine whether convening is necessary or whether a report or documentation submitted to the Committee will suffice. However, approval from the SMC is required before these cohorts are opened to accrual. The SMC may also be convened on an ad hoc basis upon request of the protocol team/sponsor or may be required to review less frequently if accrual is unexpectedly slow. Ad hoc reviews by the SMC may occur if any safety issues or concerns arise during the course of the study. Ad hoc reviews may also be triggered per the safety monitoring guidelines specified below. Lastly, if patterns of unexpected AEs are identified which potentially relate to OBR or ART, the SMC may be asked to review relevant data.

The SMC will monitor study progress, quality of study conduct, and participant safety. The SMC will generally review the same types of data reports as the Protocol Team. For ad hoc or triggered safety reviews, more limited data may be reviewed, focusing on the events that triggered the reviews. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, proceed with design modifications, or be discontinued. The SMC may also provide operational recommendations to help address any study implementation challenges that may be identified during their reviews.

The SMC will be convened to review safety data if at least one of the specified triggers for review occurs.

- Death which is at least possibly related to DLM
- Cardiac arrhythmia while on DLM, Grade 3 or 4
- Unstable dysrhythmias requiring hospitalization or treatment
- Selected elevated hepatic enzymes that are at least possibly related to study drug, and are not related to infectious hepatitis or other obvious causes, including: (1) ALT 3 × ULN AND bilirubin 2 × ULN (>35% direct bilirubin; bilirubin fractionation required) (2) ALT 3 × 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 ≥5 × ULN; regardless of symptoms; (4) Grade 4 elevation of direct bilirubin.

- Other ≥ Grade 4 adverse events (labs, signs/symptoms, diagnoses) determined to be at least possibly related to study drug.
- In addition, if >25% of participants experience a Grade ≥ 2 clinical adverse event that is at least possibly related to study drug, or if patterns of the same ≥ Grade 2 adverse event 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 experience a QTcF > 500 ms, SMC review may be requested.

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. Participants who have been discontinued from study drug as part of toxicity management will be included and treated as safety failures in the primary safety analysis. These primary analyses will be performed after the last participant of the last cohort has completed 24 weeks on study drug.

Each participant’s safety data will be summarized as: (1) the worst grade of adverse events, and (2) the worst grade of adverse events judged to be at least possibly related to study drug. Frequency distributions of these safety outcomes will be presented in aggregate and will be broken down by age cohort. Listings of all Grade 3 or 4 events will be provided, broken down by type of toxicity (hepatic, hematologic, cardiac, etc.). Listings of all other safety endpoints enumerated in Section 9.2.1 will also be provided.

The proportions of participants experiencing any of the endpoints listed in Section 9.2.1, as well as each of the endpoints listed in that section, will be presented in aggregate and broken down by age cohort, by HIV status, and among HIV-infected participants within each age cohort, with these proportions bounded by exact 95% confidence intervals. These proportions will not be provided for HIV-uninfected participants within each age cohort since there will only be three participants contributing to the denominator. Similar analyses will present the proportions of participants exhibiting any of the endpoints listed in Section 9.2.1 (as well as each of the endpoints in Section 9.2.1) events which have been judged to be at least possibly related to study medication, again bounded by exact 95% confidence intervals. Note that safety interpretations on these proportions should be limited only to the specific doses these participants received, and does not necessarily reflect the safety profile of DLM under the final recommended dose (unless all participants included in the denominator for the respective computed proportion received a dose that matches the final recommended dose for these participants). Tabulations will also be presented to summarize all Adverse Events and Serious Adverse Events that have been reported, as well as all Adverse Events which have resulted in treatment discontinuation.

If there were participants in any of the cohorts who were started at the final respective recommended dose (based on the final analysis of the PK data) and have remained on that dose for the 24-week period, a primary evaluation of safety across the 24 weeks of study drug will be performed on the data from all such participants in combined cohorts.

For all of the above analyses, those who have left the study prior to 24 weeks of exposure will be analyzed as failures.
Given that the small sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, 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 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 statistical analysis plan.

9.6.2 Secondary Analysis

9.6.2.1 Acceptability

Proportions and 95% confidence intervals will be computed for binary responses to items in the acceptability questionnaire and will be presented in aggregate, as well as broken down by age cohort, by HIV status, and among HIV-infected participants within each age cohort. For continuous outcomes, mean or median responses with accompanying 95% confidence intervals will be computed. Analyses on the acceptability endpoint, based on permanent discontinuation of DLM due to selected reasons, will be similar to those planned for the binary responses to the acceptability questionnaire.

9.6.2.2 Safety

The 24-week analyses described above for the primary analysis will be repeated as secondary analyses at Week 72.

For each cohort, every death or adverse event of Grade 3 or 4 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 drug (not related, or related).

9.6.2.3 TB Treatment Outcomes

Statistics on treatment response in children will primarily be descriptive. The proportions of children classified as having exhibited bacteriological cure and clinical (probable) cure (see definitions in Section 8.5) 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 Analysis

9.6.3.1 Viral load suppression

The proportions of children who had viral load suppression at Weeks 24, 48, and 72 will be presented in aggregate, as well as broken down by age cohort, HIV status, and among HIV-infected children within each age cohort, bounded by 95% confidence intervals.

9.6.3.2 TB treatment outcome of injectable-sparing regimen

The TB treatment outcome analysis described in Section 9.6.2.3 will be repeated among children who received injectable-sparing regimens.

9.6.3.3 Safety of injectable-sparing regimen

The safety analysis described earlier for the primary and secondary safety objectives will be repeated among children who received injectable-sparing regimens.

9.6.3.4 Association between QT prolongation and exposure to DLM

Parametric or nonparametric measures of association (e.g., Pearson’s correlation coefficient, Spearman’s correlation coefficient) will be computed, as appropriate, to describe the magnitude of association between QT prolongation and different measures of exposure to DLM (and its DM-6705 metabolite) as estimated by PK modeling. If there is sufficient number in each group, descriptive analyses will compare those with QTcF intervals below clinically meaningful cut-off values with those who were not below these cut-off values, with respect to exposure, at varying follow-up weeks. If the data allow, cross-sectional modeling at specified time points and/or longitudinal modeling of QT prolongation on exposure to DLM over time will also be performed, where age and HIV status may be included as covariates if possible.

9.6.3.5 Exploratory Analyses of biomarker data

In 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. Further details of the exploratory analyses will be provided in the Statistical Analysis Plan.
10 CLINICAL PHARMACOLOGY PLAN

10.1 PK Objectives

10.1.1 The primary PK objective of this study is to evaluate the PK of DLM, when added to OBR, in HIV-uninfected and HIV-infected children at doses determined to most likely achieve exposures similar to those achieved in adults with 100 mg twice-daily.

10.1.2 The secondary PK objective of this study is to assess the contribution of dose, age, HIV co-infection and/or co-treatment to the variability in DLM drug disposition, using population PK modeling.

10.2 Pharmacology Overview of Dosing Strategies

Dosing strategies for this study are described in detail in Section 5.1. Population PK analysis will be conducted with all the available DLM and metabolite DM-6705 concentrations measured in children to date. The joint PK analysis including data from other DLM pediatric studies is motivated by the expected similarity of the data (recently collected observations in a similar population, overlapping study sites) and the improved parameter precision obtained with more PK observations. Potential discrepancies between the historic data and the newly collected observations can be handled within the framework of nonlinear mixed-effects modeling.

Otsuka will continue to provide the necessary data required to determine an appropriate dose in each cohort, including observed concentrations at all time points, dosing history and demographics data from all children participating in trials 232/233 and information about existing population PK models. The PK data and assessments from Trial 232 and 233 for each age cohort will be available before that cohort opens. Per the Pediatric Investigational Plan (PIP) for the European Medicines Agency (EMA) for DLM from Otsuka, this will include data on at least 36 participants in total, with a goal of 6 participants in Group 1 (Age 12-<18), 6 in Group 2 (Age 6-<12), 12 in Group 3 (Age 3-<6), and 12 in Group 4 (Age 0-<3). Trial 232 will include safety assessments on Days 1-18 inclusive, and PK data from Days 1, 2, 10, 11, 13, 15, and 18. Trial 233 will include safety assessments on Days 1, 14, 28, 42, 56, 70, 84, 98, 126, 154, 183, 189, 196, 203, 210, 238, and 365, and PK data from Days 1, 14, 56, 98, 154, 182, 189, 196, 203, 210, and 238. Data collection from the two oldest cohorts in Trial 232 is already finished, and observations from 7, 6 and 6 children in Group 1, 2 and 3, respectively, are available (for PK see Figure 2).

It is important to note that the expectation is that this information (i.e., the totality of the pre-agreed-upon PIP), when provided to the EMA will be sufficient for the EMA to update their label to include the pediatric population. If it is sufficient for the EMA, the chief regulatory authority for medicines in Europe, it is sufficient for our protocol to proceed without formal age de-escalation, especially given that such a label change would result in DLM becoming widely available for use in pediatric MDR-TB patients.

Population PK modeling has been used to estimate appropriate dosing for the children in this study, by age and weight band, that is most likely to achieve exposures within the 90% prediction interval of previously observed AUC0-24h at Day 56 in adults. From observed data among children ages 3-18 years from trials 232/233, weight impacts drug exposures, as is typical for prescribed drugs. Therefore, all cohorts will receive weight-banded dosing as described in Section 5.1.2. Cohort 3 dosing is described above. Proposed doses for Cohort 4 are provided and will be
updated, as needed, once PK data are available for those doses from trial 232. There is no reason to believe, based on the adult data and the emerging results of Otsuka 232 and 233, that DLM will not be well tolerated in HIV-infected children.

10.3 Methods and Timing for PK Collections, Processing, Handling, and Storage

PK assessments will be performed for all participants to determine plasma concentrations of DLM and its DM-6705 metabolite at selected time points. Sampling will include semi-intensive (three -four samples/day) and sparse (one sample/day); this efficient sampling schema is supported by clinical trial simulations (details provided in Appendix III) and will impose the least burden on participants while yielding high quality clinically relevant data.

DLM will be directly administered by the research team on the day of PK sampling. On the two days prior to the PK visit, doses of all drugs, including DLM, OBR and ART, will be carefully documented, including the exact time of doses. Food intake will be documented and standardized across sites to include a high-fat 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.

Whole blood specimens (between 0.5 to 4.0 mL, depending on of the age of the participant) will be collected at the following times: (also described in Section 6.0)

<table>
<thead>
<tr>
<th>Visit</th>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>28</th>
<th>N samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>0</td>
<td>10</td>
<td>28±3</td>
<td>56±3</td>
<td>84±7</td>
<td>112±7</td>
<td>168±7</td>
<td>196±7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours postdose</td>
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<td>0, 2, 4, 8</td>
<td>0</td>
<td>0, 4, 8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>any</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Details regarding collection, processing, and storage of PK samples will provided in the study MOP and LPC. The design will result in 15 plasma PK samples per child, in total 540 observations. In each sample, both parent and metabolite concentrations will be measured. The metabolite will improve characterization of the PK and enable evaluation of the PK-QT relationship for the metabolite which earlier has been associated with observed QT-prolongation. The data will be combined with PK data from the Otsuka 232/233 trials and analysis of this combined dataset should provide robust information for a population PK model, sufficient to characterize adequately the effects of HIV infection and/or ART regimens on PK parameters and predict doses that will achieve PK targets for children of all ages, with and without HIV co-infection.

10.4 Interim Analysis and Dose Adjustment

It should be noted that PK data from the ongoing DLM trials (Otsuka 232 and 233) in HIV-uninfected children will help to inform the doses for this study, reducing the risk of under- or over-dosing children substantially. In addition, DLM’s safety profile is excellent as compared to many drugs used for MDR-TB and significant toxicity is unlikely; testing for the main toxicity (QT prolongation, which is generally modest) will be regular. Further, increased toxicity related to HIV infection or HIV co-treatment is unlikely. Therefore, no dose adjustments for individual
patients will be made in this small study involving only nine participants per age group in which enrollment will not be brisk and individual level PK results, thus, not immediately available.

Given that LPV/r increases concentrations of DLM and its metabolites modestly in adults and that increased concentrations of the parent drug and its metabolite could potentially result in increases in QT interval, we will conduct an interim safety and PK analysis. This interim analysis will occur when Day 56 PK and safety data are available for at least six children on a LPV/r-based regimen. The PK data for all enrolled children up to that point will be included in the analysis. The PK criteria for the interim analysis will be regarded as met if the median observed DLM $AUC_{0-24h}$ at Day 56 falls above the 25$^{th}$ percentile and below the 95$^{th}$ percentile of the adult DLM $AUC_{0-24h}$ distribution at Day 56, i.e., 5698 -13205 $\mu$g*hr/mL (Table 7). In addition, median DM-6705 $AUC_{0-24h}$ will be compared to the corresponding exposure ranges in adults. If it is found to be higher than the 75$^{th}$ percentile of the corresponding parameter observed in adults (4145 ng*hr/mL), dose adjustment downward will be considered. We will assess the fulfillment of the PK criteria for all children and separately for the groups of HIV uninfected; HIV infected on LPV/r, HIV infected on EFV, though the primary focus of the interim analysis will be the group with HIV infection taking LPV/r. DLM $C_{max}$ will also be examined to ensure that the mean DLM $C_{max}$ lies above the 25$^{th}$ percentile and below the 95$^{th}$ percentile observed in adults (289-730 ng/mL). Lastly, the $C_{max}$ of DM-6705 will be examined, however it will not be a formal criterion for attainment of PK targets, as its estimation, with this extremely long-half-life metabolite, is less certain than that of AUC.

### Table 7. Median and Percentiles used for Adult Delamanid PK Targets at Day 56

<table>
<thead>
<tr>
<th>Day 56</th>
<th>Delamanid</th>
<th>DM-6705</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{max}$</td>
<td>$AUC_{0-24h}$</td>
</tr>
<tr>
<td>Trial 204</td>
<td>ng/mL</td>
<td>ng*hr/mL</td>
</tr>
<tr>
<td>Median</td>
<td>391</td>
<td>7654</td>
</tr>
<tr>
<td>5$^{th}$ Percentile</td>
<td>176</td>
<td>3571</td>
</tr>
<tr>
<td>25$^{th}$ Percentile</td>
<td>289.0</td>
<td>5698</td>
</tr>
<tr>
<td>75$^{th}$ Percentile</td>
<td>493.8</td>
<td>9873</td>
</tr>
<tr>
<td>95$^{th}$ Percentile</td>
<td>730</td>
<td>13205</td>
</tr>
</tbody>
</table>

*For a description of Trial 204, please see Section 1.2

If the PK criteria are not met, then new enrollments in that ARV group may receive an adjusted dose, based on simulations using the updated model that incorporates all PK data collected up to that point. If there are safety issues, then the SMC will make recommendations on how to proceed with the study.

It should be noted that QT interval prolongation is the only safety concern that has been identified for DLM, and we will be performing a robust analysis assessing the relationships between drug exposures and QTcF. This analysis will be more informative for dosing recommendations than enrolling a full cohort of children at a modestly higher or lower dose, particularly given that clinically important study drug-related AEs are expected to be rare and non-study drug related AEs are common with MDR-TB treatment. Also of note, individual children on-study will have serial ECG and laboratory testing, so any individual who experiences an adverse event that meets study drug discontinuation criteria as outlined in Section 8.9 will have study drug stopped. In this way, the safety of individual participants is monitored and addressed.
10.5 Laboratory Performing the Assays

Bioanalysis of DLM and its DM-6705 metabolite will be performed centrally at the University of Cape Town Clinical Pharmacology Laboratory using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

10.6 Data Analysis Plan

Population PK parameters (primary: clearance, volume of distribution, rate of absorption which determines the outcome measures AUC and $C_{\text{max}}$) for DLM and DM-6705 will be estimated using nonlinear mixed effect models developed in NONMEM (57) starting from the previously developed model by Otsuka. Body weight, HIV-infection, age, albumin and other covariates identified or hypothesized to be of PK importance (e.g. nutritional status, TB disease severity) will be included in the analysis. Interaction effects of concomitantly administered ARV drugs will also be investigated in the covariate analysis. A detailed population PK analysis plan will be prepared separately.

In addition to the primary population PK analysis, summaries of the PK outcome metrics important for interpretation, such as AUC and $C_{\text{max}}$ will be reported for the three richer sampling occasions at Day 0, 10 and 56 (i.e. Week 1, 2 and 8).

For the purposes of this protocol, DLM exposures should be viewed as keyed to efficacy, and DM-6705 exposures will be viewed as keyed to toxicity. In the selection of doses for the final recommendations, the target exposure will be the median of the observed DLM $\text{AUC}_{0-24h}$ in adults at Day 56 (7654 ng*h/mL). The recommended doses should be aimed at generating exposures as close as possible to the target given the practical constraints, such as the formulation, practical weight banding, etc. Additionally, the typical DM-6705 exposure ($\text{AUC}_{0-24h}$ at Day 56) should not be above the upper end of the 90% prediction interval for adults at the same time point (5628 ng*h/mL). The selection process will be outlined in detail in the PK analysis plan, and will include actual targets based on most current data available in adults. If more current data are available at the time of final analysis, the PK analysis plan will be updated accordingly and finalized based on final team review. Week 8 (Day 56) was selected to allow both DLM and metabolite DM-6705 to have reached steady state.

10.7 Anticipated Outcomes

The anticipated outcomes of the study are estimates including uncertainty of primary PK parameters (clearance, volume of distribution, rate of absorption, etc.) for DLM and DM-6705 in children with and without HIV-infection and quantification of potential covariate relationships with age, weight, albumin and ARV-therapy, etc. Furthermore, the developed population model describing DLM and DM-6705 PK will be fully reported so that it can be used for future simulation of DLM dose-adjustments for children with HIV-infection if clinically relevant PK differences are identified.

PK outcome metrics, such as $\text{AUC}_{0-24h}$, $C_{\text{max}}$ and $T_{\text{max}}$ at Day 10 and terminal half-life will also be reported to facilitate comparison with Otsuka study 232. Posterior predictive checks will be performed to compare model based and empirical estimates of secondary parameters when possible.
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 (SES).

Study sites must maintain adequate and accurate research records containing all information pertinent to the study for all screened and enrolled participants, including paper-based CRFs (if used), eCRFs, 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).

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study site staff will enter required data into eCRFS, with system checks applied and data queries generated immediately upon saving the entered data. Data must be entered within the timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data will be transferred electronically to the DMC through the LDMS.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the Subject Enrollment System is available on the DMC portal at www.frontierscience.org.

11.2 Essential and Source Documents and Access to Source Data

All DAIDS policies referenced in this section are available at: https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures

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, 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
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: https://www.niaid.nih.gov/sites/default/files/qmmpolicy.pdf

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, eCRFs, 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 CFR 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 (58). This study responds to that mandate and will provide clinical research data to inform TB treatment guidelines for children. Children who take part in this study are considered vulnerable participants per the US Code of Federal Regulations, and site IRBs/ECs must consider the potential risks and benefits to infant participants as described in 45 CFR 46 Subpart D (for children).

With respect to 45 CFR 46 Subpart D, 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, and the risk
category assigned by the IRB/EC further 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.

Study sites must comply with the requirements of the DAIDS policy on Enrolling Children (including Adolescents) in Clinical Research, which is available at: https://www.niaid.nih.gov/sites/default/files/enrollingchildrenrequirements.pdf.

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 IIA), site-specific assent forms (refer to sample in Appendix IIB), 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 or each study participant; written assent should also be obtained from participants when applicable per IRB/EC policies and procedures. If an enrolled underage/minor participant reaches the legal age of independent consent during follow-up, he or she will be asked to provide written informed consent for continued study participation upon reaching the legal age of independent consent. 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 derived proven benefit from receiving DLM 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 participation in this study include risks associated with study procedures and risks associated with the study drugs.

The potential risks of DLM are described below.

The following side effects have been associated with the use of DLM in adults:

- Nausea
- Dizziness
- Vomiting
- Hypokalemia (low potassium levels)
- Paresthesias (numbness and tingling)
- Anxiety
- Tremor

Other serious side effects, that are less common include:

- QT prolongation

As mentioned above, a study of DLM in healthy adult volunteers taking ART did not show any significant impact of DLM on levels of tenofovir, lopinavir/ritonavir, or efavirenz, though lopinavir/ritonavir can cause a 20% increase in DLM exposures (34) (59). Though it is not expected, it is possible that concomitant administration of DLM in combination with OBT and ART might cause decreased exposure to ART, with a theoretical possibility of HIV treatment failure. In addition, giving DLM with ethambutol, a component of some OBR, can cause a 25% increase in ethambutol exposure, though it is unclear what the clinical significance of such an increase would be (60). Finally, it has been observed in one study that, when co-administered with DLM, lopinavir/ritonavir appeared to increase by about 30% levels of the metabolite DM-6705, which is the metabolite that has been associated with QT prolongation (60).

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 Potential Social Impacts

A contemporary account of social justice identifies multiple dimensions of human functioning as matters of fundamental ethical importance in evaluating medical and public health policies. These include: Self-determination; Attachment; Respect; Personal Security/ Safety; Health; and Reasoning/ Cognition (61). It is a basic duty of justice to avert or ameliorate systematic clusters of disadvantage involving these dimensions of well-being and, for this reason, minimizing such disadvantages in childhood is a preeminent concern of justice, because they can precipitate a cascade of even more wide ranging and deeply entrenched disadvantages over the whole course of a child’s life. Many children with HIV/MDR-TB co-infection face profoundly circumscribed life opportunities, both from disease- and treatment-related disadvantages and due to their own geo-political context and socio-political background. It is therefore a priority of justice to pursue research avenues that address their needs, ameliorate the disease- and treatment-related harms they suffer, and approach issues in a patient- and family-centered way. It is of profound social impact not only to optimize treatment and prevention of HIV/MDR-TB coinfection in children,
but to do so by the means and measures that most fully satisfy the duty of justice to avert and ameliorate clusters of disadvantages in these ethically fundamental dimensions of human well-being.

13.7 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.

13.8 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.

13.9 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.

13.10 Management of Incidental Findings

Site clinicians will inform participants (or other authorized guardians 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.

13.11 Management of New Information Pertinent to Study Participation

Participants will be provided with any new information learned over the course of the study that may affect their willingness to continue receiving study drug and/or remain in follow-up in the study.
13.12 **Post-Trial Access to Study Drug**

The adult formulation of DLM is licensed by the EMA in adults for a six-month treatment duration and is available by prescription in selected international sites to adults with MDR-TB. In addition, it is now available globally through a compassionate use program, and it is included in the Global Drug Facility. The pediatric formulation of DLM is available for this trial and is expected to become broadly available after testing is completed. Based on the clinical judgment of the site investigators and the protocol team leadership, those patients who may potentially benefit from access to DLM following the end of the trial will be referred to Otsuka’s clinical review committee for assessment. Access will be determined on a case by case basis. For those patients with persistent disease for whom DLM would not be expected to provide additional benefit, the protocol team will collaborate with international pediatric MDR-TB experts and the local TB program to help design the most effective regimen possible.

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 Human Development (NICHD), and National Institute of Mental Health (NIMH), which are part of the United States National Institutes of Health (NIH). Otsuka Pharmaceuticals will provide study drugs for this study but are not involved in sponsorship or regulatory oversight of the study.

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/clinical-research-sites/protocol-registration.

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US 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.impaactnetwork.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: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf.
14.6 **ClinicalTrials.gov**

This protocol is subject to the United States FDA Amendments Act of 2007 (FDAAA), including registration in ClinicalTrials.gov.

15 **PUBLICATIONS**

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT MOP.

16 **REFERENCES**

35. (EMA) EMA. Summary of Product Characteristics, Delamanid. 2014.


60. EMA. Otsuka Novel Products GmbH. Labelling and package leaflet: Deltyba.


### APPENDIX I: Schedule of Evaluation for All Cohorts

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screening</th>
<th>On treatment visits</th>
<th>Unsched Visit</th>
<th>Early DLM D/C only or Early DLM &amp; Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 0/ Start DLM</td>
<td>Wk 2</td>
<td>Wk 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wk 8</td>
<td>Wk 12</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Wk 16</td>
<td>Wk 20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Wk 24 (End DLM)</td>
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<tr>
<td></td>
<td></td>
<td>Visit window</td>
<td>±3 days</td>
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<td></td>
<td>±7 days</td>
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<tr>
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<td>CLINICAL EVALUATIONS</td>
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<tr>
<td>LABORATORY EVALUATIONS</td>
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</tr>
<tr>
<td>Hematology</td>
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<td>LFT</td>
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<tr>
<td>Confirmation of HIV status</td>
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<tr>
<td>TSH, fT4 if TSH is elevated</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Obtain TB isolate from routine lab</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Specimens for TB smear and culture (if indicated)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Xpert MTB/Rif</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Drug susceptibility testing if TB culture+</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Pregnancy test (blood or urine)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine TB biomarker (storage)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Pharmacology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semi-intensive PK</td>
<td>1.5-3.0mL</td>
<td>2.4mL</td>
<td>1.5-3.0mL</td>
<td>1.5-3.0mL</td>
</tr>
<tr>
<td>Sparse PK (store residual plasma)</td>
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<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
</tr>
<tr>
<td>HIV-infected participants only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>1.0mL</td>
<td>1.0mL</td>
<td>1.0mL</td>
<td>1.0mL</td>
</tr>
<tr>
<td>HIV RNA</td>
<td>3.0mL</td>
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</tr>
<tr>
<td>TOTAL BLOOD VOLUMES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1, 2 &amp; 3 (higher volumes for HIV+)</td>
<td>3-9.0 mL</td>
<td>7-11.0 mL</td>
<td>7.0 mL</td>
<td>4.0 mL</td>
</tr>
<tr>
<td>Cohort 4 (higher volumes for HIV+)</td>
<td>3-9.0 mL</td>
<td>5-9.0 mL</td>
<td>5.0 mL</td>
<td>3.5 mL</td>
</tr>
</tbody>
</table>
## APPENDIX I (cont.): Schedule of Evaluation for All Cohorts

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Off treatment visits</th>
<th>Unscheduled Visit</th>
<th>Off DLM Early Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 28 and/or 4 wks post DLM</td>
<td>Week 32 and/or 8 wks post DLM</td>
<td>Week 36 and/or 12 wks post DLM</td>
</tr>
<tr>
<td>Visit Window</td>
<td>±14 days</td>
<td>±28 days</td>
<td>±28 days</td>
</tr>
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</table>

### CLINICAL EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>Phone contact</th>
<th>History</th>
<th>Physical Exam</th>
<th>Adherence assessment</th>
<th>TB treatment outcome</th>
<th>AE Assessment</th>
<th>ECG</th>
<th>CXR</th>
<th>Audiology</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

### LABORATORY EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>Hematology</th>
<th>Chemistries</th>
<th>LFT</th>
<th>Confirmation of HIV status</th>
<th>Serum biomarkers (storage)</th>
<th>TSH, ft4 if TSH is elevated</th>
<th>Specimens for TB smear and culture (if indicated)</th>
<th>Pregnancy test (blood or urine)</th>
<th>Urine biomarker (storage)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0mL</td>
<td>2.0mL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>1.0mL</td>
<td>2.0mL</td>
<td></td>
<td>0-3.0 mL</td>
<td>0.5-1 mL</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### PHARMACOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Sparse PK 2 (store residual plasma)</th>
<th>HIV-infected participants only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5-1.0mL</td>
<td>CD4 cell count</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HIV RNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0mL</td>
</tr>
</tbody>
</table>

### TOTAL BLOOD VOLUMES

<table>
<thead>
<tr>
<th></th>
<th>Cohorts 1, 2 &amp; 3(higher volumes for HIV+)</th>
<th>Cohort 4 (higher volumes for HIV+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0mL, 0.0mL, 2.0mL, 0.0mL, 3-10.0mL, 0.0mL, 4-11.0mL, 0.0mL, 0.0mL, 0.0mL</td>
<td>0.0mL, 0.0mL, 2.0mL, 0.0mL, 3-10.0mL, 0.0mL, 3.5-10.5mL, 0.0mL, 0.0mL, 0.0mL</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 4 is required at Week 48 (20 weeks post DLM) and Week 72 (48 weeks post DLM) and may entail the collection of up to 3 mL depending on type of tests validated for use at the site, if acceptable documentation is not available.

2) Note that any extra plasma not required for DLM drug quantification will be stored for possible future PK analysis of companion drugs. No extra blood will be collected for this purpose.
APPENDIX IIA: Sample Informed Consent Form

IMPAACT 2005: A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

VERSION V1.0, dated 9 March 2017

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: IMPAACT 2005, Safety and pharmacokinetics of delamanid in infants, children and adolescents with drug-resistant tuberculosis

INTRODUCTION

We are asking your child to take part in the research study because he/she is infected with a type of tuberculosis (TB) in his/her lungs or elsewhere. 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). However, if your child has TB that is resistant to at least the two most important first-line drugs, these medications do not work anymore, and this is called multidrug-resistant TB or MDR-TB. For this reason, the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and [sites: insert site name] are doing this study to test a new anti-TB medication called delamanid (DLM) for the treatment of MDR-TB in children with or without HIV co-infection.

This consent form explains the study that your child is invited to join. Please read it, or have someone read it to you. Ask any questions you may have. We will take as much time as you need to fully understand the study. We will ask you questions to make sure we have explained the study clearly.

After you understand the study, if you decide that your child will participate, we will ask you to sign or make your mark on this form. We will offer you a copy to keep.

ABOUT THE STUDY

The study will include about 48 HIV-infected and HIV-uninfected infants, children, and adolescents, from countries around the world, less than 18 years of age with confirmed or probable MDR-TB. Children will be in the study for about 18 months (six months of taking DLM + 12 months of follow-up after stopping DLM treatment = 18 months in total).

The person in charge of the study at this clinic is [sites: insert name of Investigator of Record]. The United States National Institutes of Health is paying for the study.
1. The study is being done to help find the best amount or dose of DLM for babies, children and adolescents.

Children with MDR-TB usually take a combination of at least four drugs to help fight the TB bacteria. The World Health Organization recommends that when delamanid is used in children, it should be added to at least four other drugs to make the total equal to at least five medicines. Your child will, thus, receive multiple medicines to treat his or her MDR-TB. Please note that your child will not be getting an injectable agent (shot) as part of his or her treatment unless there are no other available treatment options. Up to now, many children with TB have gotten shots for six months as part of TB treatment. WHO recently advised that children with non-severe disease are not required to have shots. All children in our study will receive DLM and will not receive shots. You should know that this is not standard. However, because the shots can cause serious side effects like deafness, it is likely that the risks of shots outweigh the benefits when a combination of multiple good medicines can be used together.

It is important to know that there are not as many TB drugs available for children as adults because many of them have not yet been tested in children. This study will help find the best amount or dose of DLM 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 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, DLM that is needed to properly treat children with MDR-TB.

2. We would like to know how safe it is to use DLM in children and if there are any side-effects.

DLM is made by a company called Otsuka. Previous studies using DLM for children and adolescents with MDR-TB have shown us that your child may experience discomfort when taking DLM. All drugs can cause unwanted problems called “side effects, and not all potential side effects of DLM in humans are known. For this reason, we are studying DLM to see how safe it is for children and if there are any bad effects from taking DLM.

These side effects might include nausea, vomiting, trouble sleeping, or possible changes in heart and liver function. Later in this form, we will discuss in more detail these potential health risks and side effects. Please be sure to discuss this with your study doctor if your child has another disease or is taking other medications. He/she will decide if it is safe for your child to continue in this study.

3. It is your decision whether or not your child joins the study.

Deciding to allow your child to join the study is voluntary. If you choose to do so, you can change your mind and take your child out of the study at any time. Your choices will have no effect on the medical care that your child receives at this clinic. Your child’s access to services and the benefits and rights he or she normally has will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about allowing your child to join the study. You can also bring other people with you to learn about the study.

Whether or not you decide to allow your child to participate in the study, it is important that he or she receives care, including TB treatment and ART treatment (if HIV positive). We will discuss your options with you.
FINDING OUT IF YOUR CHILD CAN JOIN THE STUDY

If you decide to let your child join the study, your doctor will first do some tests to see if your child qualifies. Only children who qualify can participate.

4. We will ask questions and discuss the study requirements with you at the Screening Visit.

By signing this form, you agree to follow the instructions given by the research staff. Your study doctor will discuss the study requirements with you and tell you if your child meets these requirements to be in the study. This will be based on the results of several tests and procedures performed by study staff. At the Screening Visit, study staff will:

1. Review your child’s medical records and collect demographic information, which will include your child’s date of birth, ethnic origin and gender.
2. Physically examine your child by taking height/length, weight, and vital signs (pulse and blood pressure) and record your child’s age, gender, race, and ethnicity.
3. Ask you about your child’s medical history, including exposure to TB, symptoms of TB, TB treatment history, and MDR-TB diagnosis.
4. Ask about other medications that your child may be taking.
5. Test your child’s hearing abilities. This is a standard practice for patients who are being treated with drugs for multi-drug resistant TB. The hearing test may be repeated later during the study if your doctor thinks this is necessary.
6. Check your child’s heart beat using an electrocardiogram (ECG). This machine measures the electrical activity of the heart through pads placed on your child’s chest. This is a painless test and does not cause discomfort to children.
7. Take a picture of your child’s lungs using an x-ray, also known as a chest radiograph.
8. Take a urine pregnancy test if your child is female and has had her first menstrual period. If the test is positive, she cannot participate in this study.
9. Check your child’s TB status with either a TB skin test (TST) or IGRA (sites: populate with appropriate language depending on whether TST or IGRA will be done). For a TST, a syringe will be used to inject a very small amount (0.1 mL) of substance into the surface of the skin on your child’s arm. This substance will cause a very small bump to appear on the skin, which will tell doctors whether or not your child is infected with TB. This test is standard practice for anyone who may have been exposed and become infected with TB. [Sites: use this language instead, if you are not doing TST: The IGRA test requires a little more than a ½ teaspoon of your child’s blood (about 3.0 mL)]
10. Check your child’s TB status by having them cough up sputum. Sputum is a thick fluid that the body produces in the lungs and airways that is coughed up into the mouth. If your child cannot cough up sputum, the study staff may need to collect a sample for TB testing from the fluid in the stomach (gastric aspirate). This would require that a small tube is inserted through your child’s nose into their stomach (nasogastric tube/feeding tube) to collect the sputum.
11. Take a little more than ½ teaspoon of blood (about 3.0 mL) in order to check:
   - How well your child’s thyroid, liver and kidneys are working,
   - If your child is HIV negative or positive. There are certain HIV tests that are required for this study. If the required tests are not in your child’s medical records, we will do the tests that are needed. We would need to take a little more than a teaspoon (6.0mL) of blood for these tests.
   - Whether or not your child is pregnant (if urine test is not done). Girls who can have a baby will also be asked to provide a blood or urine sample to test for pregnancy during this visit. If your child is pregnant, she 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.
These procedures will take about 1 to 2 hours [sites: modify how much time this visit will take as needed].

If these procedures show that your child does not qualify for the study, we will tell you this and your child will not be entered into the study. We will give you information on where your child can receive medical care and other services he or she may need.

If these procedures show that your child does qualify for the study, your child will be entered into the study.

**ON THE STUDY**

5. **If your child qualifies, he or she will enter the study.**

If eligible for the study, your child will be seen by the study team at least 15 times over the course of 1 ½ years. On the first day of the study, you will receive the first dose of DLM for your child. We will show you how to give DLM to your child. It is very important that you give your child the DLM as instructed. We will take as much time as needed for you to understand the instructions and study staff will help identify strategies that will help you.

After the first visit, your child will be seen again two weeks later and then once a month for the first five months. Each of these monthly visits will take about 1 to 2 hours [sites: modify how much time this visit will take as needed]. At this time, staff will provide you with your child’s dose of DLM and perform the following examinations and tests listed below:

- **Physical Examination:** At every visit, the study staff will physically examine your child by taking a height/length, weight, and vital signs (pulse and blood pressure) and record your child’s age, gender, race, and ethnicity. We will also ask you questions about how your child is feeling, if you have noticed any changes in his/her health since the previous visit.

- **Medical History:** At every visit, we will ask questions about your child’s health and what symptoms, medications, and any illnesses your child has had. If your child is of reproductive potential (able to bear children), we ask questions about his/her sexual activity and contraception use. 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 a little more than ½ a teaspoon (about 3.0 mL) of blood at most visits. The test will check how well your child’s liver, thyroid, and kidneys are working. These tests are routine, so you will be informed of the results. Some of the blood will be used to check the amount of DLM 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. If your child is HIV positive, we will take a little less than a teaspoon of blood (4.0mL), in addition to the other blood test. This will measure 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.

- **Urine:** The study staff will collect some urine. This urine will be saved for later testing. For example, the tests may look to see how the TB disease responds to the medicine.

- **ECG:** During the visits while your child is taking DLM and the visit 4 weeks after your child has stopped taking DLM, the study team will look at your child’s heart beat using an
electrocardiogram (ECG). Special electrical wires will be 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.

- **TB testing**: At some visits, the study team will check your child’s TB status with a chest x-ray that takes a picture of your child’s lungs. Also, we may ask your child to give us a sample of sputum to identify the TB bacteria living in your child’s lungs and breathing passageways. Sputum is a thick fluid that the body produces in the lungs and airways that is coughed up into the mouth. 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, 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.

- **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 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 becomes pregnant during the study, she 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 96), then the study staff will arrange to contact her 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.

- **Acceptability Questionnaire**: At some visits while your child is taking DLM, we will ask how it felt to take the tablet (for example, how the tablet tasted or how easy or difficult it was to swallow it).

6. **At some visits, we will perform an additional procedure called a Pharmacokinetic test or “PK test.”**

Throughout the study, we will need to monitor how much DLM is in your child’s blood. We call this blood test a “PK test.” We will do two types of PK tests: “Semi-intensive PK,” and “Sparse PK”

- “Semi-Intensive PK”: We want to measure the amount of DLM in your child’s blood very closely. For these visits, your child will need to come to the clinic to have blood drawn a few times over 8 hours. This is called an “Semi-Intensive PK Visit.”
When will these Intensive PK visits take place? These visits will only happen three times:
- During the first visit when your child receives their first DLM dose (Day 0 Visit)
- Week 2 visit
- Week 8 visit

What should I do to prepare for this visit beforehand? Please do not give your child the morning dose of DLM. Please 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 DLM doses, as directed by the study staff, for seven days prior to the visit.

What will happen during a Semi-Intensive PK visit? A small plastic tube (like a “drip”) will be placed in your child’s arm to draw blood samples. This tube is attached to a plastic needle so that we can draw blood several times. We will not need to stick your child with a needle each time. The plastic needle will stay in place until all of the blood samples are drawn. [sites: modify language as appropriate to indicate procedures for the intensive PK collection.]

How much blood will be drawn? If your child is between the age of 3 and less than 18 years old, we will collect about a teaspoon of blood (4-5 mL). If your child is less than 3 years of age, we will collect a little less than ½ teaspoon of blood (1.5-2 mL). This amount of blood will be in addition to other blood tests described above.

- “Sparse PK”: At other times, we will still measure the amount of DLM in your child’s blood, but a little less intensely for “Sparse PK” visit. We will only take one blood sample at each of these visits. You will not need to bring DLM to the clinic for Sparse PK visits, so it is very important that you can tell study staff the exact time you gave DLM to your child on the sparse PK visit days.

7. Tests will be done at different laboratories.

We will do most routine tests of your child’s blood at our laboratory. We will give you the results of these tests at the next scheduled visit, or sooner if necessary. We will explain the results to you. If the tests cannot be done at our laboratory, we may send them to be done at laboratories in the United States and other countries. The results of most of these tests may not be available while the study is ongoing.

8. You are expected to follow specific instructions while your child is in the study.

If you allow your child to participate in this study, you and your child will be expected to:

- Follow the instructions given by the study staff during the study
- Provide truthful information about your child’s health and medication history and how he or she is currently feeling
- Follow the study doctor's instructions for your child to take the study drug
- Report any side effects or changes in your child’s health during the study
- Inform the research staff of any prescription medications, oral and herbal supplements and/or over-the-counter medications that your child is currently taking.
- Not give your child any prescription medications, oral or herbal supplements and/or over-the-counter medications before notifying the study staff
AFTER YOUR CHILD STOPS TAKING DLM

9. After your child has taken DLM for 6 months, he/she will stop taking it.

After stopping DLM your child most likely will continue taking their other MDR-TB treatment for some time. Even after your child’s last dose of DLM, we will still need you and your child to return to the clinic for seven more visits over a 12-month period to check how your child is doing. The study staff will perform the same examinations, blood tests, ECGs, chest x-rays, hearing test, TB tests, and PK tests that were performed during the time that your child was taking DLM. The only difference is that we will not prescribe DLM for your child during this time. The time of these visits and the type of tests that are done will vary each month. The last time you will be asked to bring your child to the clinic will be 48 weeks after your child stops taking DLM. The study staff will contact you by phone 72 weeks after your child stops taking DLM, for one final check to see how your child is doing.

ALTERNATIVE TREATMENTS

10. If you choose not to allow your child to participate in the study, he or she may receive standard treatment for MDR-TB.

If you do not want your child to participate in the study, he or she may receive standard treatment for MDR-TB. This treatment is similar to the multidrug treatment that all patients who participate in the study will receive except that standard treatment often includes shots. Treatment for MDR-TB usually includes at least four drugs depending on the type of TB your child has. Later, we will discuss the risks and benefits of these drugs.

BENEFITS OF THE STUDY

11. There may be no benefit to your child from being in the study.

Your child may or may not experience a decreasing number of TB bacteria growing in his or her body while taking DLM. Even if he or she does not personally benefit from this study, his or her participation may help to increase the knowledge about the treatment of MDR-TB and may help others in the future. You will not have to pay for study drug or procedures that are required.

RISKS AND DISCOMFORTS

12. There is little risk from the study procedures.

Most procedures are routine medical procedures, with little risk to your child. Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

13. There are some risks in taking standard treatment for MDR-TB.

All patients who choose to participate in this study will receive multidrug treatment for MDR-TB including a combination of multiple drugs from the list described below (alternative treatments). These drugs have known side effects that include, but are not limited to, the following:
<table>
<thead>
<tr>
<th>Alternative Treatments</th>
<th>Known Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>Liver problems</td>
</tr>
<tr>
<td></td>
<td>Changes in ability to see clearly</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Too much uric acid in the blood</td>
</tr>
<tr>
<td></td>
<td>Joint pain</td>
</tr>
<tr>
<td>Amikacin, Kanamycin</td>
<td>Kidney problems</td>
</tr>
<tr>
<td></td>
<td>Difficulty hearing</td>
</tr>
<tr>
<td>Ethionamide and Prothionamide, P-aminosalicyclic acid</td>
<td>Thyroid problems (including tiredness and weight gain)</td>
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<tr>
<td>Cycloserine</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Other changes in mood or thinking</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Kidney problems</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td>Levofloxacin and Ofloxacin</td>
<td>Nausea and/or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Headache and dizziness</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
</tr>
<tr>
<td></td>
<td>Sensitivity to light</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Nausea and/or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Headache and dizziness</td>
</tr>
<tr>
<td></td>
<td>Low platelets</td>
</tr>
<tr>
<td></td>
<td>Weakness/numbness in hands and feet</td>
</tr>
<tr>
<td></td>
<td>Changes in ability to see (due to damage to a nerve in the eye)</td>
</tr>
<tr>
<td></td>
<td>Too much lactic acid in the blood</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Serious allergic reaction</td>
</tr>
</tbody>
</table>

14. **There are some risks in taking the study drug, DLM.**

As of 31 January 2016, 17 previous studies gave DLM to a total of 949 adults who had MDR-TB, just like your child. The most common negative effects or “adverse events” that these adult reported when taking DLM were:

**Most common:**
- Nausea/vomiting
- Difficulty sleeping
- Headache
- Dizziness
- Joint or muscle pain

**Less common:**
- Upper abdominal pain
- Loss of appetite
- Ringing in the ear
- Diarrhea
- Chest pain or rapid heartbeat

Some other side effects that might be related to DLM are numbness and tingling, anxiety and tremor.
Sometimes, these adverse events may be due to taking DLM. But, adverse events can also happen because of an underlying disease, other medications, or the development of other illnesses. Please be sure to discuss this with your child’s doctor.

15. We will tell you about the most severe side effects of DLM.

First, you should know about the possible severe side effects. These effects are rare, but they can cause serious health problems to the following parts of the body:

- **Heart**: DLM can cause a specific kind of change to the heart called an increased “QT interval.” An increased QT interval might put your child at greater risk of having a problem with the rhythm of his/her heartbeat. In very rare cases, this can lead to death. Because of this, the protocol team will carefully monitor your child’s heart during this study when we perform an ECG (a check of the heart).

  An increase in the “QT interval” may be seen in people taking DLM and other TB drugs at the same time. 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**: The liver is an organ near the stomach. If your child gets liver problems, he or she might have yellowing of the skin or whites of the eyes; dark or tea colored urine; pale colored stools; upset stomach or vomiting; loss of appetite; pain, aching or tenderness of the right side below the ribs; or itchy skin.

- **Blood**: This could mean that your child experiences decreased blood potassium, low plasma protein (serum albumin), decreased white blood cells and platelets. This could also mean that your child experience anemia.

- **Others**: Other serious events that were reported during previous studies include the removal of a portion of the lung and bleeding after surgery.

In some studies, including those of people with MDR-TB, there were deaths among those receiving DLM compared to those not receiving the drug. However, after reviewing all of the information, study doctors concluded that the deaths were unrelated or unlikely to be related to taking DLM.

There may be other risks that are not known, including reactions that may be life threatening. All drugs have the risk of an allergic reaction that could become life threatening. You must report all problems and worries to a member of the study staff. During this study, we will make sure that your child is observed for any bad or harmful effects. The doctor will decide if it is safe for your child to continue in the study.

As the parent/legal guardian, it is important to keep DLM out of the reach of small children and persons who may not be able to read or understand the label.
16. There is a possible effect on pregnancy or unborn babies.

DLM may lead to some pregnancy complications, like early delivery or low weight of the baby at birth. We do not know if some TB medicines are more likely to cause these effects than others. We do not yet know if DLM is safe in pregnancy.

17. There could be risk of physical injury from participation.

You agree to allow your child to join this study of your own accord. You should report any discomforts, problems, or research-related injuries immediately to your child’s doctor at <insert contact information>. If he or she is injured because of being part of this study, your doctor will provide usual medical care. 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].

18. There could be risks of disclosure of your child’s information.

We will make every effort to keep your child’s information private and confidential. Study records and specimens will be kept in secure locations. All specimens and most records will be labeled only with a code number. However, your child’s names will be written on some records. Despite our best efforts to keep your child’s information private, it is possible that the information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly. Your child could feel stress or embarrassment.

**PARTICIPATION DISCONTINUATION**

19. We may take your child off study.

The study doctor may stop the study medication and your child may be asked to leave this study without your agreement.

We may take your child off the study if:

- The study is stopped for any reason
- We determine that your child cannot meet the study requirements (for example, if you move away and cannot come to the clinic)
- We determine that staying in the study might harm your child
- You or your child does not follow directions

If we ask your child to leave the study, the reasons will be discussed with you. You will be asked to allow the doctor or study nurse to perform many of the same procedures that would have occurred at the completion of your child’s study participation (see #5 above).

If your child is discontinued from the study prior to completing his or her anti-TB treatment course, the doctor or study nurse will either continue treating your child’s TB with standard treatments for multi-drug resistant TB or offer other available treatment programs for further evaluation.

If your child is discontinued from the study after completing his or her last DLM dose, we will ask to contact you by phone after your child discontinues. If you agree, we will phone you at 4, 16, 36 and 48 weeks after his or her last DLM dose to ask about your child’s medical history. If your child is pregnant at the last visit, we will also ask about the pregnancy outcome.
20. Please tell us if you want your child to leave the study.

Your child is free to leave the study at any time for any reason. The care that your child receives at this clinic will not be affected, but it is important for us to know about your decision. We will still ask you to bring your child to the clinic to perform many of the same procedures that would have occurred at the completion of your child’s study participation (see #5 above). We will answer any questions you may have and give you information on how to contact us in the future.

We will also ask to contact you by phone after your child discontinues (see #19 above).

OTHER INFORMATION ABOUT THE STUDY

21. There are no costs to you for your child being in the study.

There are no costs to you for your child's study visits, DLM medication, or procedures. [Sites: insert information about compensation/reimbursement here, e.g., You will be reimbursed for the cost of transport to study visits. For each visit, you will be given (specify amount).]

22. Your child's study records may be reviewed by study staff and groups that oversee the study.

Groups that oversee the study include:

- [insert name of site IRB/EC]
- [insert name of site IBC]
- [insert name of national Drug Regulatory Authority]
- [insert name of other local regulatory authorities]
- The United States National Institutes of Health and its study monitors
- The United States Office for Human Research Protections
- The United States Food and Drug Administration (FDA)
- The IMPAACT Network that is coordinating the study

Like the study staff, these groups are required to make efforts to keep study records private and confidential.

The results of the study may be presented publicly or published. However, no presentation or publication will use your child’s name or identify your child personally. A description of this study will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

If you want the results from this study, please notify the study staff.

Your child’s study information may be disclosed to other authorities if required by law.

23. If your child gets sick or injured, contact us immediately.

Your child’s health is important to us. We will make every effort to protect your child’s well-being and minimize risks to him or her. It is possible, however, that your child could have an illness or injury that is study-related. This means that the illness or injury occurred as a direct result of the study procedures.
If a study-related illness or injury occurs, we will treat your child or tell you where you can get the treatment your child needs. The cost for this treatment may be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health.

**WHOM TO CONTACT**

24. **If you have questions, concerns, or problems at any time, use these contacts.**

1. If you have questions about the study, contact:
   
   [sites: insert name and telephone number of investigator or other study staff]

2. If you have questions about your child’s rights as a research participant, or problems or concerns about how your child is being treated in the study, contact:
   
   [sites: insert name and telephone number of IRB contact person or other appropriate person/organization]

3. If your child has any health or other problems that may be related to his or her study participation, contact:
   
   [sites: insert name and telephone number of investigator or other study staff]

4. If you want to leave the study, contact:
   
   [sites: insert name and telephone number of investigator or other study staff]

**STORAGE AND FUTURE USE OF BLOOD AND OTHER SAMPLES**

Your child’s blood, urine or other TB samples may be collected and 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 your child is HIV-infected e.g. diagnostic or biomarker research). He or she can still participate in this study even if you decide that you do not want to have your child’s blood, urine or other samples stored for later testing.

Only approved researchers will have access to the samples. Your child’s samples will not be sold or directly used to produce commercial products. All proposed research studies using 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 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 child’s medical care, the 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. He/she 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 you or your child by allowing his/her 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 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 and other samples to be stored for use in future IMPAACT-approved, general TB- or HIV-related research studies.

__________ Yes ___________ No ___________ Date

SIGNATURES

25. If you agree to let your child participate in this study, please sign or make your mark below.

Before deciding whether to let your child participate in this study, make sure you have read this form, or had it read to you, and that all of your questions have been answered. You should feel that you understand the study, its risks and benefits, and what is expected of you and your child if you decide allow your child to join.

If you decide to allow your child to join, we will tell you any new information from this study or other studies that may affect your willingness for your child to stay in the study. You are welcome to ask questions or request more information at any time.

You do not give up any rights by signing this form.

Participant’s Name (print)

Parent’s Name (print) (Or Legal Guardian) Parent’s Signature Date

Study Staff Conducting Consent Process Name (print) Study Staff Signature Date

Witness Name (As appropriate) Witness Signature Date
APPENDIX IIB Sample Informed Assent Form

IMPAACT 2005

A Phase I/II Open-Label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children with MDR-TB

VERSION 1.0, dated 9 March 2017

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: IMPAACT 2005, Safety and pharmacokinetics of delamanid in infants, children and adolescents with drug-resistant tuberculosis

ABOUT THE STUDY

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 delamanid (DLM) 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) is not killed by the usual TB medicines. DLM has been tested in adults and in animals, but not yet in children. This study will help find the best amount or dose of DLM for babies, children and adolescents under 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. 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.

CHOOSING TO PARTICIPATE IN THE 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?**

You will have about 15 study visits over the 1½ years (18 months) that you will be in this study. Most of these visits will last about [sites please include expected duration]. At these visits, the study staff will talk with you and your parent/guardian about your health and the medicines you are taking. You will have a physical examination, and we will collect a small amount of blood and some urine 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 female and could get pregnant, you may have urine or blood collected for pregnancy tests. Included in the blood samples taken at every visit, there will be three visits called Semi- Intensive Pharmacokinetic (PK) Visits. During these visits, you will be asked to come to the clinic to have your blood drawn a few times over 8 hours, so we can test how much medication is in your blood.

DLM 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. You will be asked to take DLM twice every day, for 24 weeks. You will need to take DLM with the TB medications that you are already taking. If you are HIV positive, you will also need to take it with your antiretroviral treatment (ART).

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 96/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 1½ years (18 months) after your last dose of DLM.
- 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?**

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

- Most Common: Nausea/vomiting, difficulty sleeping, headache, dizziness, joint pain.
Less Common: Upper abdominal pain, loss of appetite, ringing in the ear, diarrhea, cheat pain or rapid heartbeat.

WHAT KINDS OF GOOD THINGS COULD COME FROM BEING IN THE STUDY?

You may or may not experience a decreasing number of TB bacteria growing in your body while taking study drug. Even if you do not personally benefit from this study, your participation may help to increase the knowledge about the treatment of multi-drug resistant TB and may help others in the future. You will not have to pay for study drug or procedures that are required.

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 AND OTHER SAMPLES

Your blood, urine 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 e.g. diagnostic or biomarker research). You can still participate in this study even if you decide that you do not want to have your blood, urine or other samples 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 and other samples to be stored for use in future IMPAACT-approved, general TB- or HIV-related research studies.

__________ Yes __________ No __________ Date

**SIGNATURE**

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
APPENDIX III: Clinical trial simulations to evaluate study design

Elin Svensson and Mats Karlsson, Uppsala University

IMPAACT 2005: A Phase I/II Open-label, Single-Arm Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination with Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in Children with MDR-TB and HIV Co-Infection

Objectives
To evaluate PK sampling strategies and samples size for characterization of DLM PK in children with and without HIV-infection. The study design should ensure ability to fulfill the PK-related study objectives and preferably fulfill the precision criteria specified by the FDA for pediatric trials (56). The criteria states that pediatric studies should be designed to have statistical power sufficient to target 95% confidence interval (CI) within 60% to 140% of the geometric mean estimate for clearance and volume of distribution. Fulfilling the criteria for clearance implies that the primary objective of the study (evaluate the PK of DLM, when added to OBR in HIV-infected and HIV-uninfected children at doses determined to most likely achieve exposures similar to those achieved in adults with 100 mg twice-daily) can be fulfilled.

Methods
A population PK model of DLM developed by Otsuka on data from MDR-TB adult patients and from 13 children 6-18 years old, with MDR-TB infection but no HIV infection (Otsuka study 232), was used as the basis for these clinical trial simulations. The model is a two-compartment model including random effects describing inter-individual variability in clearance (CL), central volume of distribution (V), inter-compartmental clearance, and absorption rate of the morning dose (Ka). Allometric scaling was applied to all disposition parameters with the theoretical coefficients (0.75 for clearances and 1 for volumes). DLM has non-linear PK, described in the model by a change in bioavailability (F) with dose (in mg) as defined by a power function:

\[ F = \left(\frac{\text{dose}}{100}\right)^{0.66} \]

The model included both additional and proportional residual error components.
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 (62) based on WHO growth standards (0-10 years) (63) and the NHANES study (10-18 years) (64). The weights of the TB-infected children were assumed to be normal compared to the international standard growth curve or lower (Z-score ≤0).

Nine participants, six with HIV-infection and three without, in each of the four cohorts were suggested as a reasonable sample size in the initial discussions of the study design. This sample size was further evaluated in the clinical trial simulations. The originally suggested timing of PK samples was based on schedules used in Otsuka study 232 and discussions with the protocol team. Reduced versions aiming to decrease the burden on the participating children were then further evaluated. A selection of investigated designs is listed in Table 8.
Table 8. Selected investigated sampling designs defined by the sample time-points (treatment day and time after dose) and the number of planned PK samples

<table>
<thead>
<tr>
<th>Design number</th>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>N samples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day</td>
<td>1</td>
<td>10</td>
<td>28±2</td>
<td>56±2</td>
<td>84±2</td>
<td>112±2</td>
<td>168±2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>h postdose</td>
<td>0, 4, 10</td>
<td>0, 2, 4, 10, 12, 14, 24</td>
<td>0</td>
<td>0, 4, 10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>h postdose</td>
<td>0, 4, 10</td>
<td>0, 2, 4, 10, 12, 24</td>
<td>0</td>
<td>0, 4, 10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>h postdose</td>
<td>0, 4, 10</td>
<td>0, 2, 4, 10, 12, 24</td>
<td>0</td>
<td>0, 4, 10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>h postdose</td>
<td>0, 4, 10</td>
<td>0, 2, 4, 6, 10, 24</td>
<td>0</td>
<td>0, 4, 10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>h postdose</td>
<td>0, 4, 10</td>
<td>0, 2, 4, 10</td>
<td>0</td>
<td>0, 4, 10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>h postdose</td>
<td>0, 4, 8</td>
<td>0, 2, 4, 8</td>
<td>0</td>
<td>0, 4, 8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

The dosing regimen for Cohort 1 and 2 was implemented as in Otsuka study 232, 100mg and 50mg (adult formulation) BID, respectively. For Cohorts 3 and 4 the pediatric formulation of DLM should be used. For Cohort 3 a dose of 40 mg (pediatric formulation) BID, the dose Otsuka has predicted to give similar exposure to the observed in Cohorts 1 and 2, was implemented. For Cohort 4 an arbitrary chosen dose of 20 mg (pediatric formulation) BID was used. The pediatric formulation was assumed to have an F of 80% of the F for the adult formulation (Otsuka information). Before Cohorts 3 and 4 in IMPAACT 2005 are opened, data from Otsuka study 232 for corresponding age-categories will be available and used to better determine the doses for Cohorts 3 and 4.

The analysis was performed in NONMEM (57), aided by the stochastic simulation and estimation (SSE) functionality in PSN (65). 1000 virtual trials were simulated assuming no difference in PK between HIV-infected and uninfected children. Parameters were re-estimated on the simulated data assuming (i) no difference in PK between HIV-infected and uninfected children (model 1), (ii) separate estimation of CL for HIV-infected and uninfected children (model 2), or (iii) separate estimation of CL for HIV-infected and uninfected and estimation of relative bioavailability for HIV-infected children compared to uninfected (model 3). The allometric coefficients and the parameter describing difference in F between adult and pediatric formulation were estimated along with the other model parameters.

The parameter precision, the probability to fulfill the FDA precision criteria (the power) and the risk of finding a significant effect of HIV when data were simulated without one (i.e. type 1 error) were evaluated. The parameter precision in apparent CL and Vss was described by 95% parametric confidence intervals at the tails of the expected weight distribution for the two formulations (7.5 and 20 kg for the pediatric formulation and 20 and 65 kg for the adult formulation). The lower and upper ends of the weight range were derived from the observational MDR-TB cohort study earlier mentioned. It can be assumed that when precision is acceptable at the extremes of the weight range, it will also be acceptable at weights...
between those values. Parametric confidence intervals were calculated based on the geometric mean and standard error of the estimates obtained in the 1000 simulated trials. The probability to achieve 95% CI within 60-140% of the geometric mean was calculated using the uncertainty in parameter estimates obtained through the covariance step ($COV$) in NONMEM. CL and V parameters were log-transformed (Eq 1 and Eq2) to render the standard error additive (Eq3).

Eq1: \( CL = \exp(\theta_1) \left( \frac{WT}{33.5} \right)^{\theta_2} \)

Eq2: \( LCL = \theta_1 + \theta_2 \log \left( \frac{WT}{33.5} \right) \)

Eq3: \( SE_{LCL} = \sqrt{\sigma_1^2 + \left( \log \left( \frac{WT}{33.5} \right) \right)^2 \sigma_2^2 + 2\sigma_1 \sigma_2 \log \left( \frac{WT}{33.5} \right)} \)

The percentage of the 1000 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 the same weights as mentioned above. The corresponding calculations were performed for V.

Actual type I error rates, i.e. the likelihood to find a statistically significant effect when there truly is none, based on simulations were evaluated for testing the effect of HIV on different primary PK parameters at the 5% level of significance. The type 1 error rate, together with the statistical power to fulfill the precision criteria, informs about the ability to assess the contribution of different covariates to the variability in DLM drug disposition, one of the exploratory objectives.

**Results**

The agreement of the simulated population and the target population was confirmed by a comparison with data from an observational MDR-TB cohort study in children from Cape Town, South Africa, including 143 participants of which 28 had HIV co-infection. The simulated weights were found to match the observed well within each cohort, as shown in Figure 3. The observational dataset only included children until age 15, while the simulated includes children up to 18 years, which explains the apparent mismatch in cohort 1.
The originally proposed sampling schedule (design 1 in Table 8) and sample size generally produced good precision in apparent CL (CL/F). Reducing the number of samples were found feasible with close to retained precision and power and results are presented either only for the final (design 6 in Table 8) or comparing original and final sampling schedule.

The geometric mean estimates and 95% CI plus 60-140% limits using the final sampling schedule and model 1 are listed in Table 9. The 95% of estimated CL/F and Vss/F relative to the expected value for original and final design and all scenarios are shown in Figure 4 and 5, respectively.

Table 9. Geometric mean and 95% CI for estimates of apparent clearance given model 1 (same CL/F for children with and without HIV infection) and corresponding reference intervals (expected).

<table>
<thead>
<tr>
<th>Weight and formulation</th>
<th>Estimated geometric mean CL/F [L/h] (95% CI)</th>
<th>Expected CL/F [L/h] (60-140%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 kg, pediatric formulation</td>
<td>2.19 (1.98,2.44)</td>
<td>2.35 (1.41,3.29)</td>
</tr>
<tr>
<td>20 kg, pediatric formulation</td>
<td>6.98 (6.3,7.73)</td>
<td>6.49 (3.89,9.09)</td>
</tr>
<tr>
<td>20 kg, adult formulation</td>
<td>7.80 (7.10,8.45)</td>
<td>7.92 (4.75,11.08)</td>
</tr>
<tr>
<td>65 kg, adult formulation</td>
<td>28.47 (25.19,32.31)</td>
<td>24.51 (14.71,34.32)</td>
</tr>
</tbody>
</table>
Figure 4. The distribution of estimated apparent clearance relative to the expected value (used in simulation) for a 7.5 and a 20 kg child getting the pediatric formulation and a 20 and 65 kg child getting the adult formulation.

Figure 5. The distribution of estimated apparent volume of distribution at steady state relative to the expected value (used in simulation) for a 7.5 and a 20 kg child getting the pediatric formulation and a 20 and 65 kg child getting the adult formulation.
The power results for HIV-infected children are listed in Table 10. The probability to obtain sufficient precision in the CL estimate is excellent for model 1 and 2 but lower for model 3 where both CL and F may differ between HIV-infected and uninfected children. Since the power for model 3 is low, it would be difficult to separately characterize two different simultaneous effects of HIV infection on CL and F, respectively. However, if there are truly two separate effects, we can at least expect to characterize the combined impact with good precision (this scenario corresponds to model 2). The power to achieve precise estimates of V is low overall. The power for the group of children without HIV-infection are the same or higher as for the HIV-infected since there are more participants and observations for in the group of uninfected which also including the data from Otsuka study 232.

Table 10. Probability (power) to achieve 95%CI within 60-140% of the geometric mean for CL and V in HIV-infected children at the low and high end of the expected weight distribution. Simulation model with same CL/F for children with and without HIV infection.

<table>
<thead>
<tr>
<th>Design</th>
<th>Model</th>
<th>CL 7.5 kg</th>
<th>CL 65 kg</th>
<th>V 7.5 kg</th>
<th>V 65 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>original</td>
<td>1</td>
<td>97.4</td>
<td>99.8</td>
<td>37.4</td>
<td>12.6</td>
</tr>
<tr>
<td>final</td>
<td>1</td>
<td>97.1</td>
<td>99.8</td>
<td>32.9</td>
<td>7.4</td>
</tr>
<tr>
<td>original</td>
<td>2</td>
<td>96.1</td>
<td>99.6</td>
<td>39.6</td>
<td>11.2</td>
</tr>
<tr>
<td>final</td>
<td>2</td>
<td>96.3</td>
<td>99.9</td>
<td>33.4</td>
<td>7.8</td>
</tr>
<tr>
<td>original</td>
<td>3</td>
<td>48.4</td>
<td>87.5</td>
<td>34.2</td>
<td>8.6</td>
</tr>
<tr>
<td>final</td>
<td>3</td>
<td>33.6</td>
<td>77.6</td>
<td>33.5</td>
<td>6.1</td>
</tr>
</tbody>
</table>

The type I error rates for the different scenarios were generally low and are presented in Table 11. The type error rate refers to how likely it is that a model with separate parameters (CL in model 2 and CL plus F in model 3) for HIV- and HIV+ subjects was significantly better than a model with the same parameters for HIV- and HIV+, given that the true model has the same parameters for HIV+ and HIV-. In other words, how likely it is to detect a statistically significant effect of HIV even though there truly is none. Further simulations to control for type I error rate can be performed when data has been collected.

Table 11. Type 1 error rates for detection of an effect of HIV.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Type 1 error</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) True: No effect of HIV (model 1)</td>
<td>-</td>
</tr>
<tr>
<td>(ii) CL different in HIV+ (model 2)</td>
<td>4.9%</td>
</tr>
<tr>
<td>(iii) F and CL different in HIV+ (model 3)</td>
<td>7.9%</td>
</tr>
</tbody>
</table>

Considerations
The parameter of importance to determine DLM doses is apparent clearance, which is estimated with good precision. That the volume of distribution is less precisely determined is of low importance since it will not affect the steady-state concentrations of DLM and therefore can be expected to have little impact on the pharmacological effect.

Additional data from study 233 is likely to be available when the analysis of IMPAACT 2005 should be performed. Metabolite concentrations will be measured and could be included in the model to increase the...
information content. The precision in the parameter estimates in the final analysis could therefore be expected to be better than in the clinical trials simulations.

A bias in the estimate of the bioavailability of the pediatric formulation was observed. It was introduced by the inclusion of observed data, probably arising from that the non-linearity parameter estimated on adults does not fitting perfectly. Excluding the observed data resulted in less biased estimates. Potentially a better description of the dose nonlinearity in F could be obtained when Otsuka have updated the population PK model to also include data from Cohorts 3 and 4 in study 232. If the parameter value obtained in adults is retained in the final model from study 232, a sensitivity analysis should be performed when data from IMPAACT 2005 is analyzed.

These clinical trials simulations were performed with the currently available model for DLM PK in children and the best estimates of parameter values. The precision in parameter estimates is not expected to change drastically within a reasonable range of difference in the parameter value compared to the expected value used in the simulation, since the information content of the data is the same.

**Conclusions**
The final sampling design and sample size of nine participants per cohort are likely to provide adequate information to fulfill the objectives of this trial.
## APPENDIX IVA: 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><strong>A</strong></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><strong>B</strong></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</td>
<td>Km</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Streptomycin*)</td>
<td>(S)</td>
</tr>
<tr>
<td><strong>C</strong></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><strong>D</strong></td>
<td>Other core second-line agents</td>
<td>Pyrazinamide</td>
<td>Z</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&lt;sup&gt;H&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>D1</td>
<td>Bedaquiline</td>
<td>Bdq</td>
</tr>
<tr>
<td></td>
<td>D2</td>
<td>Delamanid</td>
<td>Dlm</td>
</tr>
<tr>
<td></td>
<td>D3</td>
<td>p-aminosalicylic acid</td>
<td>PAS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Imipenem-cilastin</td>
<td>Ipm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meropenem</td>
<td>Mpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amoxicillin-clavulanate</td>
<td>Amx-Clv</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Thioacetazone)</td>
<td>(T)</td>
</tr>
</tbody>
</table>
APPENDIX IVB: 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 Groups A-D. This helps to construct a regimen aiming at five effective drugs per regimen. Regimens should be constructed consistent with updated international (WHO) and local guidance and practice. The suggested approach from the WHO is 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 V: 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>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin</td>
<td>15-30mg/kg once daily</td>
<td>1g vial</td>
<td>Ototoxicity, nephrotoxicity</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15-25mg/kg once daily</td>
<td>100mg, 250mg, 500mg and 1g vials</td>
<td>As for kanamycin</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15-30mg/kg once daily</td>
<td>1g vial</td>
<td>As for kanamycin</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>15-20mg/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>15-20mg/kg once daily</td>
<td>250mg, 500mg</td>
<td>As for ofloxacin; prolongation of QTc interval (less so than moxifloxacin)</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>Clofazime</td>
<td>2-3 mg/kg once daily</td>
<td>50mg, 100mg tablets/capsules</td>
<td>Skin discoloration (may also cause QT prolongation)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>10mg/kg once daily (&gt; 10 years of age) or twice daily (. 10 years of age)</td>
<td>600mg tablets and syrup</td>
<td>Headache, nausea, myelosuppression, neurotoxicity, lactic acidosis and pancreatitis</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate, Imipenem, Meropenem</td>
<td>As for bacterial infections</td>
<td>Amoxicillin/clavulanate – various formulations Meropenem – 500mg and 1g vials Imipenem – 250mg and 500mg vials</td>
<td>GI intolerance, hypersensitivity reactions, seizures, liver and renal dysfunction</td>
</tr>
<tr>
<td>High dose isoniazid</td>
<td>15-20mg/kg once daily</td>
<td>100mg tablets</td>
<td>Hepatitis, peripheral neuropathy</td>
</tr>
</tbody>
</table>
### APPENDIX VI: 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>Unlikely</td>
<td><strong>Nephrotoxicity with tenofovir</strong></td>
</tr>
</tbody>
</table>
| Fluoroquinolones              | Buffered didanosine may reduce oral absorption of all fluoroquinolones | **Psychiatric symptoms with efavirenz**  
**Hepatitis with nevirapine, efavirenz or protease inhibitors**  
**Prolongation QT interval with protease inhibitors and efavirenz** |
| Ethionamide/Prothionamide     | Unknown                      | **Peripheral neuropathy with stavudine or didanosine**  
**Psychiatric symptoms with efavirenz**  
**Hepatitis with nevirapine, efavirenz or protease inhibitors**  
**GI intolerance with zidovudine or protease inhibitors** |
| Cycloserine/Terizidone        | Renally cleared so interactions unlikely  
Nephrotoxicity caused by tenofovir could affect serum concentrations | **Peripheral neuropathy with stavudine or didanosine**  
**Psychiatric symptoms with efavirenz**  
**Stevens Johnson Syndrome with nevirapine and efavirenz** |
| PAS                           | Unlikely                     | **Hepatitis with nevirapine, efavirenz or protease inhibitors**  
**GI intolerance with zidovudine or protease inhibitors** |
| Clofazimine                   | May increase etravirine and protease inhibitor concentrations | **GI intolerance with zidovudine or protease inhibitors** |
| Linezolid                     | Unlikely                     | **Peripheral neuropathy with stavudine or didanosine**  
**GI intolerance with zidovudine or protease inhibitors**  
**Lactic acidosis with stavudine, didanosine or zidovudine**  
**Bone marrow toxicity with zidovudine** |
| Amoxicillin/Imipenem/Meropenem with clavulanic acid | Unlikely                     | **Nephrotoxicity with tenofovir** |
| Thiacetazone                  | Not advised in HIV-infected patients due to risk of Stevens-Johnson Syndrome | Not advised in HIV-infected patients due to risk of Stevens-Johnson Syndrome |
## APPENDIX VII: SUPPLEMENTAL TOXICITY TABLE FOR GRADING ELECTROCARDIOGRAM CHANGES AND POSSIBLE SYMPTOMS RELATED TO CARDIAC CONDUCTION ABNORMALITIES

<table>
<thead>
<tr>
<th>ECG Criteria: corrected QTcF interval</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note: QT corrected based on Frederica method (QTcF=QT/cubed root of RR interval).</td>
<td>QTcF ≥460msec, but &lt;480msec</td>
<td>QTcF ≥480msec, but &lt;500msec</td>
<td>QTcF ≥500msec OR QTcF &gt; 60 msec greater than baseline AND QTcF ≥480 ms</td>
<td>Life-threatening consequences (Torsades de pointes, other serious ventricular dysrhythmias)</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 - with evidence of ventricular tachycardia*:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td>⇒ syncope</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td>⇒ chest pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td>⇒ palpitations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td>⇒ dizziness</td>
<td></td>
</tr>
</tbody>
</table>

* Note that the presence of Ventricular Tachycardia (VT) is the adverse outcome to be avoided/identified; the symptoms are surrogates for “possible” VT, but if VT is demonstrated, then DLM is permanently discontinued irrespective of QTcF or symptoms. Refer to Appendix X for Toxicity Management.
APPENDIX VIII: 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 4.2.6 and serial ECGs.

Normal Heart Rate Ranges by Age (66)

<table>
<thead>
<tr>
<th>Participant’s Age</th>
<th>0 to &lt;3 Months</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>94-179</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>149**</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.
**This mean reflects age 7 days to 3 months
## APPENDIX IX: 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 DLM</td>
<td>Repeat ECG and clinical evaluation of symptoms within 72 hours</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue DLM</td>
<td>Repeat ECG and clinical evaluation of symptoms within 48 hours</td>
</tr>
<tr>
<td>Grade 3 (ECG Criteria)</td>
<td>Hold Fluoroquinolone (FQ) and DLM</td>
<td>If repeat ECG and clinical evaluation of symptoms within 72 hours continues to show Grade 3, hold the FQ and stop study drug (= Grade 4). Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the CMC and indicate in the email subject line: “Grade 3 ECG.”</td>
</tr>
<tr>
<td>Grade 3/4 (Cardiac Clinical Criteria)</td>
<td>Hold FQ and Permanently discontinue DLM</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the CMC and indicate in the email subject line: “Grade 3/4 Cardiac.”</td>
</tr>
<tr>
<td>Grade 4 (ECG)</td>
<td>Hold FQ and Permanently discontinue DLM</td>
<td>Check K+, Mg +2 and Ca +2 (corrected for albumin) and correct as necessary. Contact the CMC and indicate in the email subject line: “Grade 4 ECG.”</td>
</tr>
</tbody>
</table>

Note: STUDY DRUG USE for Cardiac Clinical Criteria meeting Grade 3 or Grade 4 are equivalent – that is permanently discontinue DLM.
## APPENDIX IX, continued

**Toxicity Management of Specific Toxicities: Hepatotoxicity**

<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 DLM</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue DLM</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, DLM should be permanently discontinued.</td>
<td>Contact the CMC.</td>
</tr>
<tr>
<td>Grade 3 – confirmation pending</td>
<td>Hold DLM while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming DLM will be unsafe and so elects to permanently discontinue.</td>
<td></td>
</tr>
<tr>
<td>Grade 3 – confirmed; presumed unrelated</td>
<td>Hold DLM</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 CMC.</td>
</tr>
<tr>
<td>Grade 3 – confirmed; presumed related</td>
<td>Permanently discontinue DLM</td>
<td>Contact the CMC.</td>
</tr>
<tr>
<td>Grade 4 – regardless of relationship</td>
<td>Permanently discontinue DLM</td>
<td>Participants should be monitored closely with more frequent visits until resolution to &lt; Grade 2. Contact the CMC.</td>
</tr>
<tr>
<td>SEVERITY</td>
<td>STUDY DRUG USE</td>
<td>FOLLOW-UP AND MANAGEMENT</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Continue DLM</td>
<td>Participants should be followed until resolution.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue DLM</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, DLM should be discontinued.</td>
<td>Contact the CMC.</td>
</tr>
<tr>
<td>Grades 3 and 4</td>
<td>Step 1: Continue DLM and temporarily discontinue one or more suspected other background MDR-TB drugs 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, DLM should be discontinued.</td>
<td>Following discontinuation of DLM, 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 CMC upon determination of Grade 3 or 4 toxicity.</td>
</tr>
</tbody>
</table>
# APPENDIX X: 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 DLM</td>
<td>Routine monitoring</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue DLM</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 DLM while awaiting confirmation of Grade 3 toxicity unless clinician believes that resuming DLM will be unsafe and so elects to permanently discontinue.</td>
<td>Contact the CMC upon determination of any Grade 3 or 4 toxicity. Indicate in the email subject line IMPAACT 2005, grade and type of toxicity.</td>
</tr>
<tr>
<td>Grade 3 – confirmed and presumed not related to DLM.</td>
<td>Hold DLM while awaiting results of evaluations.</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 CMC upon confirmation of Grade 3 toxicity. Indicate in the email subject line: IMPAACT 2005 Grade 3 and specify the toxicity.</td>
</tr>
<tr>
<td>Grade 3 – confirmed and presumed related to DLM.</td>
<td>Permanently discontinue DLM</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 CMC upon confirmation of Grade 3 toxicity. Indicate in the email subject line: IMPAACT 2005 Grade 3 and specify the toxicity.</td>
</tr>
<tr>
<td>Grade 4 and presumed related to DLM</td>
<td>Permanently discontinue DLM</td>
<td>Participants should be monitored closely with more frequent visits until resolution to &lt; Grade 2. Contact the CMC upon determination of Grade 4 toxicity. Indicate in the email subject line: IMPAACT 2005 Grade 4 and specify the toxicity.</td>
</tr>
</tbody>
</table>