A PHASE I/II, OPEN-LABEL, SINGLE ARM STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF BEDAQUILINE (BDQ) IN COMBINATION WITH OPTIMIZED INDIVIDUALIZED MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) THERAPY IN HIV-INFECTED AND HIV-UNINFECTED INFANTS, CHILDREN AND ADOLESCENTS WITH MDR-TB DISEASE

ANNEKE C. HESSELING
PROTOCOL CHAIR
DIRECTOR: DESMOND TUTU TB CENTRE, STELLENBOSCH UNIVERSITY
Highest MDR TB Burden in India, China and Russian Federation

WHO Global TB Report 2015
Low Treatment Success and High Mortality

**MDR TB:** 50% treatment success, 16% death  
**XDR TB:** 24% treatment success, 30% death

WHO Global TB Report 2015
Treatment outcome in children with MDR-TB (N=149)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N = 149 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>36 (24.2)</td>
</tr>
<tr>
<td>Probable cure*</td>
<td>101 (67.8)</td>
</tr>
<tr>
<td>Transferred out</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>8 (5.4)</td>
</tr>
<tr>
<td>Died</td>
<td>3 (2.0)</td>
</tr>
</tbody>
</table>

Includes 8 patients who stopped their therapy before indicated but were clinically well at follow up

*Seddon, Thorax, 2013*
Age related TB disease risk

Disease Progression (Percent)

Age in Years

<1  1to2  2to5  5to10  10to15

PTB
Disseminated

Marais et al. Int J Tuberc Lung Dis. 2004
Treatment of MDR-TB in HIV-uninfected and infected children could be dramatically improved with new, effective and safer drugs, with the goal of shortening MDR-TB therapy using injectable sparing regimens.

There is a high prevalence of HIV infection in children with MDR-TB international settings, which complicates treatment. Evaluations of novel TB drugs therefore must include HIV-infected children.

Bedaquiline (BDQ) was recently licensed for use in adults with MDR-TB but no data available in children.

Dramatic reduction in mortality in adults with MDR, preXDR and XDR TB on BDQ

It is important to determine the appropriate dose of BDQ, its safety and PK profiles in HIV-uninfected and infected infants, children and adolescents treated for MDR-TB
In HIV-infected and HIV-uninfected infants, children and adolescents receiving BDQ plus optimized background regimens (OBR) for MDR-TB:

- To determine the BDQ doses that achieve similar weekly exposure (area under the curve; AUC) of BDQ compared to adults taking BDQ at the standard recommended dose
- To evaluate the safety and tolerability of BDQ over 24 weeks from the initiation of study treatment
SECONDARY OBJECTIVES

- To evaluate the PK of BDQ over the 24-week dosing period, by HIV status
- To describe the long-term safety and tolerability of BDQ over a 120-week (30-month) total follow-up period, by HIV status
- To describe BDQ concentrations following BDQ treatment discontinuation at 24 weeks, from study Weeks 24 to 120, by HIV status
- To describe the MDR-TB treatment response up to 120 weeks from the initiation of the study, by HIV status
TERTIARY OBJECTIVE

- To explore longitudinal biomarkers of tuberculosis treatment response in children treated for MDR-TB
Is it reasonable to assume that children, when compared to adults, have a similar (1) disease progression and (2) response to intervention?

No to either  

Yes to both

Is it reasonable to assume a similar ER in children when compared to adults?

No

Yes

Is there a PD measurement that can be used to predict efficacy in children?

No

Yes

Conduct (1) PK studies in children aimed at achieving drug levels similar to those for adults then (2) safety trials at the proper dose.

Conduct PK studies to establish dosing, and then safety and efficacy trials in children.

Conduct (1) PK/PD studies to establish an ER in children for the PD measurement, (2) PK studies to achieve target concentrations based on ER, then (3) safety trials at the proper dose.
Table 2. Adverse Events during 120 Weeks in the Intention-to-Treat Population.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bedaquiline (N = 79)</th>
<th>Placebo (N = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median duration of overall treatment phase (range) — wk</td>
<td>91.7 (2.0–120.0)</td>
<td>94.1 (2.0–137.3)</td>
</tr>
<tr>
<td>Adverse event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>78 (99)</td>
<td>79 (98)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>55 (70)</td>
<td>56 (69)</td>
</tr>
<tr>
<td>Grade 3 or 4†</td>
<td>34 (43)</td>
<td>29 (36)</td>
</tr>
<tr>
<td>Leading to discontinuation of treatment</td>
<td>4 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Serious adverse events — no. (%)‡</td>
<td>18 (23)</td>
<td>15 (19)</td>
</tr>
<tr>
<td>Adverse event occurring in ≥20% of patients — no. (%)</td>
<td>32 (41)</td>
<td>30 (37)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (37)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23 (29)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>23 (29)</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Headache</td>
<td>20 (25)</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16 (20)</td>
<td>14 (17)</td>
</tr>
</tbody>
</table>

Diacon, NEJM, 2015
Enrollment of (HIV- and HIV +) participants commences with subjects combined across both weight bands. Enrollment into cohort paused once group (N=6 participants) completes Week 2 evaluation and up to 3 additional participants are accrued.

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

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

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

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

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

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

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

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

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

Open Cohorts 2 and 3 in parallel using groups of N=6 per cohort.
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Age and Weight</th>
<th>BDQ Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 up to 24 participants to achieve 18 evaluable (nine in each weight band)</td>
<td>≥ 6 to &lt; 18 years ≥30 kg</td>
<td>400 mg once per day for two weeks then 200 mg three times per week for 22 weeks</td>
</tr>
<tr>
<td></td>
<td>≥ 6 to &lt; 18 years ≥15 to &lt;30 kg</td>
<td>200 mg once per day for two weeks then 100 mg three times per week for 22 weeks</td>
</tr>
<tr>
<td>Cohort 2 up to 24 participants to achieve 18 evaluable</td>
<td>≥ 2 to &lt; 6 years ≥7 kg</td>
<td>Calculated using model-based dose selection</td>
</tr>
<tr>
<td>Cohort 3 up to 24 participants to achieve 18 evaluable</td>
<td>≥ 0 to &lt; 2 years ≥3 kg</td>
<td>Calculated using model-based dose selection</td>
</tr>
</tbody>
</table>
Current study status


- Projected Open to Accrual: Late March/Early April 2017

- Projected First Participant Enrolled: May 2017

- Under FDA IND
Participating sites

GHESKIO, Haiti

BJMC, India

Matlosana, Sizwe, DTTC, South Africa
The study drug, BDQ (in dissolved adult formulation), will be given in combination with individualized OBR MDR-TB medications, for 24 weeks. For HIV-infected participants, BDQ will be given in combination with an acceptable ARV therapy regimen initiated at least 2 weeks prior to enrollment. Long-term follow-up for final treatment outcome and vitality status.
**Study Duration**

- **30-day screening window**
- **2 wks daily BDQ**
- **22 wks thrice-weekly BDQ**
- **96 wks follow-up post-BDQ**

- **Enrollment**
  - Wk 1 sparse PK
  - Wk 2 intensive PK
  - Sparse PK
DESIGN: Modified Age-de-escalation approach

- The oldest age group (Cohort 1) will accrue first, and will proceed to simultaneous accrual of the two younger age groups
- Cohort 2 and Cohort 3 will open at the same time if formal PK targets and safety criteria have been met in Cohort 1
Sample Size

- Up to 72 participants will be enrolled to achieve at least 54 evaluable participants
  - Cohort 1: ≥ 6 to < 18 years of age at enrollment (Balanced by weight: ≥ 15 to < 30 kg AND ≥ 30 kg)
  - Cohort 2: ≥ 2 to < 6 years of age at enrollment
  - Cohort 3: ≥ 0 to < 2 years of age at enrollment
- All evaluations to be done in groups of 6
- In each cohort, at least six participants will be HIV-infected
Inclusion Criterion 4.1.2

Age at enrollment:

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

- **Cohort 1**: At least 15 kg
- **Cohort 2**: At least 7 kg
- **Cohort 3**: At least 3 kg
Criterion 4.1.4

Documented HIV status as defined in

Section 4.3.1
(for HIV-infected participants)

OR

Section 4.3.2
(for HIV-uninfected participants)
Either confirmed or probable MDR-TB:
Confirmed intra-thoracic (pulmonary) MDR-TB, with or without one of the following forms of extrathoracic TB:
- Peripheral TB lymphadenitis
- Pleural effusion or fibrotic pleural lesions
- Stage 1 TB meningitis
- Miliary and abdominal TB
- Other non-disseminated forms of TB disease
The following will be also be included:

- Rifampin mono-resistant TB (RMR-TB, routinely treated as MDR-TB), or where additional INH resistance has not been confirmed
- Pre-XDR (MDR plus resistance to either a fluoroquinolone or a second-line injectable agent)
- XDR-TB disease will be included,

Note: RMR-TB, MDR-TB, pre-XDR-TB and XDR-TB are therefore collectively referred to here as “MDR-TB,” for the purposes of the protocol.
Inclusion Criterion 4.1.5 (cont.)

Documentation of MDR-TB (including at least RMR-TB, MDR-TB including pre-XDR and XDR-TB) diagnosis, must be obtained, with confirmation of phenotypic, molecular or genotypic evidence of drug resistance, prior to enrollment.

OR
Probable [11] MDR-TB (or RMR, pre-XDR or XDR-TB): A presumptive diagnosis of MDR-TB based on well-documented clinical symptoms or signs of TB with radiological changes (in the case of intrathoracic TB), or extrathoracic disease manifestations described under 4.1.5, in combination with documented exposure to a confirmed MDR-TB source [2], [10] or with documented failure to respond to a first-line regimen, and where adherence was well documented. The clinical decision has been made to routinely treat for MDR-TB. A reasonable attempt should, however, have been made to attempt and document a bacteriological diagnosis.
Initiated on an OBR MDR-TB regimen as per routine treatment decision, at least two weeks but not more than 12 weeks prior to enrollment, and tolerating the regimen well at enrollment.
Inclusion Criterion 4.1.7

*If HIV-infected:*
Initiated an acceptable ART regimen (BDQ compatible) defined as either ZDV+3TC+ABC or NVP+2NRTIs at least two weeks prior to enrollment (switch post-24 weeks BDQ)
Inclusion Criterion 4.1.8, 9

• If male and engaging in sexual activity that could lead to pregnancy of the female partner:
• Agrees to use a barrier method of contraception (i.e., male condom) throughout the first 28 weeks on study (i.e., until four weeks after discontinuation of BDQ)
• If female and of reproductive potential, defined as having reached menarche and not having undergone a documented sterilization procedure (hysterectomy, bilateral oophorectomy, or salpingotomoy):
  • Negative pregnancy test at screening within 48 hours prior to enrollment
If female, of reproductive potential (defined as in 4.1.9), and engaging in sexual activity that could lead to pregnancy:
Agrees to avoid pregnancy and to use at least two of the following contraception methods throughout the entire period of study participation: condoms, diaphragm or cervical cap, IUCD, hormonal-based contraception. It is required that the method would have had to be initiated at the time of study entry.
Inclusion Criterion 4.1.11

Among **Cohort 3 participants**, no documentation that estimated gestational age at birth was less than 37 weeks. **Note:** Infants born to HIV-infected women will be eligible for enrollment in Cohort 3 regardless of feeding mode and receipt of ARVs for prevention of perinatal transmissions).
P1108: Summary of Key Exclusion Criteria
Exclusion Criterion 4.2.2

Known or presumed severe extrapulmonary manifestations of TB, including Grades 2 and 3 TB meningitis, and osteo-articular TB
Exclusion Criterion 4.2.3 and 4.2.4, 5

- Pregnant or lactating
- 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
- Mean QTcF interval of > 460 ms (mean value of QT interval, corrected using Fredericia correction, on ECG performed in triplicate)
Clinically relevant ECG changes including but not limited to:

- Pathological Q-waves (defined as $> 40$ ms or depth $> 0.4-0.5$ mV);
- Evidence of ventricular pre-excitation;
- Evidence of complete or incomplete left bundle branch block or right bundle branch block
- Evidence of second or third degree heart block;
- Intraventricular conduction delay with QRS duration $> 120$ ms
- Age-related bradycardia as defined by sinus rate less than lower limit as indicated in Appendix VII.
- Known personal or family history of long QT syndrome
Exclusion Criterion 4.2.8

Having a ≥ Grade 2 for any of the following abnormalities at the time of screening or known within 30 days prior to enrollment:

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

Note: Retesting and screening of the abnormalities listed above may be done as long as the screening period of 30 days is observed. The last/latest values will be used for purposes of final screening decisions.
Exclusion Criterion 4.2.9

Having participated in other clinical studies with investigational agents or devices, within eight weeks prior to enrollment
Exclusion Criterion 4.2.10

Currently taking any of the disallowed medications specified in Section 5.7. If taking any disallowed medications, a “washout period” of three days or more prior to Entry is required.
<table>
<thead>
<tr>
<th>Appendix I: Schedule of Evaluation for All Cohorts (1, 2 and 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
</tr>
<tr>
<td>Informed consent</td>
</tr>
<tr>
<td>Documentation of HIV status</td>
</tr>
<tr>
<td>History</td>
</tr>
<tr>
<td>Physical exam</td>
</tr>
<tr>
<td>Pill dispensing</td>
</tr>
<tr>
<td>Adherence assessment</td>
</tr>
<tr>
<td>TB disease status and severity</td>
</tr>
<tr>
<td>Tuberculin Skin Testing</td>
</tr>
<tr>
<td>ECG</td>
</tr>
<tr>
<td>CXR</td>
</tr>
<tr>
<td>Audiology</td>
</tr>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
</tr>
<tr>
<td>Hematology</td>
</tr>
<tr>
<td>Chemistries</td>
</tr>
<tr>
<td>LFT</td>
</tr>
<tr>
<td>TSH (FT4 if TSH is elevated)</td>
</tr>
<tr>
<td>Serum biomarkers (storage)</td>
</tr>
<tr>
<td>Cohort 1: lactate to local lab</td>
</tr>
<tr>
<td>Cohort 1: lactate/pyruvate</td>
</tr>
<tr>
<td>Pregnancy test</td>
</tr>
<tr>
<td>Specimens for TB micro lab</td>
</tr>
<tr>
<td>Urinalysis</td>
</tr>
<tr>
<td>Urine biomarker (storage)</td>
</tr>
<tr>
<td>Intensive PK</td>
</tr>
<tr>
<td>Sparse PK</td>
</tr>
<tr>
<td><strong>HIV-Infected only</strong></td>
</tr>
<tr>
<td>HIV-1 RNA PCR (viral load)</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUMES (higher volumes for HIV^+^)</strong></td>
</tr>
<tr>
<td>Cohort 1</td>
</tr>
<tr>
<td>Cohort 2</td>
</tr>
<tr>
<td>Cohort 3</td>
</tr>
</tbody>
</table>
### Appendix I (cont.): Schedule of Evaluation for All Cohorts (1, 2 and 3)

<table>
<thead>
<tr>
<th></th>
<th>Week 32 (8 wks post BDQ)</th>
<th>Week 40 (16 wks post BDQ)</th>
<th>Week 48 (24 wks post BDQ)</th>
<th>Week 60 (36 wks post BDQ)</th>
<th>Week 72 (48 wks post BDQ)</th>
<th>Week 96 (72 wks post BDQ)</th>
<th>Week 120/End of Study (96 wks post BDQ)</th>
<th>Unsched Visit</th>
<th>Early Study D/C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Documentation of HIV status(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical exam</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>TB treatment outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>CXR</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LABORATORY EVALUATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td></td>
</tr>
<tr>
<td>Chemistries</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td>2.0 mL</td>
<td></td>
</tr>
<tr>
<td>LFT</td>
<td>x</td>
<td>x</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>TSH (ft4 if TSH is elevated)</td>
<td>2.0mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum biomarkers (storage)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5-1.0mL</td>
</tr>
<tr>
<td><strong>Cohort 1: lactate</strong></td>
<td>lactate/pyruvate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort 1: lactate</strong></td>
<td>lactate/pyruvate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy test</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Specimens for TB micro lab</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Urine biomarkers (storage)</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sparse PK</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td>0.5-1.0mL</td>
<td></td>
</tr>
<tr>
<td><strong>HIV-Infected only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA PCR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0mL</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td></td>
<td></td>
<td>1.0 mL</td>
<td>1.0 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BLOOD VOLUMES (higher volumes for HIV+)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>6.0mL</td>
<td>8-9.0mL</td>
<td>5-9.0mL</td>
<td>4.0mL</td>
<td></td>
</tr>
<tr>
<td>Cohort 2</td>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>6-7.0mL</td>
<td>4.0mL</td>
<td>6.0mL</td>
<td>6.0mL</td>
<td>4-5.0mL</td>
<td>5-9.0mL</td>
<td></td>
</tr>
<tr>
<td>Cohort 3</td>
<td>5.5-6.5mL</td>
<td>3.5mL</td>
<td>5.5-6.5mL</td>
<td>3.5mL</td>
<td>5.5mL</td>
<td>5.5mL</td>
<td>3.5-4.5mL</td>
<td>4-8.0mL</td>
<td>3.5mL</td>
</tr>
</tbody>
</table>

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

\(^2\) If TST is not available at the site, IGRA may be done. This would require that an additional 3-4 mL of blood be collected at these time points.

\(^3\) If lactate is >3mmol/L, additional 2.0mL for repeat test will be necessary; refer to LPC and Appendix IX: Toxicity Management of Specific Toxicities: Lactate.
Clinical Assessments: History

- TB exposure history
- Symptoms of TB
- TB treatment history
- MDR-TB diagnosis
- Determination of reproductive potential
- Sexual activity and contraceptive use
- AEs and concomitant medications
Clinical Assessments: Physical Examination

- Respiratory
- Cardiovascular
- Other organ systems
- Height
- Weight
- Vital signs (temperature, blood pressure, pulse and respiratory rate)
Adherence

- **Routine TB drugs (all participants)**
  - In-hospital: Adherence to BDQ will be documented with pill counts and a TB dispensing card
  - Outpatient: Children may be treated on an ambulatory basis at local TB clinics and adherence assessment will be done by the site’s research team using a TB dispensing card and ARV treatment card (as relevant). Local models of care (e.g. community-based TB treatment supporter or other health care worker or a trained family member) may be used for adherence support for ambulatory care.

- **ARV drugs (HIV-infected participants only)**
TB disease spectrum and severity

- At least one respiratory specimen (expectorated sputum, induced sputum or gastric aspirate) will be collected (if indicated)
  - Sputum will be collected in older children
  - Induced sputum or gastric aspirates will be collected in children unable to expectorate sputum spontaneously, as per local standard of care
- See protocol Section 8.3 for more details
- Important that children have been appropriately investigated for confirmation of TB and DST
Laboratory Assessments: Blood

- CBC with differential and platelets
- Lactate, pyruvate (Cohort 1 only, see protocol Section 8.7 for more detail)
- Chemistries:
  - Creatinine, electrolytes (i.e., Na+, Cl, HCO₃, K+, Ca²⁺), albumin, and Mg ²⁺
  - ALT, AST, direct and total bilirubin
- TSH (and fT₄ if TSH is elevated)
- Pregnancy testing (urine or blood) *if female of reproductive potential*
- HIV testing, *if required documentation of HIV status is not available*
- Serum biomarkers (stored for future use)
Blood (for HIV-infected participants)

- HIV-1 RNA PCR
- Lymphocyte subsets (to include CD4/CD8 counts and percentages)
- HIV genotyping to follow (future version of protocol)
Laboratory Assessments: Urine

- Pregnancy testing (urine or blood) \textit{if female of reproductive potential}
- Urinanalysis (routine)
- Urine biomarkers (stored for future use)
Sputum/other clinical samples

- Collect for mycobacterial testing (confirmation possible in 40% of cases)
  - At least one other sputum/other sample (expectorated sputum, induced sputum or gastric aspirate) should be obtained
  - FNA/other samples as clinically indicated
ECG

- Obtain on study-specific ECG machine (see protocol Section 8.6 for more detail)
- Must be interpreted based on age-specific criteria
Chest X-Ray

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

- Baseline measures will be completed at Weeks 8, 16 and 24 on participants who have been started on injectable agent as part of the OBR (WHO shorter regimen contains minimum 4 months’ injectable)
PK Collections: Sparse

- Dosing of BDQ should be directly observed
- Dosing times of BDQ, OBR and ARVs before the PK sampling must be recorded for the previous day as well as the preceding day.
- Store residual PK sample
- Weeks 1, 4, 8, 12, 16, 20, 24, 32, 40, 48, 60, 72, 96, and 120
PK Collections: intensive

- Dosing of BDQ should be directly observed. The dosing times of BDQ, OBR and ARVs before the PK sampling must be recorded for the previous day as well as the preceding day.
- Sample at pre-dose and 2, 4, 6, and 8 hours post-dose
- Week 2
** See Section 3 of LPC

- Frequent shopping to UCT pharmacology lab (every group of 6 children who reach week 2 will trigger PK analysis of all available data)
- Core PK communication group to be set up
- Clear communication with UCT Lab manager critical: Jennifer Norman