IMPAACT P1108

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

A Study of the International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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

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DAIDS Study ID #11884
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Version 2.0
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 Council for Harmonisation Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____
Signature of Investigator of Record Date

_____
Name of Investigator of Record
(printed)

ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Amino Transferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Amino Transferase
ATS	American Thoracic Society
AUC	Area Under the Curve
BDQ	Bedaquiline
C_{avg}	Average plasma concentration
CBC	Complete Blood Count
CDC	United States Centers for Disease Control and Prevention
CFU	Colony-forming Units
CFR	Code of Federal Regulations
CFZ	Clofazimine
CI	Confidence Interval
Cl/F or CL	Clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
COVID-19	Coronavirus Disease 2019
CRMS	Clinical Research Management System
CRF	Case Report Form
CRPMC	Clinical Research Products Management Center
CS	Cycloserine
CYP3A	Cytochrome P450 Enzyme 3A
CXR	Chest X-Ray
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
D/C	Discontinuation
DLM	Delamanid
DMC	Data Management Center
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
DR-TB	Drug-Resistant Tuberculosis
DST	Drug Susceptibility Testing
DTG	Dolutegravir
EAE	Expedited Adverse Event
EBA	Early Bactericidal Activity
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFV	Efavirenz

EIA	Enzyme Immunoassay
EMA	European Medicines Agency
ERC	Endpoint Review Committee
ETH	Ethionamide
FDA	US Food and Drug Administration
fT4	Free Thyroxine
GCLP	Good Clinical Laboratory Practices
GCS	Glasgow Coma Scale
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICF	Informed Consent Form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Network
IND	Investigational New Drug
INH	Isoniazid
IoR	Investigator of Record
IQR	Interquartile Range
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
LFT	Liver Function Tests
LFX	Levofloxacin
LPC	Laboratory Processing Chart
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
LZD	Linezolid
M2	Bedaquiline Mono-desmethyl Metabolite
MDR-TB	Multidrug-Resistant Tuberculosis
MOP	Manual of Procedures
M.tb	Mycobacterium tuberculosis
MXF	Moxifloxacin
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PAS	Para-aminosalicylic acid
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PID	Participant Identification Number
PK	Pharmacokinetic
PRO	DAIDS Protocol Registration Office
PZA	Pyrazinamide
QTcF	Corrected QT interval by Fridericia
RIF	Rifampin
RMR-TB	Rifampin-mono-resistant Tuberculosis
RNA	Ribonucleic Acid
RR-TB	Rifampin-resistant Tuberculosis
RSC	Regulatory Support Center
RSR	Remote Source Review
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCORE	DAIDS Site Clinical Operations and Research Essentials Manual

SD	Standard Deviation
SDMC	Statistical and Data Management Center
SES	Study Enrollment System
SID	Study Identification Number
SMC	Study Monitoring Committee
SoE	Schedule of Evaluations
SOP	Standard Operating Procedure
TB	Tuberculosis
TBM	TB Meningitis
TIW	Three times per week
t_{max}	Time of maximum drug concentration
TSH	Thyroid Stimulating Hormone
TZD	Terizidone
US	United States
VQA	Virology Quality Assurance
VT	Ventricular Tachycardia
WB	Western Blot
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis

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SCHEMA

Purpose: To evaluate the pharmacokinetics (PK), safety, and tolerability of bedaquiline (BDQ) in infants, children, and adolescents.

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

Study Population: Infants, children, and adolescents routinely treated for clinically diagnosed or confirmed intra-thoracic (pulmonary) rifampin-resistant tuberculosis (RR-TB) and/or selected forms of extrathoracic RR-TB, who have received 1-12 weeks of routine RR-TB treatment prior to enrollment.

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

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

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

Study Duration: Approximately 6.5 years total. Accrual is expected to require approximately 4.5 years and participants will be followed for a minimum of 72 weeks after their last dose of BDQ (i.e., up to a total of 96 weeks of follow-up for each participant).

Study Treatment: BDQ given as part of an individualized RR-TB treatment regimen for 24 weeks. For participants living with HIV, BDQ will be given in combination with an acceptable antiretroviral (ARV) therapy regimen initiated at least two weeks prior to enrollment.

Cohort	Age and Weight	BDQ Dosing
Cohort 1 Up to 24 participants to achieve 18 evaluable (approximately nine in each weight band)	≥ 6 to < 18 years ≥30 kg	*Participants ≥30 kg:* 400 mg once per day through the intensive PK sampling visit*, then 200 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants >7 to <30 kg* 200 mg once per day through the intensive PK sampling visit*, then 100 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit *Participants ≥ 3 to ≤ 7 kg:* 100 mg once per day through the intensive PK sampling visit*, then 50 mg three times per week on Monday, Wednesday, and Friday through the Week 24 visit
	≥ 6 to < 18 years ≥15 to <30 kg	
Cohort 2 Up to 30 participants to achieve 18 evaluable	≥ 2 to < 6 years >7 kg	
Cohort 3 Up to 30 participants to achieve 18 evaluable	≥ 0 to < 2 years ≥3 kg	

*Intensive PK sampling will be performed at the Week 1 or Week 2 visit following receipt of at least 14 and no more than 17 BDQ daily doses, including any non-study BDQ doses taken prior to study entry.

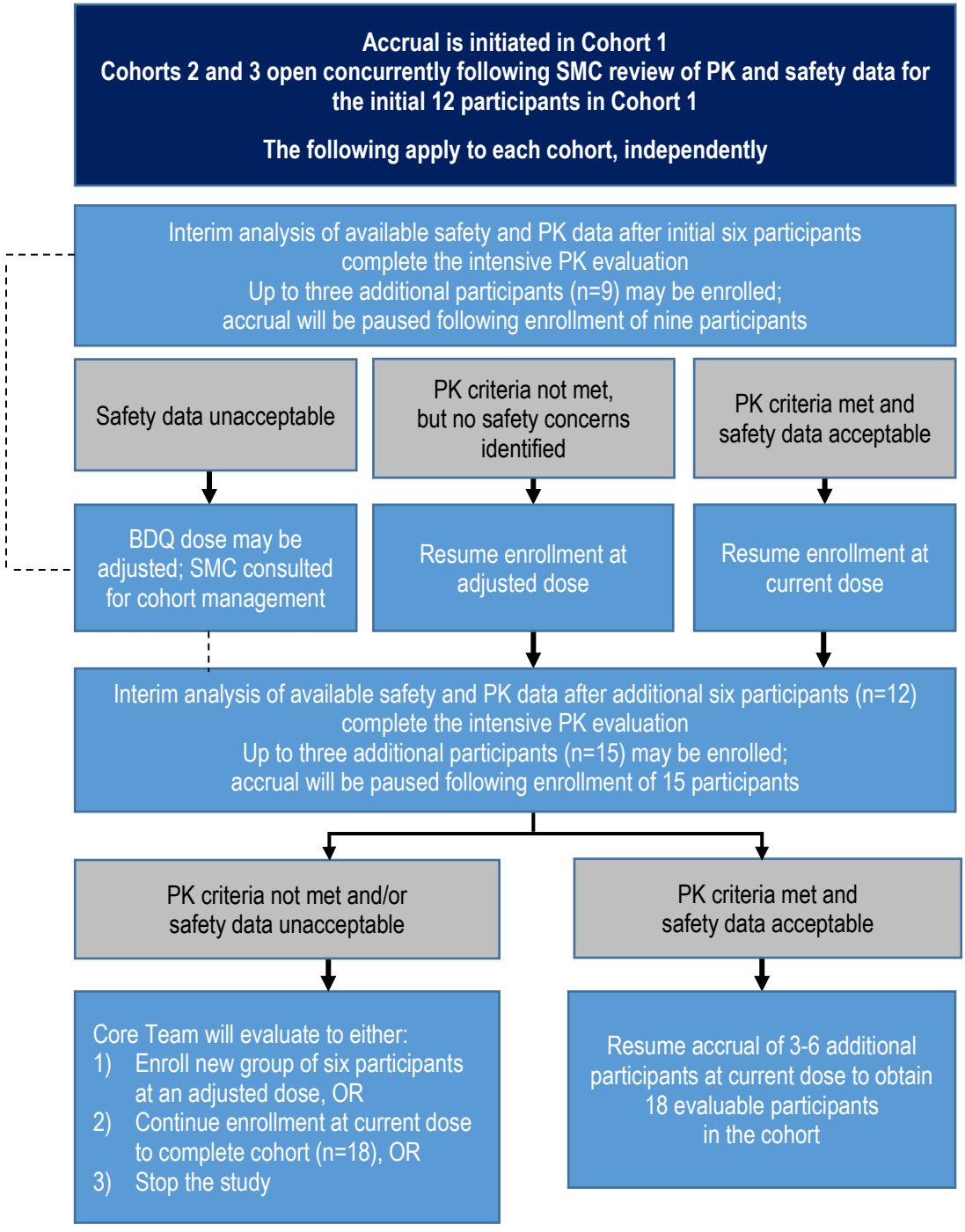
Primary Objectives

- Determine the BDQ doses that achieve similar weekly exposure (area under the curve (AUC)) of BDQ compared to adults taking BDQ at the current standard recommended dose.
- Evaluate the safety and tolerability of BDQ over a 24-week dosing period.

Secondary Objectives

- Evaluate the PK of BDQ over the 24-week dosing period, by HIV status.
- Describe the long-term safety and tolerability of BDQ over a 96-week total follow-up period, by HIV status.
- Describe BDQ concentrations following BDQ discontinuation and through 72 weeks after BDQ discontinuation, by HIV status.
- Describe the RR-TB treatment response up to 96 weeks from initiation of the study, by HIV status.

Figure 1
Overview of Study Design



1 INTRODUCTION

1.1 Background

Global epidemiology of tuberculosis
Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* (*M.tb*), which most commonly affects the lungs, but often spreads to other organs. In 2020, there were approximately 10 million incident TB cases globally (1). Surveillance for pediatric TB has traditionally been limited and case detection poor due to the paucibacillary nature of disease in children (less than 10% of pulmonary TB in young children is smear-positive); inability to cough and expectorate on demand in younger children; and limited programmatic focus. Per the World Health Organization (WHO) 2022 Consolidated Guidelines on Tuberculosis, approximately 1.1 million children and young adolescents (below 15 years of age) develop TB every year (2). Developing countries have the highest pediatric TB burden with more than 75% of cases occurring in 22 high-burden TB countries (3). Human immunodeficiency virus (HIV) contributes significantly to pediatric TB disease burden and excess mortality (4).

Epidemiology of drug-resistant TB (DR-TB)
Rifampin-resistant tuberculosis (RR-TB), defined as *M.tb* resistant to at least rifampin (RIF), is a threat to global public health. RR-TB includes multidrug-resistant (MDR)-TB, defined as *M.tb* resistant to both isoniazid (INH) and RIF; RIF mono-resistant (RMR)-TB, defined as *M. tb* resistant to RIF but susceptible to INH; pre-extensively drug-resistant (pre-XDR)-TB defined by resistance to INH and RIF and a fluoroquinolone; and extensively drug-resistant (XDR)-TB, defined by resistance to INH, RIF, a fluoroquinolone (levofloxacin (LFX), moxifloxacin (MXF)) and one other Group A drug (bedaquiline (BDQ) or linezolid (LZD)). Collectively, these are defined as RR-TB in protocol Version 2.0 for this study and as specified in inclusion criterion 4.1.5. There remains a high global burden of RR-TB with an estimated 465,000 incident cases occurring in 2019, 78% of which are MDR-TB (3, 5). The WHO has not formally reported on the burden of RR-TB in children; however, current model-based estimates suggest that at least 25,000 to 32,000 new cases of MDR-TB occur in children 0-14 years of age each year globally (6, 7). Presently, there are no estimates for the burden of RR-TB in adolescents, a group with high risk of HIV acquisition and poor TB treatment outcomes.

The challenges of identifying and appropriately treating TB in children are compounded by the increasing rates of RR-TB globally. Adults with RR-TB often experience prolonged diagnostic delay, resulting in transmission of these strains to children. Until recently, detection of drug resistance required mycobacterial culture and drug susceptibility testing; recent advances including rapid and highly accurate molecular tools such as Xpert MTB/RIF Ultra (8, 9) promise to increase the number of RR-TB cases detected and reduce diagnostic delay. RR-TB in children is usually transmitted from a source case rather than developed from drug-susceptible TB. TB in children is usually paucibacillary and often culture-negative, with a lower risk for acquired drug resistance (10).

Burden of Pediatric RR-TB
There are limited representative surveillance data on DR-TB in children. A prevalence study from Cape Town, South Africa, was completed to assess the burden of pediatric RR-TB in conjunction with HIV disease between March 2013 and February 2017. Drug susceptibility testing (DST) for INH and RIF was completed on initial isolates from each child less than 13 years old with culture-confirmed TB; isolates resistant to INH and RIF were tested for resistance to fluoroquinolones and second-line injectable agents. The study enrolled 587 culture-confirmed children, with a median age of 34 months (interquartile range (IQR) 14-79 months). DST was

available in all (100%): 78 (13.3%) of strains had INH or RIF resistance; 18 (3.1%) were INH mono-resistant; 13 (2.2%) were RIF mono-resistant; and 47 (8.0%) were resistant to both INH and RIF (MDR). Therefore 60 (10.2%) were RR-TB cases. Ofloxacin resistance was present in 15/47 (31.9%) of MDR-TB isolates, and nine of 47 (19.1%) isolates were resistant to amikacin (7 of 47 were XDR-TB). The overall prevalence of HIV disease was 74/573 tested (12.9%) (11). In 2008, data from Johannesburg, South Africa, indicated a high overall prevalence of MDR-TB in children under 14 years with a prevalence of INH-resistance of 14.2% (N=21) (95% CI, 9.0-20.9%) and MDR-TB prevalence of 8.8% (N=13) (95% CI, 4.8-14.6%). The majority (53.9%) of children with MDR-TB were also living with HIV (12). However, vertical transmission of HIV is rapidly declining globally, with less than 3% of infants in South Africa born with HIV; therefore, lower HIV prevalence in children with MDR-TB is likely.

As new rapid and more accurate molecular tools endorsed by the WHO are rolled out and widely implemented in children located in high-TB burden settings, the number of all RR-TB and pediatric RR-TB cases is likely to increase significantly. This increase will be due to more cases clinically diagnosed in children with documented exposure to RR-TB or confirmed RR-TB.

Management and treatment outcomes of RR-TB in children
RR-TB in children is frequently associated with delays in diagnosis and treatment, and there are multiple challenges in the diagnosis, including the inability to produce spontaneous sputum samples in young children and the paucibacillary nature of TB in most children. At most, 10-15% of children with pulmonary TB are sputum smear-positive and approximately 30% culture-positive (13) and of these approximately 66% positive by Xpert. In the absence of bacteriologic confirmation, the majority of children are treated empirically and presumptively for RR-TB, either based on history of exposure to an adult with DR-TB together with symptoms suggestive of TB in the child or based on poor response to first-line treatment (14). In a study of children less than 15 years of age with culture-positive MDR-TB, the median time to MDR-TB treatment initiation (N = 102) was significantly shorter in the presence of a known adult MDR-TB index case (15). These data indicate the importance of adult contact information in addition to bacteriological ascertainment in the appropriate management of children with RR-TB.

In general, antituberculosis therapy is given as directly observed therapy (DOT) for the duration of outpatient treatment (ambulatory care), with hospitalization depending on the severity of disease, social considerations, and local standard of care. If admitted to a hospital, children are typically discharged to continue their TB treatment at their local TB clinic. Treatment is typically continued for at least nine months following the first negative culture in the case of bacteriologically confirmed cases, and children with more extensive drug resistance may be treated for longer periods. Children with clinically diagnosed TB that is not bacteriologically confirmed may be treated for a shorter duration, generally 9-12 months, depending on the severity of disease and treatment response (16).

In contrast to adults with RR-TB, outcomes among children treated for RR-TB are generally good. A 2015 systematic review and individual patient data meta-analysis including 975 children with MDR-TB (75% bacteriologically confirmed, 37% living with HIV) found that 78% were successfully treated. Severe TB, HIV, and malnutrition were associated with poor treatment outcomes and higher risk of death (17). Despite these good outcomes, RR-TB treatment for children remains lengthy and complex with frequent toxicities. The WHO's Guideline Development Group meeting in July 2018 resulted in important changes to TB treatment recommendations. Drug groupings were substantially revised, with MXF, LFX, BDQ, and LZD included in the highest priority (Group A) drugs for constructing RR-TB regimens, and injectable drugs moved down in priority (21). WHO guidelines now recommend that injectable agents in

children be used only when all-oral treatment options are not possible (see Appendix IIB) (18). Both the WHO shorter 9-11 months RR/MDR-TB treatment regimen and longer individualized (all-oral) regimens can now be used in children of all ages, as both BDQ and delamanid (DLM) have been conditionally recommended by the WHO in children of all ages (2, 22).

BDQ, developed by Janssen, is a diarylquinoline compound with a novel mechanism of action against *M.tb*: the inhibition of mycobacterial adenosine triphosphate synthase. BDQ was licensed by the United States (US) Food and Drug Administration (FDA) in 2012 and the European Medicines Agency (EMA) in 2014. It is widely recommended for use in adults and older children with RR-TB by the WHO, based on strong evidence of improved treatment outcomes and reduced mortality in adults and adolescents with RR-TB (23). BDQ is a WHO class A drug for the treatment of RR-TB, indicating its current and future importance in RR-TB treatment regimens. The FDA approved a 20 mg pediatric formulation of BDQ as part of combination therapy in the treatment of children (five years and older and weighing at least 15 kg) with pulmonary MDR-TB based on data from 30 children without HIV five to less than 18 years old (24). The WHO recommends the 20 mg and the 100 mg BDQ tablets as part of routine care in children with RR-TB down to age six years. As of March 2022, the WHO has also conditionally recommended the use of BDQ in children with MDR/RR-TB below six years of age, based on preliminary data from 12 children in P1108; however, further data on dosing and safety are needed (2, 18, 25). BDQ is licensed and available in several countries.

In settings where there is a high burden of RR-TB and extensive experience in the management of pediatric RR-TB, treatment is based on international recommendations and the available literature (26) and locally available drugs. High-dose (15-20 mg/kg) INH is used in many cases, as there is evidence that resistance due to *inhA* promoter region mutations usually confer low-level INH resistance (27). A recent early bactericidal activity (EBA) study in adults confirmed that high-dose INH has a similar good EBA in INH-resistant patients with an *inhA* mutation conferring INH resistance when compared with normal-dose INH in INH-susceptible cases (28). If no other treatment option is available, an injectable drug (amikacin) could be used for four to six months rather than for the duration of therapy to limit potential toxicity. LFX is the fluoroquinolone generally prescribed to young children less than eight years of age, as MXF (available in 400 mg tablets), the drug of choice for older children and adults, has a bitter taste and is unpalatable as a crushed formulation with most currently available formulations.

In this study, participants will receive BDQ as part of an individualized RR-TB treatment regimen as recommended by WHO and at doses selected based on formal protocol-defined PK target ranges and safety criteria. Given that LFX shows a lower risk for QT prolongation than MXF and BDQ can increase the risk for QT prolongation, LFX is the preferred fluoroquinolone for P1108 participants and in general for patients receiving BDQ, especially when given in combination with other QT-prolonging drugs like clofazimine (CFZ). To ensure that (in addition to BDQ) there are at least four effective drugs in the regimen, other background TB drugs may include the following: LFX, CFZ, ethionamide (ETH), para-aminosalicylic acid (PAS), cycloserine/terizidone (CS/TZD), high dose INH, or LZD, depending on the drug resistance pattern, local standard of care, and available drugs. DLM may only be administered in P1108 participants with prior approval from the P1108 Core Team (see Section 5.7). Pretomanid is not recommend in children given insufficient pediatric PK and safety data.

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

Hypothyroidism is frequently reported in children treated for RR-TB receiving a regimen containing ETH and/or PAS (29). Clinical data, serum thyroid stimulating hormone (TSH), and free thyroxine (fT4) levels, completed as standard of care, were retrospectively assessed in 137 South Africa children receiving antituberculosis treatment including ETH. Abnormal thyroid function tests were recorded in 79 (58%) children and were specifically high among children on regimens including PAS and in children living with HIV (29).

Vomiting and nausea are frequently reported in children receiving second-line TB therapy. In 44 children treated for MDR-TB disease receiving a regimen that included ETH, the most common adverse effect was vomiting, which occurred in 14 (32%) (30). Adverse effects may be more frequent in children treated for pre-XDR or XDR-TB, although published data are currently limited.

In summary, adverse effects including hearing impairment, hypothyroidism, nausea, and vomiting are frequently reported in children receiving routine second-line antituberculosis drugs for the treatment of RR-TB and are thus expected and unavoidable in children receiving any new drug, including BDQ, as part of RR-TB treatment. Potential BDQ side effects, including QTc-prolonging effect, are addressed in Section 13.5. The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1108 study will fill a key gap in providing definitive dosing and safety data of BDQ in children with RR-TB across the age spectrum, which will inform the evaluation of future child-friendly treatment regimens. Given the use of newer drug regimens in P1108, adverse events (AEs) which merit specific evaluation are QTc interval prolongation (BDQ, fluoroquinolones, CFZ); peripheral neuropathy; myelosuppression; vision loss (LZD); and arthralgia/arthritis (fluoroquinolones).

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 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 will facilitate their inclusion and assessment during treatment in much-needed treatment shortening trials, especially for RR-TB, where treatment regimens are currently still 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 (PK) sampling, and post-treatment follow-up in children living with and without HIV with different RR-TB disease spectrum will allow for robust evaluation of candidate biomarkers for TB treatment response in the future. These will contribute towards informing future trials on shorter treatment durations for RR-TB. The P1108 study will include serial clinical, radiological, and bacteriological evaluation and long-term follow-up, providing an ideal platform to test promising biomarkers of TB treatment response. Proposed biomarker work to evaluate TB treatment response in children in P1108 includes work on serum proteomic markers which have shown promise in adult treatment cohorts. This work includes sampling approaches

using minimal volumes and coinciding with sampling for other study evaluations. This additional work will pose minimal burden on participants while yielding potentially useful data on methods for objective TB treatment response measurement in children with RR-TB.

Effect of HIV on the management of RR-TB
In children with a new diagnosis of HIV, antiretroviral (ARV) treatment is typically started rapidly (usually within one to four weeks after the initiation of RR-TB treatment), given the high mortality of children with HIV and TB and RR-TB (12, 15). All children with TB and HIV therefore require rapid initiation of antiretroviral therapy (ART) as per WHO guidelines (31).

Children living with HIV and RR-TB complicate the management of TB owing to potential drug interactions and overlapping toxicities. There are limited data on the impact of the second-line TB drugs on the PK of commonly used ARVs like lopinavir/ritonavir (LPV/r) or efavirenz (EFV) or the effects of ARVs on PK of second-line TB drugs, but clinically important drug interactions are not predicted with most current second-line TB drugs. However, BDQ is metabolized by cytochrome P450 enzyme 3A (CYP3A), and BDQ concentrations are predicted to be significantly reduced by EFV based on data from adult trials; therefore, EFV cannot be used with BDQ. BDQ concentrations are also increased by LPV/r and are not affected by nevirapine (NVP). The therapeutic margin for BDQ is not well defined, so it is unclear what the clinical effects of reduced or increased BDQ concentrations will be. With LPV/r, both BDQ and BDQ mono-desmethyl metabolite (M2) concentrations are increased, but the combination is allowed for use in routine care (32-34) (see Section 1.2). Dolutegravir (DTG) and other integrase inhibitors can be used with BDQ given the lack of significant drug-drug interactions observed to date (35, 36).

Need for pediatric RR-TB PK data and appropriate formulations
Child-friendly formulations, although critically needed, are not routinely available for all second-line TB drugs. Several gaps remain in PK knowledge of second-line TB drugs in children and the effects of age and HIV diagnosis/treatment on TB drug PK. For most first-line TB drugs, exposures in children are lower than in adults, even when given the same mg/kg body weight dosages (37-40). HIV diagnosis/treatment (41), nutritional status (42), and genetic profile (38, 43) also impact drug disposition. While Phase III trials for the treatment of TB disease in children (with paucibacillary disease) are not required once efficacy has been established in adults (44), timely evaluation to establish appropriate dosing needed to achieve adult-equivalent exposures and ensure drug safety in children of different ages with and without HIV is critical to ensure access to improved treatments to children, along with formulation development work in parallel. There is a need for high-quality formulations that are child-friendly and operationally feasible to give by TB programs. Suspensions generally do not deliver accurate dosing and have variable shelf life. Dispersible tablets, ideally scored, are more suitable pediatric formulations. In this study, site investigators have access to the adult 100 mg BDQ formulation, which is dissolvable, and a novel scored dispersible 20 mg pediatric formulation (Janssen) option for participants in Cohorts 2 and 3. The BDQ 20 mg formulation has been shown to be bio-equivalent to the adult formulation in healthy adult volunteers (i.e., there is not a formulation effect) (24, 45).

Both the 100 mg adult formulation and the 20 mg pediatric BDQ formulations can be given to children, including children living with HIV, provided that these formulations are available. The BDQ 100 mg formulation is FDA-approved and licensed in many countries. The BDQ 20 mg pediatric formulation (for use in much younger children only, i.e., who cannot swallow a tablet), by Janssen is available for evaluation in children and was approved by the FDA in 2020 for use in children five years and older weighing at least 15 kg. This new 20 mg formulation can be acquired by countries that use the Global Drug Facility for procurement. Until further research is conducted, there is a risk that BDQ will be used off-label without the much-needed safety and PK

data in children, including in children living with HIV who are at risk of more severe RR-TB, poorer nutrition, and poorer TB treatment outcomes.

Most other second-line TB drugs currently used for the treatment of RR-TB in children, except for DLM, are only available in adult formulations and are routinely used in children of all ages, including in younger children and infants (where they are routinely crushed and given with liquids). The currently licensed 100 mg BDQ tablet is palatable, is easily breakable, and crushable. The tablet is not film-coated, is not a delayed-released tablet, and crushes and dissolves very readily, based on field observation. Therefore, minimal effect of administering the crushed 100 mg tablet dissolved in liquid in very young children is expected. A separate complementary study was conducted in 2015 to evaluate the effect of crushing BDQ on PK in healthy adult volunteers, in consultation with the US National Institutes of Health (NIH) Division of AIDS (DAIDS), which informed the use of the 100 mg BDQ formulation in P1108 and beyond. This study ("BDQ CRUSH") has been completed and showed that dissolving the adult BDQ 100 mg tablet reached bio-equivalent plasma exposures compared to when given as whole tablets in healthy adult volunteers (46). These data have paved the way for pragmatic use of the 100 mg formulation in the P1108 trial and in routine care, which is needed since access to the pediatric formulation will depend on in-country licensure and availability.

1.2 Prior Research

Drug information for BDQ and considerations for study design
BDQ, developed by Janssen, is a diarylquinoline compound with a novel mechanism of action against *M.tb*, the inhibition of mycobacterial adenosine triphosphate synthase (see Figure 2). *In vitro*, BDQ has potent activity against drug-susceptible and drug-resistant *M.tb* isolates and is also bactericidal against dormant (non-replicating) *M.tb* In the murine TB model, BDQ is as active as the triple combinations of INH, RIF, and pyrazinamide (PZA), with BDQ accelerating clearance of bacilli and displaying synergy with PZA. Similarly, BDQ enhances the antibacterial activity of second-line drug combinations in the murine model of RR-TB (47). The results of the first Phase II placebo-controlled study (TMC207-C208; NCT00449644) showed that the addition of BDQ to a five-drug RR-TB regimen resulted in significantly shorter time to culture conversion compared to placebo. The 160 adults in this study with newly diagnosed, smear-positive RR-TB received either 400 mg of BDQ once daily for two weeks followed by 200 mg three times per week (TIW) for 22 weeks, or placebo—both in combination with a preferred background regimen. The primary efficacy end point was the time to sputum-culture conversion in liquid broth. Participants were followed for 120 weeks from baseline. BDQ reduced the median time to culture conversion, as compared with placebo, from 125 days to 83 days (hazard ratio (HR) in the BDQ group, 2.44; 95% confidence interval (CI), 1.57 to 3.80; $p<0.001$ by Cox regression analysis) and increased the rate of culture conversion at 24 weeks (79% vs. 58%, $p=0.008$) and at 120 weeks (62% vs. 44%, $p=0.04$). On the basis of WHO outcome definitions for MDR-TB, cure rates at 120 weeks were 58% in the BDQ group and 32% in the placebo group ($p=0.003$). The overall incidence of AEs was similar in the two groups. In summary, the addition of BDQ to a preferred optimized background regimen for 24 weeks resulted in faster culture conversion and significantly more culture conversions at 120 weeks, as compared with placebo (TMC207-C208; NCT00449644) (39, 48-50). BDQ was licensed for use in adults with MDR-TB by the FDA in 2012 and by the EMA in 2014.

Findings from the second Phase IIb trial of BDQ in adults, a multi-center, open-label, single-arm trial (TMC207-C209; NCT00910871), were published in late 2015. This trial was conducted to confirm the safety and efficacy of BDQ. Newly diagnosed or previously treated patients ≥ 18 years of age with MDR-TB (including pre-XDR-TB or XDR-TB) received BDQ for 24 weeks

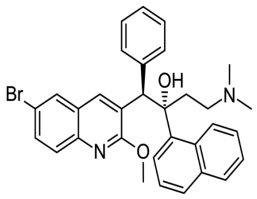
with a background regimen of antituberculosis drugs continued according to national TB Programs of relevant countries' treatment guidelines. Participants were assessed during and up to 120 weeks after starting BDQ. Among 233 participants, 63.5% had MDR-TB, 18.9% had pre-XDR-TB and 16.3% had XDR-TB, with 87.1% having taken second-line drugs prior to enrollment and 16 participants (6.9%) died. Twenty participants (8.6%) discontinued before week 24, most commonly due to AEs or MDR-TB-related events. AEs were generally those commonly associated with background MDR-TB treatment. In the efficacy population (n=205), culture conversion (missing outcome classified as failure) was 72.2% at 120 weeks, and 73.1%, 70.5% and 62.2% in MDR-TB, pre-XDR-TB and XDR-TB participants, respectively. Addition of BDQ to a background regimen was well tolerated and led to good outcomes in this clinically relevant patient cohort with MDR-TB (51). The early observed mortality risk has not been observed in subsequent trials or programmatic data (23, 52).

In a retrospective study of all routinely treated South African adults and adolescents between July 2014 and March 2016, a BDQ-containing regimen was given to 743 (4.0%) of 18,542 patients with MDR/RR-TB and 273 (25.4%) of 1,075 patients with XDR-TB. Of the 1,016 patients who received BDQ, 128 deaths (12.6%) were reported, while there were 4,612 deaths (24.8%) among 18,601 patients on the standard regimens. BDQ was associated with a significant reduction in the risk of all-cause mortality for patients with MDR-TB or RR-TB (HR 0.35, 95% CI 0.28–0.46) and XDR-TB (0.26, 0.18–0.38) compared with standard regimens (23). Also, further studies with replacement of second-line injectables with BDQ showed improved results at 12 months: 162 patients who received BDQ substitution and 168 controls were analyzed; 70.6% were living with HIV. Unfavorable outcomes occurred in 35 of 146 (23.9%) patients in the BDQ group versus 51 of 141 (36.2%) in the control group (relative risk, 0.66; 95% CI, 0.46 –0.95). Delayed initiation of BDQ was independently associated with failure to achieve sustained culture conversion (adjusted odds ratio for every 30-day delay, 1.5; 95% CI, 1.1–1.9). Mortality rates were similar at 12 months (11 deaths in each group; p=0.97) (53).

Another important development in the TB field is the continued success of the Nix-TB trial (NCT02333799). This open-label, single-arm, Phase III study, which opened in 2015, evaluated a regimen of BDQ, LZD, and pretomanid for six months among adults with XDR-TB or with RR-TB treatment failure or intolerance. In the final intent-to-treat analysis six months after treatment end, 98 of 109 (90%) participants had a favorable outcome (54).

Preliminary Studies
BDQ In Vitro PK and preclinical toxicology

Figure 2
BDQ Structure



The major metabolic pathway identified *in vitro* (subcellular fraction and hepatocytes) and *in vivo* in several preclinical species including mice, rats, rabbits (*in vitro* only), dogs, monkeys, and in humans was N-demethylation to M2 followed by further N-demethylation to M3. M2 was the major circulating metabolite in mice, rats, dogs, and humans following repeated administration.

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

Implications of preclinical toxicology findings for this study
Cationic amphiphilic drugs like BDQ can cause phospholipidosis, characterized by the accumulation of phospholipids in cells. Phospholipidosis is thought to be an adaptive response rather than a manifestation of direct cellular toxicity, but phospholipidosis may have clinical consequences, including prolonged QT interval, myopathy, hepatotoxicity, nephrotoxicity, or pulmonary dysfunction (55). These effects are generally reversible with drug discontinuation (55). There is no reliable biomarker predictive of drug-related phospholipidosis, and animal models do not appear to predict human responses well (56). A theoretical concern with BDQ use is potential mitochondrial toxicity, which may be associated with phospholipidosis, although, to the knowledge of the P1108 Protocol Team, no specific evidence of BDQ-induced mitochondrial toxicity has been reported. M2 induces phospholipidosis *in vitro* at lower concentrations than BDQ. Comparing with *in vivo* reference compounds, M2 can be identified as a stronger phospholipidosis-inducer than BDQ (57). This may explain the higher tissue to plasma ratio observed *in vivo* for M2. *In vitro*, M2 has been shown to be a stronger inducer of phospholipidosis than amiodarone, and M2 induced phospholipidosis at lower concentrations than BDQ (1.2 μM vs. 7.3 μM, respectively). Taken together, the results suggest that M2 is the main driver behind the toxicity- and phospholipidosis-related issues in the preclinical safety profile of BDQ. In humans, since M2 concentrations are low (25-30% compared to BDQ) the safety profile is expected to be better than in the preclinical species (Table 1). In P1108, participants will be followed long-term, and serial electrocardiograms (ECGs) will be performed; however, it should be noted that there is not clear evidence that QT prolongation caused by BDQ is a phospholipidosis-related phenomenon (see Table 1).

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

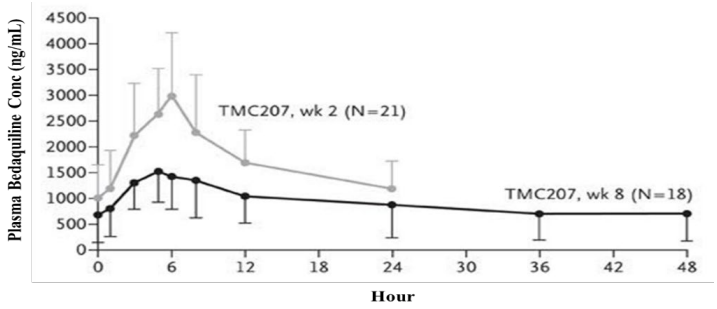
		Results C208 Stage 2	
		TMC207	M2
Week 2 (n = 26)[a]	C_{min} (ng/mL)	728 ± 257	332 ± 122
	C_{max} (ng/mL)	2763 ± 1185	467 ± 157
	$C_{ss,avg}$ (ng/mL)	1371 ± 529	383 ± 130
Week 24 (n = 17)[b]	C_{min} (ng/mL)	356 ± 170	120 ± 57
	C_{max} (ng/mL)	1267 ± 435	178 ± 71
	$C_{ss,avg}$ (ng/mL)	584 ± 197	152 ± 53

C_{min} = minimum plasma concentration, C_{max} = maximum plasma concentration, $C_{ss,avg}$ = average plasma concentration over the dosing interval
[a] n = 30 for C_{min}, n = 29 for C_{max}
[b] n = 18 for C_{min}, n = 19 for C_{max}

BDQ Clinical Pharmacokinetics and Metabolic Drug Interactions
In adults, BDQ is well absorbed with a time to maximum drug concentration (t_{max}) of five hours. Dose-proportionality of maximum plasma concentration (C_{max}) and area under the curve (AUC) is seen up to 700 mg with single doses and 400 mg with multiple doses. The average terminal elimination half-life of BDQ is 132 days and is 112 days for its M2 metabolite. Administration with food increases bioavailability by 95%. In individuals of black race, concentrations of BDQ are appreciably lower (52%) compared to individuals of non-black race (58). BDQ is metabolized by oxidative metabolism via the CYP3A4 isoenzyme to its N-desmethyl metabolite, M2. The M2 metabolite has activity against *M.tb*, but it is three- to six-fold less potent.

Mean plasma concentration–time profiles for BDQ given as 400 mg given once daily for two weeks and for BDQ 200 mg thrice-weekly following eight weeks of dosing among patients with MDR-TB are shown in Table 1 and Figure 3. Mean (± standard deviation (SD)) peak (C_{max}), minimum plasma concentration (C_{min}), and average plasma concentration (C_{avg}) of BDQ at Week 2 were 3270±1144, 956±557, and 1770±701 ng/mL, respectively, and at Week 8 were 1659±722, 620±466, and 902±535 ng/mL.

Figure 3
BDQ Concentration-Time Curves



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

Figure 4
BDQ Concentrations Over 2 Weeks

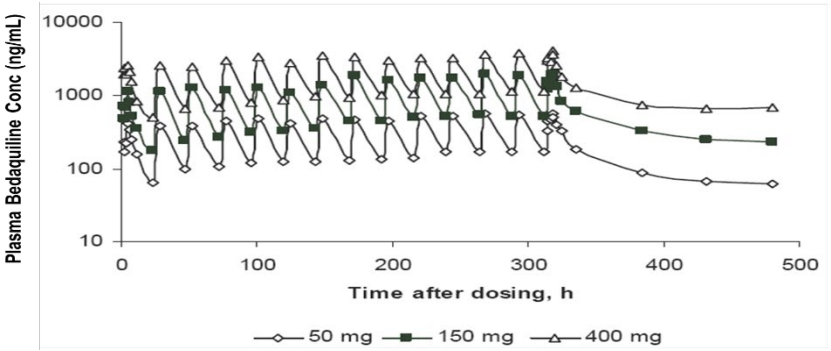


Figure 5
Model-Predicted Weekly BDQ Exposure to Week 3

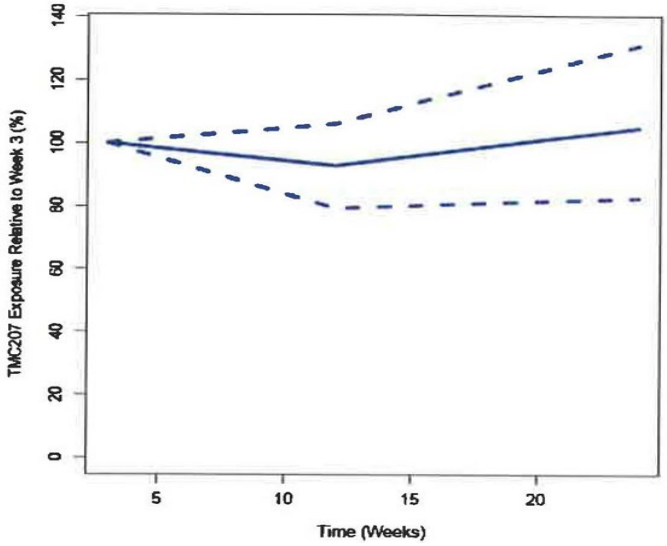
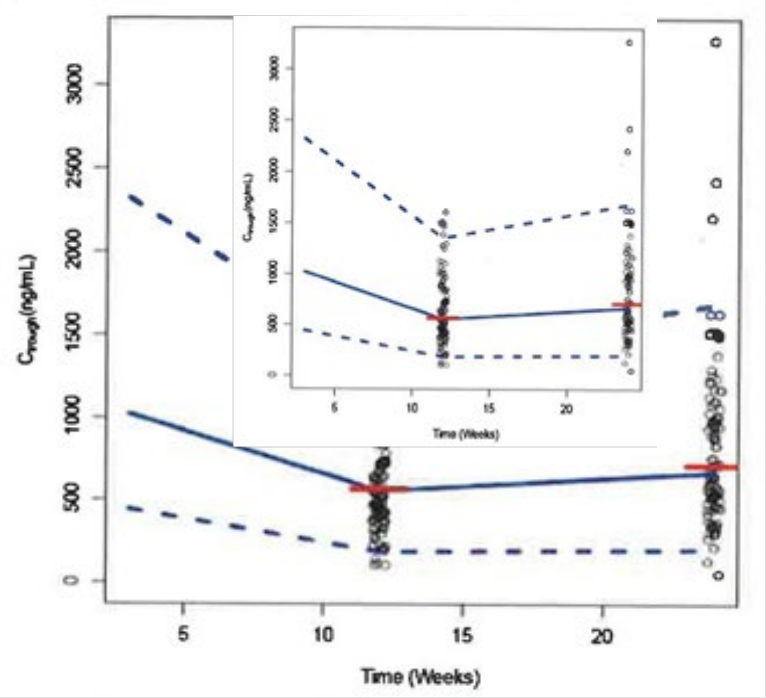


Figure 6
Comparison of the Model-Predicted and Observed Trough Concentrations in Plasma at Week 12 and 24 (Population Pharmacokinetic Model)



However, in many cases a terminal $t_{1/2}$ and amount of drug associated with the deep compartment contributes little to the overall accumulation and total area. Therefore, the effective half-life (half-life estimated using data collected over the 24-hour dosing interval) is sometimes more useful than a terminal half-life. The effective $t_{1/2}$ for BDQ is calculated at 21.2 hours. Key parameters are the elimination rate constant and dosing interval (t). This shorter, effective $t_{1/2}$ explains why concentrations as seen in the concentration-time profile of BDQ plateau by day 14.

Using data from animal models, PK data from humans, and knowledge about relative concentrations and relative activity of M2 compared to BDQ, the average target plasma BDQ concentration in humans was set at about 600 ng/mL (i.e., 2 x 300 ng/mL or an AUC_{24} of 14.4 µg.h/mL) prior to embarking on clinical efficacy trials. However, in the Phase II trials to date, at the dose tested, no clear exposure-response relationship was seen, so target concentrations are not well defined. Thus, in clinical trials, the PK/pharmacodynamic (PD) target has not been established, and the 600 ng/mL target has not been confirmed. However, when given at a dose of 400 mg once daily for 14 days followed by 200 mg thrice weekly for 22 weeks, the drug was effective, so it seems reasonable to target adult exposures achieved in the Phase II trials in dose finding trials in children.

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

Pharmacokinetic and safety data in children

Data from the registrational Janssen trial in children (TMC207-C211, NCT02354014), an open-label, multicenter, single-arm study which is evaluating the pharmacokinetics, safety/tolerability, antimycobacterial activity and dose selection of BDQ in children (birth to <18 years) living with MDR-TB, indicate that the selected BDQ doses in children were safe and well tolerated and resulted in appropriate exposures based on standard adult PK targets. Results of the primary analysis to date include 24 weeks' follow-up data for Cohort 1 (≥12 to <18 years; approved adult tablet at the adult dosage) and Cohort 2 (≥ 5 to <12 years; age-appropriate 20 mg tablet given at half the adult dosage). Fifteen children were enrolled in each of Cohorts 1 and 2; 53% and 40% of Cohort 1 and Cohort 2 children had confirmed/probable pulmonary MDR-TB. Most children completed 24 weeks BDQ/background TB treatment regimen (Cohort 1: 93%; Cohort 2: 67%). The geometric mean BDQ AUC_{168h} values of 119,000 ng·h/mL (Cohort 1) and 118,000 ng·h/mL (Cohort 2) at Week 12 were within 60-140% (86,200-201,000 ng·h/mL) of adult target values. Few AE-related drug discontinuations or serious AEs occurred, and no QTcF >460 ms during BDQ/background TB treatment regimen or deaths occurred. Of MGIT-evaluable participants, 6/8 (75%) Cohort 1 and 3/3 (100%) Cohort 2 children converted their culture (59).

Use of BDQ in patients living with HIV on ART

Patients with RR-TB who are living with HIV will require concurrent RR-TB and HIV treatment. However, ART options are currently limited in the context of BDQ treatment—specifically because BDQ is metabolized by CYP3A, and its therapeutic window is not well-defined. BDQ therefore cannot be used with EFV, which reduces BDQ exposure substantially. In some countries, EFV is being replaced by DTG in first-line ART regimens for children down to six years of age or down to 20 kg (60). With recent approval of DTG in infants and young children, the age limit is expected to change—DTG was approved by the FDA in 2020 for children and infants down to four weeks of age (24) and an FDA tentatively-approved generic pediatric dispersible formulation is being rolled out in many countries. LPV/r increases BDQ exposure substantially, but exposure to the M2 metabolite responsible for AEs is limited and, therefore, is currently used in combination with BDQ (34). Triple or quadruple nucleoside reverse transcriptase inhibitor (NRTI) regimens are available but are therapeutically inferior to first-line ART regimens. NVP can be used with BDQ, but patients with moderate to high CD4 counts cannot safely receive this drug, and it is associated with important liver and skin toxicities.

Data on drug-drug interactions between BDQ and ART among patients with HIV/TB diagnoses remain limited. Studies to date have mostly evaluated the effects of ARV drugs together with single-dose BDQ in healthy volunteers living without HIV. The effect of LPV/r on the PK of BDQ was evaluated in 16 adults living with HIV (61). Treatment A included single-dose BDQ 400 mg and Treatment B LPV/r 400/100 mg twice daily (bid) for 24 days, with co-administration of single-dose BDQ 400 mg on day 11. Results of this study indicated CYP3A4 inhibition by LPV/r on the PK of BDQ and its metabolite M2. Co-administration of LPV/r 400/100 mg bid increased exposure (AUC_{336h}) to BDQ by 22% and decreased exposure to M2 by 41%, consistent with the role of CYP3A4 in metabolizing BDQ to M2. However, the long half-life of BDQ and M2 resulted in a carry-over between the two sampling occasions, and only a part of the total AUC was captured during the sampling period. The decrease in M2 exposure is a consequence due to the fact that BDQ is metabolized slower, hence the generation of M2 is slower and an even smaller part of the total M2 exposure is captured during the sampling period. Consequently, the non-compartmental analysis generating the results above is a biased representation of what would happen during prolonged administration (62). A model-based analysis of the same data predicted that BDQ concentrations would be increased as LPV/r substantially reduced BDQ clearance to 25% (17-35%) and M2 clearance to 59% (44-69%) of original values (32). However, true steady

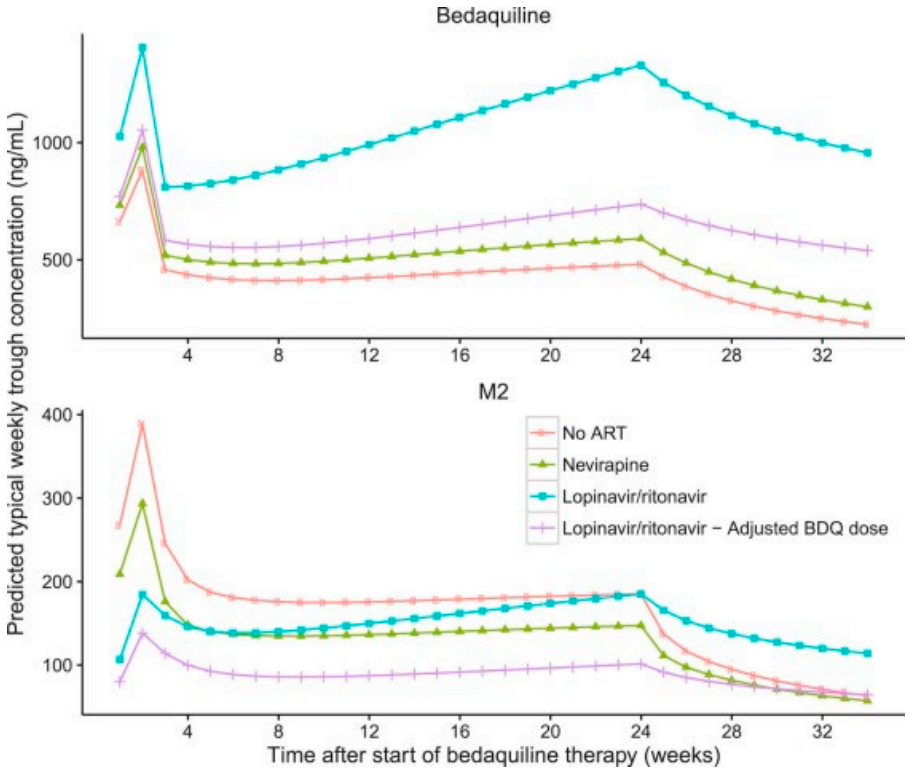
state is generally not reached within the 24 weeks dosing period, hence the observed effects would be smaller.

Furthermore, the effect of NVP on the PK of BDQ was investigated in adults living with HIV (N = 16). For BDQ and M2, PK profiles were assessed up to 336 hours post-dose after each administration of BDQ. For NVP, pre-dose concentrations were measured on the last three days prior to the second dose of BDQ (days -3, -2, and -1); on the day of administration of the second dose of BDQ (day 1); and subsequently on days 2, 3, 4, 8 and 15. Co-administration of steady-state NVP did not significantly impact BDQ or M2 exposure. (61) The metabolic ratio (AUC ratio M2/ BDQ) was not significantly affected by NVP. Additionally, NVP pre-dose concentrations were comparable before and after co-administration of single-dose BDQ. In a study involving healthy participants living without HIV receiving single-dose BDQ alone or with multiple-dose EFV, EFV appeared to reduce BDQ concentrations by about 20% (63). Nonlinear mixed effects modeling to estimate the effects of EFV on BDQ and M2 concentrations at steady state suggest that reductions around 50% should be expected (64).

In a study led by the University of Cape Town International PK specialty lab, sampling was conducted on 48 adults treated for RR-TB (17 not on ARVs, 17 on NVP, and 14 on LPV/r). Intensive PK sampling (nine blood samples over 48 hours) was conducted once participants were in the maintenance dose phase (200 mg TIW) of BDQ. There was no significant difference (p = 0.502) between the median BDQ plasma $AUC_{0\text{-}48h}$ in µg.hr/mLin participants on NVP (35.2 [IQR 28.4-64.2]) compared to participants not on ARVs (34.7 [27.5-52.8]). Similarly, there was no significant difference between the median BDQ maximum concentration (C_{max} in µg/ml), M2 AUC, and M2 C_{max} in participants on NVP. Median BDQ $AUC_{0\text{-}48h}$ was significantly higher (p = 0.003) in participants on LPV/r (67.0 [51.9-88.3]) compared to participants not on ARVs. The median BDQ C_{max} was non-significantly higher (p=0.23) in participants on LPV/r compared to participants not on ARVs. There was no significant difference in median M2 AUC and M2 C_{max} in participants on LPV/r. However, the participant group with LPV/r had been on treatment substantially longer than the no ARVs group (median of 95 days vs 43), hence the degree of M2 accumulation was not the same and direct comparisons could be misleading. A model-based analysis able to compensate for the difference in treatment duration between participants in the study suggested that M2 exposures during co-administration with LPV/r will be lower than without LPV/r during the treatment period, but remain higher after end of treatment (as illustrated in Figure 7) (33). In conclusion, there was no significant difference in BDQ and M2 PK parameters between participants on NVP and participants not on ARVs. The median exposure of BDQ in participants on LPV/r was higher than in participants not on ARVs, and the ratio varies over the time of treatment (2-3-fold higher). The clinical significance of this remains to be determined (34) as LPV/r continues to be routinely used in patients receiving BDQ in TB programs.

A retrospective data analysis including 46 of the participants from the above-mentioned study investigated the potential effect of CFZ co-administration on BDQ and M2 PK. Thirty of the participants were treated with CFZ at the time of the BDQ PK sampling. No significant effect of CFZ could be detected on either BDQ or M2 PK. However, the study was not designed to look at this drug-drug interaction and the CIs of the estimates were wide, hence a clinically significant effect cannot be excluded (65).

Figure 7
Predicted typical BDQ and M2 trough concentrations a black MDR-TB patient of 35 years on standard BDQ dosing (400 mg daily for two weeks, thereafter 200 mg three times weekly until Week 24) without interacting co-administration (red dots), with concomitant nevirapine (green triangles), with concomitant ritonavir-boosted lopinavir (LPV/r) (blue squares) and for the adjusted BDQ dosing (300 mg daily for 2 weeks, thereafter 100 mg three times weekly until Week 24) with LPV/r co-administration (purple plusses).



No PK studies of BDQ have been conducted to date in children living with HIV. The Janssen C211 study is evaluating BDQ in children without HIV aged 5-17 years. However, the P1108 study aims to evaluate BDQ in children with and without HIV aged zero to less than 18 years. Only ARV drugs shown or proposed to have limited interaction with BDQ in adult studies will be used in participants in this study. The use of EFV will not be allowed.

DTG, an integrase inhibitor, does not induce or inhibit CYP3A, and its metabolism is not expected to be affected by BDQ or DLM (35). Further, DTG may be increasingly available in international settings as a first-line treatment for children and infants living with HIV, given evolving international HIV treatment guidelines and June 2020 FDA approval of DTG in infants and children. Adults who are receiving BDQ are already increasingly switched to DTG-containing regimens in such settings. This study provides an opportunity to use a DTG-based ART together with the newest, most promising antituberculosis drugs for children with both RR-TB and HIV.

For P1108, EFV is not allowed with BDQ administration. From the above discussion, ARVs that are therefore allowed to be co-administered with BDQ in this study are the NRTIs, NVP, LPV/r,

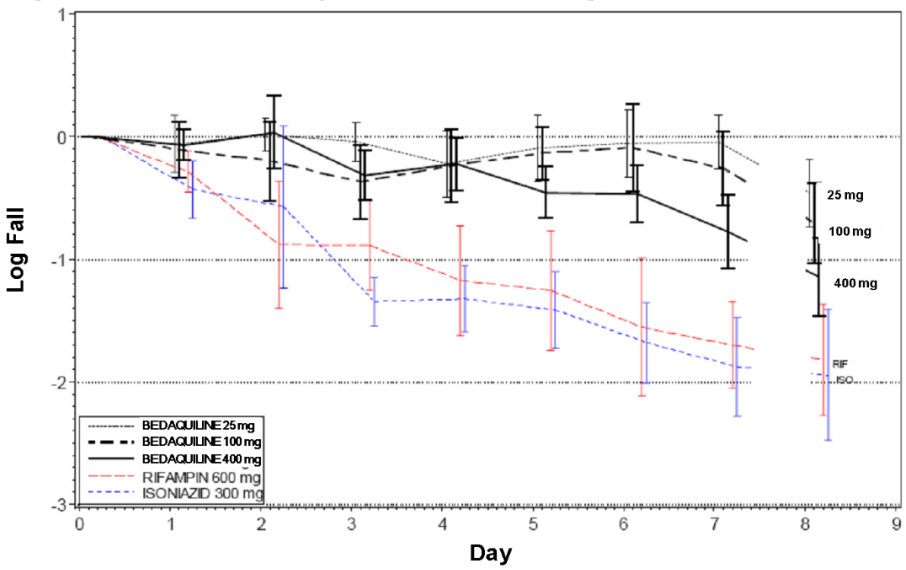
and integrase strand transfer inhibitors (e.g., DTG and raltegravir), or another regimen approved by the P1108 Core Team prior to enrollment.

Use of BDQ in Children with Intrathoracic TB and Limited forms of Extrathoracic TB
Given that there are no data on BDQ penetration of cerebrospinal fluid, there does not at present appear to be an additional substantial benefit of including children with advanced stages of TB meningitis (TBM), given the limited potential additional benefit offered by BDQ in these children. Potential participants with TBM Stages 2B and 3 will therefore be excluded from this study.

Children with intrathoracic (pulmonary) TB and selected forms of extrathoracic RR-TB are included in P1108, based on the risk/benefit assessment of treating children who have difficult to treat RR-TB with BDQ. Children with miliary, abdominal, and osteoarticular TB will be considered for inclusion.

Efficacy Studies of BDQ
In a separate EBA study, 75 treatment-naïve patients with smear-positive pulmonary TB were randomized to once daily oral BDQ (25 mg, 100 mg, or 400 mg), RIF 600 mg, or INH 300 mg for seven days (66). Bactericidal activity was expressed as the $\log_{10}$ decrease in colony-forming units (CFU)/ml sputum/day (Figure 8). The decrease in $\log_{10}$CFU counts (±SD) from baseline to Day 7 was 0.04 ±0.46 for BDQ 25 mg (N = 14), 0.26 ±0.64 for BDQ 100 mg (N = 14), 0.77 ±0.58 for BDQ 400 mg (N = 14), 1.88 ±0.74 for INH (N = 11) and 1.70 ±0.71 for RIF (N = 14). BDQ demonstrated bactericidal activity, but onset was delayed. Significant bactericidal activity of BDQ 400 mg was observed from Day 4 onward and was similar in magnitude to INH and RIF CFU declines over the four to seven-day period. It was well tolerated with no drug related serious AEs.

Figure 8
Bactericidal Activity of Different Anti-TB



In the first stage of a two-stage, Phase 2, randomized, controlled trial, 47 randomly assigned participants who had newly diagnosed MDR pulmonary TB either received BDQ (400 mg daily for two weeks, followed by 200 mg TIW for six weeks) (23 participants) or placebo (24 participants) in combination with a standard five-drug, second-line antituberculosis regimen (50).

Most AEs were of mild or moderate intensity and of a type known to occur commonly in patients with TB or in patients undergoing the standard drug regimen for MDR-TB. Only nausea occurred significantly more frequently for BDQ than placebo (26% vs. 4%, p = 0.04). No consistent or clinically relevant changes in heart rate or electrocardiographic QRS or PR interval were observed during the study. The results of bacterial culture of sputum showed that more participants were TB culture-negative at eight weeks in the BDQ group, 47.6% versus 8.7% in the placebo group. In addition, BDQ reduced the time to culture conversion. The probability of becoming culture-negative on any given day within the eight-week treatment period was 11.8 times higher in the BDQ group, versus in the background regimen alone, with HR (95% CI): 11.8 (2.26, 61.3); p = 0.003 by Cox regression analysis. Mean sputum CFU count declined more rapidly for BDQ than placebo. Over prolonged follow-up in Stage 2, time to culture conversion over 24 months was reduced in the BDQ plus background therapy group compared to the placebo plus background therapy group with a HR of 2.25 (95% CI 1.08-4.71); further, BDQ appeared to reduce the risk of acquired drug resistance to companion agents (49). A longitudinal analysis of the quantitative culture data from the phase II studies showed that individual weekly average BDQ concentration was significantly linked with the rate of decline of bacterial load. The estimated EC50 was 1.42 mg/L (95% CI 1.00–2.05), which is higher than the median observed average concentration in the continuation phase of BDQ treatment, but falls within the observed range (67, 68). These Phase II results validate adenosine triphosphate synthase as a viable target.

Based on the available data, WHO recommends BDQ is used in children six years and older and greater than 15 kg and conditionally recommends the use of BDQ as part of an all-oral treatment regimen in children below six years of age based on preliminary data from 12 participants in P1108, with a clear recommendation to obtain more definitive dosing and safety data in children below six years of age (2, 3). In “Treatment of drug-resistant tuberculosis – an official American Thoracic Society (ATS)/US Centers for Disease Control and Prevention (CDC)/European Respiratory Society/Infectious Diseases Society of America clinical practice guideline” the recommendation regarding BDQ use in children is that studies are ongoing in lower age groups and weights (69). Based on expert opinion, for children greater than six years of age and weight 15–30 kg, half the adult dose can be used (200 mg/d x two weeks then 100 mg M/W/F for 22–24 weeks). This opinion is based on P1108 provisional data supplied to both WHO and ATS/CDC. BDQ use at the adult dose is approved for children/adolescents >12 years and >30 kg body weight. P1108 does not assess the efficacy of BDQ in children, since efficacy studies are not needed in children if efficacy has been established in adults for the treatment of TB disease. Rather, this study aims to establish the optimal dose for children of all ages, at a given established adult PK target; generate safety data in children; and investigate other pediatric-relevant considerations including tolerability.

Safety, including long-term safety, and tolerability of BDQ
The following is a summary of AEs with use of BDQ in Phase I and II trials to date in adults. In the study of the effect of NVP on the PK of BDQ in adults living with HIV (N = 16), the most frequently reported AEs were nasopharyngitis (50%), headache (31.3%) and increased gamma-glutamyltransferase (25%). One participant reported two serious AEs (grade 3 diarrhea and dehydration) considered related to HIV (70). In the study of the effect of LPV/r on the PK of BDQ in 16 adults with HIV, the most frequent AEs were diarrhea (44%) and headache (25%). There were no grade 3 or 4 AEs in the study, except for one participant with grade 3 lipase increase seven days after intake of BDQ in the Treatment A group (61).

In the published adult Phase II data (C208) by Diacon et al. including data from 160 adults with MDR-TB, there were 79 participants in the BDQ group and 81 in the placebo group. More participants in the BDQ group than in the placebo group died: whereas two deaths were reported

among the 81 participants in the placebo group, ten deaths occurred among the 79 BDQ treated participants with no causal pattern evident (48). One of the deaths in the BDQ group was due to a motor vehicle accident that occurred at 130 weeks of follow-up, and this participant was not included in further analyses. In the FDA assessment, both deaths in the placebo group appeared to be related to progression of disease, as did five of the nine deaths in the BDQ group. Among the four other participants in the BDQ group who died, there was no apparent common cause of death. One of the deaths among BDQ-treated participants occurred during the 24-week trial period; the median time to death in the remaining eight participants in the BDQ group was 329 days after the participant last received BDQ. The unexpected finding of a mortality imbalance is an important concern; however, the length of time between the last receipt of BDQ and death makes it difficult to discern a mechanism by which BDQ could be directly related to the deaths, even if BDQ's long half-life is considered. No participant in the BDQ group who died had a prolonged corrected QT interval by Fridericia (QTcF) at study visits preceding their death. In addition to inclusion of these data in the BDQ product label, the indication for BDQ use in adults is currently limited to patients with MDR pulmonary TB for whom an effective treatment regimen cannot be constructed without including BDQ (e.g., because of resistance to other drugs). For this population, the FDA assessment is that the benefits of BDQ outweigh the risks (71). Data from more recent Phase IIB studies (e.g., TMC207-C209) do not confirm this early observed excess mortality in adults with MDR-TB or XDR-TB (51). Deaths were significantly reduced in MDR-TB and XDR-TB participants receiving BDQ in their regimen compared to those on standard regimen without BDQ in a retrospective study of patients in the South African National TB program (72).

When designing studies of BDQ in new populations including children both with and without HIV, with possible differences in drug accumulation and/or metabolism, longer term safety monitoring with physical examinations, measures of mitochondrial and hepatic health and drug and metabolite accumulations may be important. Given the unexpected finding of the mortality imbalance in the initial adult Phase II trial, this study in children with and without HIV will therefore include long-term safety assessment (96 weeks total follow-up, including 72 weeks after BDQ discontinuation), in combination with extensive safety monitoring. Although accumulation of BDQ and M2 have not been linked to this mortality imbalance in adults, in this study BDQ levels will continue to be measured long-term after BDQ discontinuation, until BDQ/M2 are likely to be undetectable, to define exposures over time in children, who may possibly metabolize BDQ and M2 differently from adults. In P1108 Cohort 1 participants, careful monitoring of lactate concentrations and lactate/pyruvate ratios has not supported mitochondrial toxicity concerns; therefore, lactate concentrations and lactate/pyruvate ratios monitoring has been discontinued in protocol Version 2.0, based on consultation with the IMPAACT Study Monitoring Committee (SMC).

QT prolongation with BDQ and drugs commonly used to treat RR-TB
QT prolongation, especially in the presence of concomitant fluoroquinolone and/or CFZ therapy, is a concern amongst adults. Prolongation of QT interval has been reported in adults on MXF, and in thorough QT studies, MXF is often used as the positive control drug (73), yet MXF does not cause arrhythmias. For BDQ, there has been no clear relationship between BDQ concentrations and QTc interval prolongation. Only a weak association has been found between the M2 metabolite and QTc prolongation in adults (74). Of note, QT prolongation is thought to be associated with cumulative drug exposure, and among adults taking BDQ, QT prolongation reaches its peak about 16-18 weeks after starting treatment, then plateaus after that. Based on the BDQ package insert, the BDQ dose and frequency of dosing are reduced following the first two weeks of treatment. Specifically, the recommended dose in adults and children 12 to less than 18

years of age of 400 mg given daily for two weeks (loading dose) is followed by 200 mg thrice-weekly over 22 weeks.

There are limited pediatric data, but MXF is increasingly used in children with RR-TB. The careful evaluation of potential cardiotoxic effects of novel agents used in combination with fluoroquinolones in children is thus required. LFX causes lesser-magnitude QT changes than MXF, particularly at standard doses (75). Moreover, LFX has been used successfully to treat children who were contacts of patients with MDR-TB in the setting of an outbreak in Chuuk, Micronesia, at doses of up to 20 mg/kg per day, once daily (76). It is currently the fluoroquinolone of choice used for the treatment of RR-TB in children less than eight years of age in high burden settings such as South Africa and appears to have limited cardiotoxic effects in children studied to date. Thee et al. (77) found in a study of N=23 children (four living with HIV) treated for MDR-TB and receiving a dose of 15 mg/kg LFX that LFX exposures (sampled at t_0, and at 1, 2, 4, 6 and 8 hours post dose), that the median C_{max} [µg/ml], median $AUC_{(0-8)}$ [µg·h/ml] and mean t_{max} [h] for LFX was 6.71 (IQR 4.69-8.06), 29.89 (IQR 23.81-36.39) and 1.44 (SD 0.51), respectively. The mean QTc was 369 ms (SD 21.9) for LFX. Children seem to eliminate LFX faster than adults, leading to a drug exposure about half of that in adults following a standard oral dose (LFX 750mg). No QTc prolongation (QTc >450ms) occurred. In a follow-up study on PK and safety of LFX, ECG results were available in 41 children, median age 2.1 years (range: 0.2-4.8 years); 20 (49%) were male and 10 (24%) were living with HIV. All children living with HIV were on ART. The mean (SD) change in QTcF from 0 to 2 hour reading was 4.7 ms (27.3) with no child having a QTcF >450 (78).

QT prolongation caused by BDQ together with the use of a fluoroquinolone and possibly in combination with use of CFZ, another drug commonly used in the treatment of RR-TB and with potential QT wave effect, should therefore be carefully monitored in children.

In summary, the available safety data in adults, when BDQ is given as described above, do not indicate significant safety concerns precluding the evaluation of safety and PK of BDQ in children. Careful cardiac monitoring, however, continues to be warranted, given the potential use of BDQ in combination with other QTc prolonging drugs including LFX, CFZ, and DLM. IMPAACT P1108 will include frequent ECG monitoring in all participants (see Section 8.6).

Study Formulation
The 100 mg adult tablet formulation of BDQ will be available for all cohorts, and participants in Cohorts 2 and 3 may receive the BDQ pediatric formulation (20 mg dispersible scored tablets) as an alternative option. If the pediatric BDQ formulation is not available, or is not preferred (e.g., based on pill burden), younger children will receive the 100 mg formulation dissolved as needed based on findings from the IMPAACT "BDQ CRUSH Study" described above.

1.3 Rationale

The treatment of RR-TB in children can be further dramatically improved with new, effective, and safer drugs, with the goal of further shortening RR-TB therapy using shorter and acceptable injectable-sparing regimens and reducing adverse effects and poor tolerability. The emergence of XDR-TB requires a wider choice of medications. A significant percentage of children in international settings with RR-TB still have HIV, despite declining vertical HIV transmission rates, which complicates RR-TB treatment. Evaluations of novel TB drugs and regimens therefore must include children living with HIV.

This study proposes to evaluate the novel TB drug, BDQ, in infants, children, and adolescents treated for RR-TB disease. The goals of this study are to determine the appropriate dose of BDQ in children in the context of current routine RR-TB treatment regimens and to understand the practical dosing of this drug in the context of multiple interacting drugs commonly used for HIV treatment.

This study will assess the safety and PK of BDQ in children aged 0-17 years in three pragmatic age cohorts. As designed, it allows for the timely enrollment of young children and children with HIV, recognizing the critical need at this time to understand the safety, PK, and drug-drug interactions of BDQ in young children and when given with ARV medications. BDQ doses used in this study will be determined by protocol-specified criteria for PK and safety and will be informed by ongoing analyses of emerging BDQ PK and safety data in children using both available formulations, and in the context of the rapidly evolving DR-TB treatment landscape.

1.4 Hypothesis

BDQ will be well tolerated and will demonstrate an acceptable safety and PK profile in infants, children, and adolescents with RR-TB, living with and without HIV.

2 OBJECTIVES

2.1 Primary Objectives

2.1.1 Determine the BDQ doses that achieve similar weekly exposure (AUC) of BDQ compared to adults taking BDQ at the current standard recommended dose.

2.1.2 Evaluate the safety and tolerability of BDQ over a 24-week dosing period.

2.2 Secondary Objectives

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

2.2.2 Describe the long-term safety and tolerability of BDQ over a 96-week total follow-up period, by HIV status.

2.2.3 Describe BDQ concentrations following BDQ discontinuation and through 72 weeks after BDQ discontinuation, by HIV status.

2.2.4 Describe the RR-TB treatment response up to 96 weeks from initiation of the study, by HIV status.

2.3 Exploratory Objective

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

3 STUDY DESIGN

This is a multicenter, Phase I/II, open-label, single-arm, exposure-based dose-finding study to evaluate the PK, safety, and tolerability of BDQ given as part of an individualized RR-TB treatment regimen for the treatment of confirmed or clinically diagnosed intra-thoracic RR-TB and/or selected forms of extrathoracic RR-TB in infants, children, and adolescents.

Guidance for constructing a pediatric RR-TB regimen is provided in Appendix IIB and drug groups routinely used for the RR-TB treatment is provided in Appendix IIA. Refer to inclusion criterion 4.1.7 for allowable ART regimens in participants living with HIV.

The study will consist of a screening period of up to 30 days and a treatment period of approximately two weeks with BDQ daily dosing (including any non-study BDQ doses taken prior to Entry) followed by BDQ TIW dosing after the intensive PK sampling and through the Week 24 visit. Therefore, the total duration on BDQ will be approximately 24 weeks. All participants will be followed on study for 72 weeks after their last dose of BDQ, for a total of 96 weeks of follow-up. Participants who discontinue BDQ early and remain on study will have study follow-up visits for approximately 72 weeks after discontinuation of BDQ dosing.

Intensive PK sampling will be performed at the Week 1 or Week 2 visit (see Sections 6.3 and 6.4) following administration of at least 14 and no more than 17 BDQ daily doses, including the BDQ dose administered on the day of intensive PK sampling and any non-study BDQ doses taken prior to Entry. Sparse PK sampling will also be performed during BDQ treatment and following BDQ discontinuation per Appendix I, Schedule of Evaluations (SoE).

3.1 Cohort Approach

At least 54 and up to 84 participants will be enrolled in the study across three age cohorts, as follows:

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

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

The BDQ dose for Cohort 1 was predetermined based on modeling of adult data and knowledge of developmental pharmacology of BDQ's metabolic pathways. However, BDQ doses may be adjusted, as needed, following evaluation of interim PK data. The optimal BDQ doses for Cohorts 2 and 3 were calculated using a model-based approach and based on interim data from Cohort 1, with weight banding as applicable (see Section 10).

Refer to Section 4 for the study eligibility criteria and a description of the study recruitment, screening, and enrollment process. Participants will be enrolled at study sites in Haiti, India, and South Africa.

3.2 Cohort Management

Study accrual will begin with Cohort 1 only. Cohorts 2 and 3 will be opened concurrently once PK criteria have been met and the safety data are acceptable, as outlined below, in at least 12 participants in Cohort 1 and the SMC has reviewed the PK and safety data for these participants. Participant enrollment will be managed similarly across all cohorts, as further described below.

The PK criteria will be considered to have been met in a given cohort if the predicted typical exposure (summary statistic) BDQ weekly AUC at steady state is within the 90% prediction interval of estimated adult steady state exposure (i.e., 50-400 µg*h/mL). In Cohort 1, PK data for participants in the two weight bands will be analyzed collectively. Participant safety data review processes are described in Section 9.5.2.

Once at least six participants in a cohort complete the intensive PK visit, the team will review the PK data (i.e., all intensive and available sparse PK data) and available safety data for the first six participants. During this time, up to three additional participants may be accrued. If up to three additional participants are enrolled during the interim PK analysis, the team will consider available PK and safety data from these participants, in addition to the initial six participants, in evaluating the relevant dose for the cohort. After nine participants are enrolled in a cohort, accrual will be temporarily paused until the interim PK analysis is completed. If a participant is determined to be non-evaluable, the participant will be replaced as described in Section 9.4.

Individual BDQ dose adjustment for clinical purposes is permitted during the study in consultation with the Core Team and clinical care provider to allow for appropriate individual clinical management. Individual BDQ dose adjustments may also be considered if exposures ($AUC_{0\text{-}24h}$) are unacceptable or concerns are identified.

If there are unexpected delays in accrual, such as delays in evaluating the intensive PK data in groups of six participants, PK assays may be completed for individual participants, upon request from the Core Team. Modeling of BDQ PK data will be performed as needed throughout the study based on available PK data.

3.2.1 Safety is acceptable and PK criteria are met

If safety data are acceptable per Section 9.5.2 and the PK criteria are met in the initial six participants in a cohort, accrual will resume, and the next interim analysis will take place once 12 participants have enrolled in a cohort and completed the intensive PK sampling. The team will then review the PK data (i.e., all intensive and available sparse PK data) and available safety data for the 12 participants. Up to three additional participants may be enrolled during this time. After a total of 15 participants have been enrolled in a cohort, accrual will be temporarily paused until the interim analysis is completed. If up to three additional participants are enrolled during the interim PK analysis, the team will consider available PK and safety data from these participants in evaluating the relevant dose for the cohort. If a participant is determined to be non-evaluable, the participant will be replaced as described in Section 9.4.

Following review of the interim PK and safety data by the Core Team (and SMC review for Cohort 1 only), if the PK criteria are met and safety data are acceptable in at least 12 evaluable participants, then accrual will resume to achieve 18 evaluable participants per cohort.

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

If the safety data are unacceptable (see Section 9.5.2) in the first six evaluable participants in a cohort, a BDQ dose adjustment may be made, and cohort management will be conducted in consultation with the SMC.

If the PK criteria are not met in the first six evaluable participants in a cohort, but there are no safety concerns, then accrual to complete the next group of six participants (n=12) may proceed at an adjusted BDQ dose as determined by the Core Team.

Once at least 12 evaluable participants in a cohort complete the intensive PK sampling at the intensive PK visit, the team will review the PK data (i.e., all intensive and available sparse PK data) and available safety data for the 12 participants. As described above, available PK and safety data from up to three additional participants (n=15) may also be considered during the interim analysis. If the PK criteria are not met and/or the safety data are unacceptable, then the Core Team will use PK modeling and available safety data to determine if a new group of six evaluable participants should be enrolled at an adjusted dose, additional participants enrolled at current dose, or to stop the study. If additional participants are enrolled, then the dose evaluation procedures described above will be followed until at least 18 evaluable participants are enrolled in a cohort, or the maximum sample size of 24 participants in Cohort 1, 30 participants in Cohort 2, and 30 participants in Cohort 3 is achieved.

4 STUDY POPULATION

This study will be conducted among infants, children, and adolescents less than 18 years of age treated for clinically diagnosed or confirmed intra-thoracic (pulmonary) RR-TB and/or selected forms of extrathoracic RR-TB. Participants will be selected for this study according to the criteria in Sections 4.1 and 4.2 and the guidelines in Sections 4.3 and 4.4. 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 to be enrolled in this study; in these criteria, "entry" is used to refer to the day of enrollment in the study at the Entry visit:

4.1.1 Parent or guardian is willing and able to provide written informed consent for potential participant's study participation; in addition, when applicable per institutional review board (IRB)/ethics committee (EC) policies and procedures, potential participant is willing and able to provide written assent for study participation.

4.1.2 Age at entry:

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

4.1.3 Weight at entry:
- Cohort 1: At least 15 kg
- Cohort 2: Greater than 7 kg
- Cohort 3: At least 3 kg

4.1.4 HIV status determined based on testing meeting requirements in Section 4.3.

4.1.5 For the purposes of this protocol, "RR-TB" collectively refers to the following: RMR-TB (routinely treated as RR-TB), or where additional INH resistance has not been confirmed (i.e., isolated Xpert MTB/RIF-positive resistant cases); MDR-TB (resistance to both rifampin and INH); pre-XDR-TB (MDR/RR-TB and resistance to any fluoroquinolone); and selected XDR-TB disease (MDR/RR-TB and fluoroquinolone and LZD resistance, but excluding XDR-TB with probable or confirmed BDQ resistance), according to case definitions of pediatric TB per WHO definitions (79) and as per local pediatric TB guidelines.

Participant has either bacteriologically confirmed or probable RR-TB, as defined below, based on available medical records, chest x-ray (CXR), and/or other evaluations performed during the Screening period at the discretion of the site investigator (refer also to Section 6.1):

Bacteriologically confirmed intrathoracic (pulmonary) RR-TB, and/or any of the following forms of extrathoracic TB:

- Peripheral TB lymphadenitis
- Pleural effusion or fibrotic pleural lesions
- Stage 1 TBM or clinically stable Stage 2A TBM*
- Osteoarticular TB, including spinal TB
- Other non-disseminated forms of TB disease

Bacteriologically confirmed RR-TB is defined as*:*
Culture (phenotypic), or molecular (genotypic) confirmation (e.g., Xpert MTB/RIF Ultra, WHO-endorsed line probe assay, with or without additional proof of INH resistance), and with evidence (WHO-endorsed molecular line probe assay results or with evidence from phenotypic drug susceptibility testing) of RR-TB. Documentation of RR-TB must be obtained, with confirmation of phenotypic or molecular evidence of drug resistance, prior to entry.

OR

Probable RR-TB (or clinically diagnosed RR-TB) with the inclusion of intrathoracic and/or extrathoracic TB as listed below:

- A presumptive diagnosis of RR-TB based on well-documented clinical symptoms or signs of TB with chest radiological changes (in the case of intrathoracic TB), and/or any of the following extrathoracic disease manifestations:
  - Peripheral TB lymphadenitis
  - Pleural effusion or fibrotic pleural lesions
  - Stage 1 TBM or clinically stable Stage 2A TBM*
  - Osteoarticular TB, including spinal TB

- Other non-disseminated forms of TB disease

AND

One of the following:
- Documented exposure to an RR-TB source case with bacteriologically confirmed pulmonary TB (either molecular or culture confirmation as specified above)
- The potential participant has documented failure to respond to a first-line regimen, and where adherence was well documented

AND

The clinical decision has been made to routinely treat for RR-TB.

*TBM Stage 1: Potential participant is alert and orientated without focal neurological deficit with Glasgow Coma Scale (GCS) score 15.
TBM Stage 2A: Potential participant with GCS score 15 with neurological deficit, OR GCS score 13–14 with or without neurological deficit (80).

4.1.6 Participant is on an RR-TB regimen as per local standard of care for at least seven days and not more than 12 weeks prior to entry, and tolerating the regimen well at entry, as determined by the site investigator based on available medical records.

Note: Participants may have received up to seven doses of non-study BDQ during the seven days prior to study enrollment. The date and dose amount of non-study BDQ doses must be available in medical records.

4.1.7 *For potential participants living with HIV*: At least 14 days prior to entry, initiated an acceptable ART regimen defined as zidovudine/lamivudine/abacavir; NVP and two NRTIs; LPV/r and two NRTIs; an integrase class drug including dolutegravir or raltegravir with two NRTIs; or another regimen approved in advance by the Core Team.

4.1.8 At entry, the participant has the following laboratory test results according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (refer to Section 7.3.3 for guidance on severity grading):

- Absolute neutrophil count (normal or grade 1)
- Creatinine (normal or grade 1)
- Aspartate Amino Transferase (AST) (normal or grade 1)
- Alanine Amino Transferase (ALT) (normal or grade 1)
- Total bilirubin (normal or grade 1)

Note: Laboratory tests may be repeated during the screening period, with the latest results used for eligibility determination.

4.1.9 *If male and engaging in sexual activity that could lead to pregnancy of the female partner*: At entry, participant agrees to use a barrier method of contraception (i.e., male condom) until four weeks after discontinuation of BDQ.

4.1.10 *If female and of reproductive potential, defined as having reached menarche and not having undergone a documented sterilization procedure (hysterectomy, bilateral oophorectomy, or salpingotomy)*: Negative pregnancy test within five days prior to entry.

4.1.11 *If female of reproductive potential as per inclusion criterion 4.1.10 and engaging in sexual activity that could lead to pregnancy*: At entry, participant agrees to avoid pregnancy and to use at least two of the following contraception methods from entry through completion of study follow-up: condom, diaphragm or cervical cap, intra-uterine contraceptive device, hormonal-based contraception.

4.1.12 *For Cohort 3 participants less than six months of age*: Gestational age at birth greater than or equal to 37 weeks as determined by the site investigator based on parent/guardian report and/or available medical records.

4.2 Exclusion Criteria

Potential participants must be excluded from the study if any of the conditions specified below are identified during the screening period. The screening period begins when informed consent is obtained and ends immediately prior to enrollment. For criteria involving a potential participant's medical history, it is expected that each exclusionary condition will be assessed at screening and subsequently reviewed and confirmed to be non-exclusionary on the day of study entry, prior to enrollment.

4.2.1 Has any documented or suspected clinically significant medical condition or any other condition (excluding HIV and TB) that, in the opinion of the site investigator, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives.

4.2.2 Known or presumed severe extrapulmonary manifestations of TB, including Stages 2B and 3 TBM as determined by the site investigator based on participant/parent/guardian report and/or available medical records.

4.2.3 Participant is breastfeeding a child based on participant/parent/guardian report and/or available medical records.

4.2.4 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 as determined by the site investigator based on participant/parent/guardian report and available medical records.

4.2.5 QTcF interval greater than 460 ms (i.e., ECG mean triplicate value greater than 460 ms) at screening.

Note: The centralized ECG read should be used during screening for eligibility determination.

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

4.2.7 Known personal or family history of long QT syndrome as determined by the site investigator based on participant/parent/guardian report and/or available medical records.

4.2.8 Within eight weeks prior to entry, participation in other clinical studies with investigational agents or devices, unless approved in advance by the Core Team.

4.2.9 Taking any prohibited medications specified in Section 5.7 within three days prior to entry based on participant/parent/guardian report and/or available medical records.

4.3 Determination of HIV Status

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

HIV status must be determined prior to study entry as specified below. Assessment of whether a potential participant is presumed to be living with or without HIV will be based on available medical history information. HIV testing will then be performed as needed to determine each participant's status as specified in the remainder of this section.

Test results to determine HIV status as specified below must be available for final eligibility determination and prior to enrollment at the Entry visit. All samples collected for study testing to determine HIV status must use test methods approved for each site by the IMPAACT Laboratory Center.

4.3.1 Presumed Living Without HIV

For potential participants initially presumed by study staff to be living without HIV based on available medical history information and/or participant/guardian report, HIV testing must be performed in the study site's designated testing laboratory during the study screening period per Sample #1 requirements in Section 4.3.3. Potential participants with negative results from this testing will be considered living without HIV at Entry. Potential participants with positive results should be referred to non-study sources of HIV care and treatment as soon as possible. These potential participants may be considered for entry into the study as living with HIV if HIV infection is confirmed per the requirements in Sections 4.3.2 and 4.3.3 and if initiated an acceptable ART regimen at least 14 days prior to Entry as defined in inclusion criterion 4.1.7.

For Cohort 3 HIV-exposed participants enrolled in the study as living without HIV, HIV testing must be performed in the study site's designated testing laboratory at the Week 48 (24 weeks post BDQ), Week 96/End of Study (72 weeks post BDQ), and early study discontinuation visits,

unless adequate source documentation as outlined in Section 4.3.2 is available to confirm HIV infection. If adequate source documentation is not available, and participants are presumed to be living without HIV at these visits, HIV testing per Sample #1 requirements in Section 4.3.3.2 should be performed at these visits. If the results from this testing are positive, additional HIV testing per Sample #2 requirements in Section 4.3.3.2 should be performed as soon as possible and prior to the next study follow-up visit to confirm the participant is living with HIV. If the participant is confirmed to be living with HIV, the participant should be referred to non-study sources of HIV care and treatment, and no further HIV testing in the study is required, unless clinically indicated.

4.3.2 Presumed Living With HIV

For potential participants initially presumed to be living with HIV based on available medical history, HIV status must be confirmed based on test results from two samples collected from two separate blood collection tubes per the Sample #1 and Sample #2 requirements in Section 4.3.3. Test results may be obtained from medical records or from testing performed during the study screening period.

- For results obtained from medical records, adequate source documentation, including the date of specimen collection, date of testing or date of test result, name of test/assay performed, and test result, must be available in study records prior to study entry. Requirements related to laboratory operations (e.g., Good Clinical Laboratory Practices (GCLP), or Virology Quality Assurance (VQA)) and related to regulatory authority approvals (e.g., FDA) do not apply to results obtained from medical records.
- If adequate source documentation is not available, Sample #1 and/or Sample #2 should be collected during the study screening period and tested in the site's designated testing laboratory. If both samples are tested using antibody tests, at least one of the samples must 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 VQA-certified laboratory.

4.3.3 HIV Testing Requirements

All study-specific samples tested to determine HIV status must be whole blood, serum, or plasma. HIV testing methods and algorithms must be approved for each site by the IMPAACT Laboratory Center. Testing methods should be FDA-approved, if available.

4.3.3.1 Cohort 1 and Cohort 2

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

Sample #1 requirements for participants with no exposure to breast milk in the past 28 days:

- Two rapid antibody-based tests from different manufacturers or based on different principles and epitopes, which may include use of a combination antigen-antibody-based rapid test.
  - *For potential participants presumed to be living without HIV:* For study eligibility purposes, determination that a participant is living without HIV may be confirmed by a negative result from one FDA-approved HIV rapid test (i.e., it is not necessary to perform two rapid tests). If the rapid test result is positive, a second rapid test should be performed as specified above.

- *For potential participants presumed to be living with HIV*: Two rapid tests should be performed.

- One enzyme immunoassay (EIA) or Western Blot (WB) or immunofluorescence assay or chemiluminescence assay
- One HIV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR)
- One quantitative HIV ribonucleic acid (RNA) PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Sample #1 requirements for participants with any exposure to breast milk in the past 28 days:

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

Note: If the participant's mother or the participant is receiving ARVs, then an HIV DNA assay may be more sensitive.

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

Sample #2 requirements for participants with no exposure to breast milk in the past 28 days:

- Rapid antibody-based 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. Combination antigen-antibody based rapid tests may be used.
- One EIA or WB or immunofluorescence assay or chemiluminescence assay
- One HIV DNA PCR
- One quantitative HIV RNA PCR (above the limit of detection of the assay)
- One qualitative HIV RNA PCR
- One total HIV nucleic acid test

Sample #2 requirements for participants with any exposure to breast milk in the past 28 days:

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

Note: If the participant's mother or the participant is receiving ARVs, then an HIV DNA assay may be more sensitive.

4.3.3.2 Cohort 3

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

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

Note: If the participant's mother or the participant is receiving ARVs, then an HIV DNA assay may be more sensitive.

4.4 Co-Enrollment Considerations

Co-enrollment in other trials is not precluded, although careful consideration must be given to study visit burden, blood draw volumes, and interpretation of outcome data across studies. Given these considerations, requests for co-enrollment in treatment and observational studies must be approved in advance by the protocol teams of both studies. Requests for such approval should be emailed to the P1108 Core Team.

4.5 Recruitment, Screening, and Enrollment Process

Participant recruitment methods for the study may vary across sites and by HIV status. Generally, infants, children, and adolescents with RR-TB in international settings, where this study 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, if admitted. For ambulatory care, RR-TB treatment would typically be dispensed by the TB clinic and supported by the parent/guardian 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. Further information is provided in study-specific recruitment and retention standard operating procedures (SOPs) completed by each participating site.

Before initiating in-person contact with a potential participant, parent, and/or guardian, study staff are expected to follow institutional policies for pre-screening for potential coronavirus disease 2019 (COVID-19) or other relevant infectious disease exposures (excluding TB) consistent with current local clinical practice, public health, and/or infection control guidelines. This may involve, for example, pre-screening prior to a scheduled visit by telephone and/or pre-screening prior to entry into the site facility on the day of a scheduled visit. Potential participants identified with current symptoms suggestive of COVID-19, or with recent test results or contacts that require quarantine or isolation, should not initiate the study screening process until symptoms have resolved and quarantine or isolation requirements have been completed. Likewise, if COVID-19 symptoms, test results, or contacts requiring quarantine or isolation are identified after the study screening process has been initiated, screening should be suspended until symptoms have resolved and quarantine or isolation requirements have been completed.

Upon identification of a potentially eligible participant, study staff will provide information about the study to the potential participant and/or their guardian as appropriate based on the age and maturity of the potential participant, guided by site SOPs and applicable IRB/EC policies and procedures. Potential participants/guardians who express interest in learning more about the study will be provided additional information and education as part of the study informed consent and assent processes. As described in the IMPAACT Network Manual of Procedures (MOP), the informed consent process will include detailed review of the study informed consent form (ICF) and time to address any questions or concerns the potential participant/guardian may have, as well as an assessment of understanding before proceeding to the informed consent decision. Potential participants who meet applicable IRB/EC criteria for provision of assent will undergo an age-appropriate assent process. Informed consent and assent processes will be fully documented, consistent with the DAIDS requirements referenced in Section 11.2. Refer to Section 13.3 for further information on informed consent and assent procedures for this study.

Eligibility screening will be initiated after written informed consent, and assent if applicable, are obtained (i.e., informed consent, and assent if applicable, must be obtained before any study-specific screening procedures are performed). Written informed consent and assent (if applicable) should also be obtained prior to collecting information to complete the Screening Case Review (see Section 6.1). Screening evaluations must be performed within 30 days prior to enrollment (i.e., including the day of study enrollment at the Entry visit) and may be repeated during the 30-day Screening visit window, with the latest outcomes used for eligibility determination. In the event that the 30-day screening visit window 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. Documentation and test results from all required screening evaluations as specified in Section 6.1 must be available for final eligibility determination prior to enrollment at the Entry visit.

Each site must establish SOPs for eligibility determination; roles and responsibilities for performing the required screening procedures; roles and responsibilities for assessing and confirming eligibility; and procedures for documenting the process, taking into consideration the required timing from enrollment for applicable eligibility criteria as specified in Sections 4.1 and 4.2 and the Screening Case Review process.

The Data Management Center's (DMC) Study Enrollment System (SES) will be used to assist with tracking the screening and enrollment process. When informed consent is obtained, a participant identification number (PID) will be assigned, and a study-specific screening number will be obtained for the potential participant through the SES. For potential 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) and study drug prescribing information. For potential participants found to be ineligible for the study, or who do not enroll in the study for any reason, limited demographic information and reasons for non-enrollment will be entered into an electronic case report form (eCRF).

4.6 Participant Retention

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

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:

- The participant re-locates away from the study site (with no options for transfer to another site) or is otherwise determined to be lost-to-follow-up.
- The participant fails to comply with the study requirements so as to cause harm to themself or seriously interfere with the validity of the study results in the opinion of the investigator and/or the study sponsor.
- Female participant of reproductive potential who reports sexual activity that could lead to pregnancy is not willing or able to use two methods of contraception (see Section 8.7).

- Male participant engaging in sexual activity that could lead to pregnancy of a female partner is not willing or able to use a barrier method of contraception until four weeks after discontinuation of BDQ (see Section 8.7).
- Investigator or designee determines that continued participation in the study would be unsafe or otherwise not in the best interest of the participant, in consultation with the Core Team.
- The study is stopped or canceled by the sponsor or government or regulatory authorities.
- Site participation in the study is canceled by the sponsors, government or regulatory authorities, or site IRBs/ECs.
- Participant (or guardian) elects to enroll participant in another clinical research trial not approved by the Core Team for co-enrollment.

For any participant who is withdrawn or terminated from the study prior to scheduled completion of follow-up, study staff should document the reason(s) for withdrawal or termination and make every effort to complete final evaluations as described in Section 6.13. As part of the informed consent process, participants will be asked to permit additional contact if the participant withdraws from the study prior to the scheduled duration of study follow-up. In these cases, when consent has been obtained for continued contact, participants will be considered to be on study and participation will be limited to participant contacts as specified in Section 6.10.

If the circumstances that led to a participant's withdrawal or termination change (e.g., they return to the study site area after having re-located previously), the site investigator or designee should contact the Core Team to discuss options for resuming follow-up.

5 STUDY DRUG

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

5.1 Study Drug Formulations

BDQ is supplied as 100 mg tablets and/or as dispersible 20 mg scored tablets.

BDQ fumarate is a white to almost white powder and is stated to be insoluble in aqueous media in the package insert. BDQ 100 mg oral tablets contain 120.89 mg of BDQ fumarate, which is equivalent to 100 mg of BDQ. The BDQ 20 mg functionally scored tablet contains 24.18 mg of BDQ fumarate, equivalent to 20 mg of BDQ. The 20 mg tablets may be evenly divided into two 10 mg halves for dosing purposes. Only participants in Cohorts 2 and 3 may receive the BDQ pediatric formulation (20 mg scored tablet), based on preference and availability.

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

5.2 Study Drug Regimens

Cohort 1 participants will receive BDQ as defined in Table 2; however, dosing may change following safety and PK analysis as outlined in Section 3. For Cohorts 2 and 3, BDQ dosing is determined using model-based selection methods and a weight-banded approach, based on

available data from Cohort 1 and emerging information from other studies (see Sections 8, 9, and 10) using both formulations. Participants in Cohorts 2 and 3 will receive BDQ as defined in Table 3; however, dosing may change following interim safety and PK analysis as outlined in Section 3.2 and with the availability of the novel pediatric formulation.

For all cohorts, study drug (BDQ) will be initiated at Entry and continued through the Week 24 visit as indicated in Table 2 and Table 3. During the initial daily dosing phase, participants will receive at least 14 and no more than 17 BDQ daily doses, including the BDQ dose administered on the day of intensive PK sampling and any non-study BDQ doses taken prior to enrollment. BDQ daily dosing will be initiated (or continued, if applicable) at Entry and continued through the intensive PK sampling at the Week 1 or Week 2 visit based on the date of initiation of BDQ daily dosing, including any non-study BDQ doses take prior to enrollment. For example, participants who received seven non-study BDQ doses prior to Entry will have intensive PK sampling at the Week 1 visit on Days 6-9. Alternatively, participants who received three non-study BDQ doses prior to Entry may have intensive PK sampling scheduled at the Week 1 visit on Day 10 or at the Week 2 visit on Days 11-13. For participants who initiate BDQ daily dosing at the Entry visit, the intensive PK sampling will take place at the Week 2 visit. BDQ TIW dosing will be initiated following the intensive PK sampling visit and continued until the Week 24 visit (inclusive). See Section 6.7 for details regarding the final BDQ dose administration during the Week 24 visit and/or visit window. See Section 5.3 for further guidance on study drug administration.

The BDQ dose should only be changed at protocol-specified and interim study visits based on the participant's weight at the visit. A further clarification applies to on-treatment visits with intensive and sparse PK sampling. At these visits, if a dose change is indicated based on the participant's weight measured at the visit, the dose change should be implemented after the PK sampling is completed. The BDQ dose given at the visit should be the same dose the participant was receiving immediately prior to the visit. Thereafter, the next BDQ dose given (after the PK sampling is completed) should be the changed dose based on the participant's current weight.

Following interim analysis of PK and safety data for Cohorts 2 and 3, if the Core Team determines that a dose adjustment is warranted for these cohorts because the PK criteria in Section 3.2 are not met and/or safety concerns are identified, then the selected dosing option in Appendix XI will be communicated to sites in a Memorandum of Operational Instruction approved by the Core Team. Each site must confirm receipt of the memorandum distributed by the protocol team prior to implementation of the dose regimen change. The site Investigator of Record (IoR) is responsible for ensuring that the memorandum is distributed to relevant study staff and that the site pharmacist is aware of any dose regimen changes. If the appropriate dose and/or regimen option is not included in the protocol, then an updated dosing table or regimen option will be provided through a protocol amendment.

Table 2
Cohort 1 BDQ Dosing

Age	Weight	Entry through the Intensive PK visit	After the intensive PK sampling visit and through the Week 24 visit
≥ 6 to < 18 years	≥30 kg	BDQ 400 mg once daily, every day Given as four ***100 mg tablets*** to equal 400 mg per dose Total weekly dose of 2,800 mg	BDQ 200 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses Given as two ***100 mg tablets*** to equal 200 mg per dose Total weekly dose of 600 mg
	≥15 kg to < 30 kg	BDQ 200 mg once daily, every day Given as two ***100 mg tablets*** to equal 200 mg per dose Total weekly dose of 1,400 mg	BDQ 100 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses Given as one ***100 mg tablet*** to equal 100 mg per dose Total weekly dose of 300 mg

Table 3
Cohort 2 and Cohort 3 BDQ Dosing

Age	Weight	Entry through the Intensive PK visit	After the intensive PK sampling visit and through the Week 24 visit
≥ 0 to < 6 years	> 7 kg to < 30 kg	BDQ 200 mg once daily, every day Given as two ***100 mg tablets*** *or* Given as ten ***20 mg tablets*** to equal 200 mg per dose Total weekly dose of 1400 mg	BDQ 100 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses. Given as one ***100 mg tablet*** *or* Given as five ***20 mg tablets*** to equal 100 mg per dose Total weekly dose of 300 mg
	≥ 3 kg to ≤ 7 kg	BDQ 100 mg once daily, every day Given as one ***100 mg tablet*** *or* Given as five ***20 mg tablets*** to equal 100 mg per dose Total weekly dose of 700 mg	BDQ 50 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses Given as half of a ***100 mg tablet*** *or* Given as two and one-half ***20 mg tablets*** to equal 50 mg per dose Total weekly dose of 150 mg

5.3 Study Drug Administration

For participants who are able to do so, BDQ 100 mg tablets should be swallowed whole with 10-20 mL of water and taken with food. Refer to the P1108 MOP for further administration instructions.

BDQ 20 mg tablets can be administered in one of the following ways as per the package insert: The tablets may be given whole or split into two equal halves of 10 mg tablets swallowed with water and taken with food; dispersed in water and administered with a beverage or soft food; or crushed and mixed with soft food (e.g., yogurt, apple sauce, mashed banana, or porridge). Refer to the P1108 MOP for further administration instructions.

Only participants in Cohorts 2 and 3 may take the BDQ 20 mg tablet formulation or the BDQ 100 mg tablet formulation based on preference (e.g., pill burden); the BDQ 20 mg formulation is encouraged for Cohort 3. Administration of the BDQ 20 mg pediatric formulation or BDQ 100 mg tablet should be determined in consultation with the participant and/or their guardian to ensure adherence to the study drug regimen. Participants should ideally take the same BDQ formulation from Entry through the Week 24 visit; however, participants may switch formulations, if needed. The Core Team must approve of participant BDQ formulation changes in advance. The BDQ formulation taken should be source documented and entered in appropriate eCRFs, including date of formulation changes, as applicable. See further detailed instructions regarding standard pill cutting, crushing, preparation of the dissolved formulation, and weight banding approaches in the P1108 MOP.

The first dose of study drug at Entry will be administered by study staff. Competency of the participant and/or caregiver/guardian to properly prepare and administer BDQ doses must be documented in the participant's chart by study staff at the Entry visit. BDQ doses after the Entry visit can be prepared and administered by participants and/or caregivers/guardians. *However, administration of BDQ should be observed by study staff at all on-treatment visits.*

At Entry, the pharmacist will dispense a sufficient quantity of study drug to last, at a minimum, through the participant's next scheduled visit. BDQ daily dosing will continue through the intensive PK sampling visit. Upon completion of intensive PK sampling at the Week 1 or Week 2 visit (see Sections 5.2, 6.3, and 6.4), TIW BDQ dosing will be initiated and continued through the Week 24 visit (i.e., Days 161-175). When taken TIW on Monday, Wednesday, and Friday, there should be at least 48 hours between doses.

Participants and/or their caregiver/guardian will be instructed not to administer BDQ at home on the day of intensive and sparse (pre-dose) PK sampling at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 visits. At these visits, BDQ will be administered at the clinic and observed by study staff as specified in Section 6 for the PK sampling collection.

The final BDQ dose should ideally be administered on the day the participant completes 24 weeks of BDQ treatment (i.e., 168 days), including any non-study BDQ doses taken prior to enrollment, at the site on the day of the Week 24 visit. If it is not feasible to conduct the Week 24 visit on day 168 of BDQ dosing, it is recommended that participants still complete BDQ treatment on (or close to) 168 days of BDQ dosing. If the Week 24 visit is scheduled prior to day 168 of BDQ dosing, BDQ may be dispensed for administration after the Week 24 visit through 168 days of BDQ dosing. If the final BDQ dose is not administered at the site during the Week 24 visit, then study staff should contact participants and/or their caregivers/guardians to confirm and document the date, time, and dose amount of the final BDQ dose administered within the Week

24 visit window. See further guidance and considerations for final BDQ dose administration and the Week 24 visit in Section 6.7.

The date, time, and dose amount administered for the two BDQ doses prior to each on treatment visit with PK sampling (i.e., Weeks 1, 2, 4, 8, 12, 16, 20, and 24 visits) should be documented and entered in eCRFs. Study staff will contact participants and/or their caregivers/guardians prior to the scheduled visit to confirm this dosing information. See further guidance in Section 6 for rescheduling visits if dosing information for BDQ doses taken prior to on treatment visits with PK sampling is not confirmed.

If a dose is missed from Entry through the intensive PK sampling visit (i.e., during BDQ daily dosing phase), participants should NOT make up the missed dose but should take their next dose as scheduled (see Table 2 and Table 3). After the intensive PK sampling is completed and TIW dosing is initiated, if a dose is missed, participants should take the missed dose as soon as possible and within 48 hours, and then resume the TIW schedule, maintaining 48 hours between doses. For example, if a dose is missed on a Wednesday and taken on the Thursday, the next dose should be given on the Saturday; Monday-Wednesday-Friday dosing can then restart the following week. There must be 48 hours between doses in the BDQ TIW dosing phase following the intensive PK sampling visit.

5.4 Study Drug Acquisition and Accountability

BDQ 20 mg tablets will be supplied by Janssen. Both BDQ 100 mg and 20 mg tablets will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities.

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

5.5 Study Drug Adherence Assessment and Counseling

DOT is expected to be used for BDQ administration throughout the study. Sites should work closely with participants and/or caregivers/guardians and with hospital and clinic personnel, as relevant, to ensure BDQ adherence and provide resources to document dosing of BDQ, other RR-TB treatment, and ARVs, as appropriate. Adherence to other routine RR-TB and ARV medications, where relevant, will be documented as described in Section 5.6.

5.5.1 In-Hospital BDQ Adherence

Adherence to study drug (daily through the intensive PK visit, and TIW thereafter through the Week 24 visit) will be documented with pill counts and a drug-dispensing card; ward dispensing charts may be used in addition to treatment card and recording of dispensing completed by hospital personnel or study personnel, as relevant.

5.5.2 Outpatient BDQ Adherence

Following hospital discharge as per local standard of care, participants may be treated on an ambulatory basis at local TB clinics, and adherence assessment will be done by the site using a TB dispensing card (TB treatment card) and ARV treatment card (as relevant). Local models of care (e.g., community-based TB treatment supporter or other healthcare worker or a trained family member/caregiver/guardian) may be used for adherence support for ambulatory care. If non-adherence is noted, adherence counseling may be provided by clinic and/or pharmacy staff consistent with local standards of care and site SOPs. Counseling should be provided in a client-centered manner, tailored as needed to the information, skills-building, and support needs of each participant and/or their caregiver/guardian administering BDQ.

5.6 Concomitant Medications

ARVs and RR-TB medications other than BDQ will not be provided by the study and will be obtained locally by the site as per local standard of care. In addition, all participants receiving high-dose INH as part of their TB treatment regimen may receive Vitamin B_6 (pyridoxine) per local standard of care. Sites may also directly support routine RR-TB treatment regimens or ARVs, based on local standard of care.

In addition to ARVs and other RR-TB medications, a log of all concomitant medications taken throughout the study must be source documented as part of the participant's medical and medication history obtained at each study visit (see Section 6). This includes, but is not limited to, prescription and non-prescription (over-the-counter) medications; vaccines and other preventive medications; contraceptives; co-trimoxazole; vitamins and other nutritional supplements; antifungals; other antibiotics; anti-epileptics; and alternative, complementary, and traditional medications and preparations. All TB medications, Vitamin B_6 (pyridoxine), ARVs, and other concomitant medications will be entered in eCRFs consistent with protocol Section 6 and applicable form instructions.

Based on the potential risks of BDQ, all sites should closely monitor participants taking concomitant medications that are potentially QT prolonging and consult the Core Team regarding the clinical management of any such participants as outlined in Section 5.7.1.

5.7 Prohibited and Precautionary Medications

5.7.1. Precautionary Medications During BDQ Administration

CFZ during BDQ administration is considered a precautionary medication. A list of other precautionary medications with potential QT prolonging effects is available on the study webpage at: https://impaactnetwork.org/studies/p1108. Sites should avoid the use of these medications whenever possible, including potentially stopping medications prior to enrollment as determined by the site investigator, in consultation with the Core Team.

The Core Team must be notified of any instances in which precautionary medications are required for participants as soon as possible and within three days of site awareness regarding options for management of participants who may require these medications.

The concurrent use of DLM with BDQ has been shown to be safe in adult studies (2, 81). While the use of DLM during BDQ administration is not prohibited in this study, it is considered

precautionary and must be discussed with the Core Team on an individual basis prior to administration of study drug. The Core Team may approve use of DLM if no other options to construct an effective RR-TB regimen are available. An adverse neuropsychiatric effect has been observed in children on DLM and should be carefully monitored in participants taking DLM. Sites must also inform the Core Team of plans to monitor participants taking DLM for potential neuropsychiatric effects.

5.7.2. Prohibited Medications During BDQ Administration

If an enrolled participant is identified as requiring a prohibited medication while receiving BDQ, the Core Team should be notified as soon as possible and within three business days of site awareness, ideally prior to administration of a prohibited medication. If use of a prohibited medication cannot be avoided, permanent discontinuation of BDQ, with subsequent termination from the study, may be required.

HMG-CoA reductase inhibitors (statins) are prohibited during BDQ administration. In addition, the following medications are prohibited during BDQ administration and for four weeks after the last dose of BDQ:

- Systemic use of moderate and strong CYP3A4 inhibitors (e.g., azole antifungals: ketoconazole, fluconazole, voriconazole, itraconazole, ketolides such as telithromycin; and macrolide antibiotics) for more than two weeks. *Note*: azithromycin and clarithromycin may be administered with BDQ.
- Systemic use of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's wort [Hypericum perforatum], rifamycins, and systemic, multiple dosing of dexamethasone)
- EFV. Administration of any other boosted protease inhibitors is not permitted without approval by the Core Team. *Note:* LPV/r may be administered.

Note: Older participants who are virologically suppressed on EFV may be switched to a study-approved ART regimen (see inclusion criterion 4.1.7) for the duration of BDQ dosing and for four weeks after the last dose of BDQ. This switch must occur ***at least 14 days before starting BDQ***, with Core Team approval obtained in advance as required per inclusion criterion 4.1.7.

6 STUDY VISITS AND PROCEDURES

Overviews of the study visits and evaluations schedule, and blood draw volumes for each visit, are provided in Appendix I. This section presents additional information on visit-specific study procedures.

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

All visits should be conducted as close as possible to specified target visit dates and within the visit windows. Procedures specified to be performed at a given study visit should ideally be performed on the same day. However, if this is not possible (e.g., if a participant must leave the clinical research site before all procedures can be performed) and unless otherwise specified, visits may be split, with procedures performed on more than one day within the visit window.

All study visits and procedures must be documented in accordance with DAIDS requirements 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.

Note: For sites that may experience operational disruptions due to COVID-19, guidance for study implementation during periods of disruption is provided in Appendix XII.

6.1 Screening Visit

Refer to Section 4.5 for a description of the study recruitment, screening, and enrollment process. Study-specific screening procedures may only be initiated after written informed consent, and assent if applicable, is obtained. Screening evaluations must be performed within 30 days prior to enrollment (i.e., including the day of enrollment at the Entry visit). Multiple visits may be conducted within this timeframe to complete all required screening procedures, if necessary.

The results of tests performed as part of clinical care may be abstracted from participant medical records and used for Screening if the tests meet the requirements specified in Section 6.16 and performed within the visit window. Operationally, specimen collection for required evaluations should be performed to minimize needle sticks, when possible.

After written informed consent, and assent if applicable, is obtained for potential participants and all screening evaluations are performed, a Screening Case Review as specified in the P1108 MOP should be submitted to the Core Team (impaact.p1108core@fstrf.org). This email should be submitted as soon as possible after all screening evaluations are performed and laboratory test results obtained to ensure that the Core Team has at least three business days to review and respond with findings and recommendations within the 30-day screening window. The Core Team will respond with any potential findings and recommendations. The site IoR or designee should incorporate feedback from the Core Team into the final eligibility determination for the potential participant at the Entry visit and prior to enrollment.

For potential participants who do not meet the eligibility criteria, screening may be discontinued once ineligibility is determined, including the Screening Case Review process.

Screening Visit Procedures *(within 30 days prior to enrollment)*		
Administrative and Regulatory		• Obtain written informed consent (and assent if required per site IRB/EC guidelines) • Assign PID • Obtain screening number from SES • Assess eligibility • Complete Screening Case Review
Clinical		• Obtain available medical records and medical and medication history • Determine HIV Status (see Section 4.3) • Perform complete physical exam • Perform ECG • Perform CXR • Assess TB disease status and severity (see Section 8.3) • *If participant is known to be RR-TB culture positive:* Contact the TB laboratory where the RR-TB diagnosis was made to ask for the isolate to be sent to the site DAIDS-approved TB lab for microbiology testing if available
Laboratory	**Blood**	Collect blood for: • Hematology: Complete blood count (CBC) with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • Liver Function Tests (LFT): ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • HIV testing (*if needed for determination of HIV status per inclusion criterion 4.1.4*) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) *Note: a negative pregnancy test must be obtained within five days prior to enrollment (see inclusion criterion 4.1.10)* • *If informed consent for storage and future use is obtained*: TB biomarkers
	Urine	Collect urine for: • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)
	Respiratory Specimen	*For all participants*: Collect sputum or gastric aspirate for TB microbiology testing*

*At least one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) will be collected for all potential participants at Screening. Collection of other specimens for TB testing may be performed at the site investigator's discretion and per local standard of care to confirm eligibility per inclusion criterion 4.1.5. Induced sputum or gastric aspirates will be collected in participants 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 participant for the duration of the study. See Section 8.4 and Laboratory Processing Chart (LPC).

All screening procedures are expected to be performed within 30 days prior to enrollment and as specified in Sections 4.1 and 4.2. 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
- HIV testing need not be repeated for participants previously determined to be living with HIV
- Previously documented medical and medication 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 Entry Visit (Day 0)

All Entry visit procedures should be performed on the day of enrollment. Entry visit procedures that may provide information relevant to eligibility for the study (e.g., medical history, physical exam) should be performed first, prior to final eligibility determination. For potential participants found to be ineligible for the study on the day of enrollment, enrollment should not occur.

Additional requirements for sequencing of procedures at the Entry visit are as follows:

- Final eligibility determination and confirmation must precede enrollment
- Enrollment must precede prescribing of study drug
- Prescribing of study drug must precede dispensing and administering of study drug

For all participants, BDQ daily dosing will continue through the intensive PK sampling visit, and participants should not receive more than 17 days of BDQ daily dosing, including any non-study BDQ doses taken prior to study drug administration at the Entry visit. BDQ TIW dosing will be initiated after the intensive PK sampling is completed. See Sections 6.3 and 6.4 for more information on visit schedule considerations for the intensive PK sampling at the Week 1 or Week 2 visit, respectively.

Applicable reminders should be provided prior to the scheduled Week 1 visit. The date, time, and dose amount administered for the two BDQ doses preceding the Week 1 visit should be confirmed prior to the visit. If this dosing information is not confirmed for the last BDQ dose taken prior to the Week 1 visit, the Week 1 visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date.

For participants that will have intensive PK sampling at the Week 1 visit (see Section 6.3):
Additional reminders should be provided for the intensive PK sampling, including arrangements for transportation and hospital admission, if applicable. The date, time, and dose amount administered for the two BDQ doses preceding the intensive PK visit should be confirmed prior to the visit. If this dosing information is not confirmed for the last BDQ dose taken prior to the Week 1 visit, the visit should be rescheduled within the allowable visit window, with adherence support provided to ensure appropriate dose administration on days preceding the rescheduled visit date. The participant and/or caregiver/guardian should be reminded not to administer the BDQ dose at home on the day of the intensive PK sampling at the Week 1 visit.

Entry 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 of study enrollment in the participant's file
Clinical		• Update medical and medication history since last visit* • Perform complete physical exam* • Perform ECG • Assess TB disease status and severity (see Section 8.3)
Study Drug		• Provide information on potential study drug side effects • Prescribe and dispense study drug for administration at the visit and in-home administration • Provide meal and administer first dose of study drug • Provide study drug storage and administration instructions and adherence counseling for in-home administration
Laboratory	**Blood**	Collect blood for: • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) ***Note*: For hematology, chemistries, and LFT, if the Entry visit is within seven days of specimen collection for these tests at the Screening visit, then hematology, chemistries, and/or LFT are not required to be done at the Entry visit unless clinically indicated*** • *For participants taking PAS or ETH*: TSH (and fT4 if TSH is elevated) • *If informed consent for storage and future use is obtained and visit is more than 14 days from Screening*: TB biomarkers *If participant is living with HIV, collect additional blood for:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages) • *If viral load ≥ 1,000 copies/mL*: Perform ARV genotypic resistance testing at the next scheduled visit or earlier as per the site investigator's discretion
	Urine	Collect urine for: • Urinalysis
	Respiratory specimen	*For participants with bacteriologically confirmed RR-TB diagnosis*: Collect sputum or gastric aspirate for TB microbiology testing**
Other	**Audiology**	*For participants taking an injectable TB medication*: Conduct audiology assessment as per local standard of care

*Perform prior to enrollment

***For participants with bacteriologically confirmed RR-TB at diagnosis per inclusion criterion 4.1.5*: At least one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) should be collected. Induced sputum or gastric aspirates will be collected in participants 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 participant for the duration of the study. Other types of specimens may be collected if routinely done by the clinical site as per local standard of care, in addition to sputum or gastric aspirate specimens. See Section 8.4 and LPC.

6.3 Week 1 Visit

The Week 1 visit is targeted to take place on Day 7, counted from the date of enrollment as Day 0, with an allowable window of -1 to +3 days (i.e., Day 6 – 10).

Participants who received non-study BDQ doses prior to Entry and will have intensive PK sampling at the Week 1 visit:

For participants who took non-study BDQ doses prior to the Entry visit and will complete at least 14 days of BDQ daily dosing during the visit window, including non-study BDQ doses, the intensive PK sampling may take place during the Week 1 visit. The intensive PK sampling should be scheduled ideally on day 14 of BDQ daily dosing. If this is not feasible, the intensive PK sampling may be scheduled on day 15, 16, or 17 of BDQ daily dosing (including the dose to be administered at the intensive PK visit) if these dosing days are within the Week 1 visit window. For example, participants that received five non-study BDQ daily doses prior to Entry may have the intensive PK sampling scheduled on day 14, 15, or 16 of BDQ dosing (i.e., Days 8, 9, or 10 on study). Participants that received six or seven non-study BDQ doses prior to Entry must have the intensive PK sampling performed at the Week 1 visit on day 14 and up to day 17 of BDQ daily dosing.

Requirements for sequencing of procedures at the Week 1 visit are as follows:

- Pre-dose intensive PK sample must be collected prior to observed administration of BDQ.
- ECGs should be performed within one hour before or after the pre-dose intensive PK sampling and 4-6 hours after BDQ administration.
- Other laboratory assays may be collected at any time during the visit, and preferably at the time of PK sampling collection.

BDQ TIW dosing will be initiated after the intensive PK sampling is completed (see Section 5.3). At the Week 1 visit, applicable reminders should be provided for the scheduled Week 2 visit (see Section 6.4). The participant and/or caregiver/guardian should be reminded not to administer BDQ at home on the day of sparse PK sampling at the Week 2 visit.

Participants who initiated BDQ treatment at Entry and participants who will not have intensive PK sampling at the Week 1 visit:

Sparse PK sampling will be performed at the Week 1 visit and must precede observed administration of BDQ by study staff. Otherwise, there is no required sequencing of procedures or specimen collections at this visit.

Applicable reminders should be provided for the intensive PK sampling at the Week 2 visit, including arrangements for transportation and hospital admission, if applicable (see Section 6.4). The date, time, and dose amount administered for the two BDQ daily doses preceding the Week 2 visit should be confirmed prior to the visit. If this dosing information is not confirmed for the last BDQ dose taken prior to the Week 2 visit, the visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date. The participant and/or caregiver/guardian should be reminded not to administer the BDQ dose at home on the day of intensive PK sampling. BDQ daily dosing will continue through the intensive PK sampling at the Week 2 visit.

Week 1 Visit Procedures *(Day 7, -1 to + 3 days)*	
Clinical	• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam • *For participants that will have intensive PK sampling at this visit:* Perform ECG within one hour before or after the pre-dose PK sampling and 4-6 hours after observed dose of study drug • Identify, review, and update AEs • Perform additional evaluations as applicable per Section 8 and/or if clinical indicated (consult the Core Team if indicated)
Study Drug	• Record date, time, and dose amount of the two BDQ doses taken prior to the visit • Prescribe and dispense study drug for in-clinic administration as needed • Provide meal and observe study drug administration following sparse or intensive pre-dose PK sampling, as applicable (see below) • Prescribe and dispense study drug for in-home administration as needed • Provide adherence counseling as needed
Laboratory	*For participants that will have intensive PK sampling at this visit:* Collect blood for intensive PK sampling at the following time points (at each time point collect 1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3): – Prior to observed dose of study drug – 2 hours (±15 minutes) after observed dose of study drug – 4 hours (±15 minutes) after observed dose of study drug – 6 hours (±15 minutes) after observed dose of study drug – 8 hours (±15 minutes) after observed dose of study drug *For participants that will <u>not</u> have intensive PK sampling at this visit:* Collect blood for sparse PK sampling prior to observed study drug administration (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) *For all participants*, collect blood for: • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries)

6.4 Week 2 Visit

The Week 2 visit is targeted to take place on Day 13, counted from the date of enrollment as Day 0, with an allowable window of -2 to +1 days (i.e., Day 11 – 14).

At the Week 2 visit, applicable reminders should be provided for the scheduled Week 4 visit (see Section 6.5). The participant and/or caregiver/guardian should be reminded not to administer BDQ at home on the day of sparse PK sampling at the Week 4 visit.

Participants who will have intensive PK sampling at the Week 2 visit:

Participants that did not have intensive PK sampling at the Week 1 visit will have intensive PK sampling performed at the Week 2 visit. The intensive PK sampling should be scheduled ideally on day 14 of BDQ daily dosing. If this is not feasible, the intensive PK sampling may be scheduled on day 15, 16, or 17 of BDQ daily dosing, as applicable within the Week 2 visit window. For example, participants that received four non-study BDQ daily doses prior to Entry and did not have intensive PK sampling at the Week 1 visit on day 14 or 15 of BDQ dosing (i.e., Day 9 or 10 on study) will have intensive PK sampling at the Week 2 visit scheduled on day 16 or 17 of BDQ daily dosing (i.e., Day 11 or 12 on study). Participants that did not initiate BDQ daily dosing prior to Entry will have intensive PK sampling performed at the Week 2 visit on day 14 or 15 of BDQ daily dosing (i.e., Day 13 or 14 on study). For all participants, BDQ TIW dosing will be initiated after the intensive PK sampling is completed (see Section 5.3).

Requirements for sequencing of procedures at the Week 2 visit are as follows:

- Pre-dose intensive PK sample must be collected prior to observed administration of BDQ.
- ECGs should be performed within one hour before or after the pre-dose intensive PK sampling and 4-6 hours after BDQ administration.
- Other laboratory assays may be collected at any time during the visit, and preferably at the time of PK sampling collection.

Participants who completed intensive PK sampling at the Week 1 visit:

Sparse PK sampling will be performed at the Week 2 visit and must precede observed administration of BDQ by study staff. Otherwise, there is no required sequencing of procedures or specimen collections at this visit.

Week 2 Visit Procedures *(Day 13, -2 to + 1 days)*		
Clinical		• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam • *For participants that will have intensive PK sampling at this visit:* Perform ECG within one hour before or after the pre-dose PK sampling and 4-6 hours after observed dose of study drug • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated)
Study Drug		• Record date, time, and dose amount of the two BDQ doses taken prior to the visit • Prescribe and dispense study drug for in-clinic administration as needed • Provide meal and observe study drug administration following sparse or intensive pre-dose PK sampling, as applicable (see below) • Prescribe and dispense study drug for in-home administration as needed • Provide adherence counseling as needed
Laboratory	**Blood**	*For participants that will have intensive PK sampling performed at this visit:* Collect blood for intensive PK sampling at the following time points (at each time point collect 1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3): – Prior to observed dose of study drug – 2 hours (±15 minutes) after observed dose of study drug – 4 hours (±15 minutes) after observed dose of study drug – 6 hours (±15 minutes) after observed dose of study drug – 8 hours (±15 minutes) after observed dose of study drug *For participants that will <u>not</u> have intensive PK sampling performed at this visit:* Collect blood for sparse PK sampling prior to observed study drug administration (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) *For all participants*, collect blood for: • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries)

6.5 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 ± 7 days (i.e., Day 21 – 35). The date, time, and dose amount administered for the two BDQ doses preceding the Week 4 visit should be confirmed prior to the visit. If this dosing information for the <u>last BDQ dose taken prior to the Week 4 visit</u> is not confirmed, the Week 4 visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date.

Sparse PK sampling must precede observed administration of BDQ by study staff. Otherwise, there is no required sequencing of procedures or specimen collections at this visit.

Week 4 Visit Procedures *(Day 28 ± 7 days)*		
Clinical		• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam • Perform ECG • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated)
Study Drug		• Record date, time, and dose amount of the two BDQ doses taken prior to the visit • Prescribe and dispense study drug for in-clinic administration as needed • Provide meal and observe study drug administration following sparse PK sampling • Prescribe and dispense study drug for in-home administration as needed • Provide adherence counseling as needed
Laboratory	**Blood**	Collect blood for*:* • *Prior to observed study drug administration:* Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) *If participant is living with HIV, collect additional blood for:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages) • *If viral load ≥ 1,000 copies/mL*: Perform ARV genotypic resistance testing at the next scheduled visit or earlier as per the site investigator's discretion
	Urine	Collect urine for*:* • Urinalysis • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)
	Respiratory Specimen	*For participants with bacteriologically confirmed RR-TB diagnosis*: Collect sputum or gastric aspirate for TB microbiology testing*

*At least <u>one</u> respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) should be collected. Induced sputum or gastric aspirates will be collected in participants 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 participant for the duration of the study. See Section 8.4 and LPC.

6.6 Week 6 Visit

The Week 6 visit is targeted to take place on Day 42, counted from the date of enrollment as Day 0, with an allowable window of ± 7 days (i.e., Day 35 – 49).

Applicable reminders should be provided for the scheduled Week 8 visit (see Section 6.7). The participant and/or caregiver/guardian should be reminded not to administer BDQ at home on the day of sparse PK sampling at the Week 8 visit.

Week 6 Visit Procedures *(Day 42 ± 7 days)*	
Clinical	• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated)
Study Drug	• Prescribe and dispense study drug for in-home administration as needed • Provide adherence counseling as needed

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

The Week 8, 12, 16, 20, and 24 visits are targeted to take place on Days 56, 84, 112, 140, and 168, respectively, counted from the date of enrollment as Day 0, with visit windows as outlined below:

- Week 8 has an allowable window of ± 7 days (i.e., Day 49 – 63)
- Week 12 has an allowable window of ± 14 days (i.e., Day 70 – 98)
- Week 16 has an allowable window of ± 14 days (i.e., Day 98 – 126)
- Week 20 has an allowable window of ± 14 days (i.e., Day 126 – 154)
- Week 24 has an allowable window of ± 7 days (i.e., Day 161 – 175)

The date, time, and dose amount administered for the two BDQ doses preceding each on treatment visit should be confirmed prior to the visit. If this dosing information is not confirmed for the last dose of BDQ taken prior to the visit, the visit should be rescheduled within the allowable visit window, with adherence support provided to help ensure appropriate dose administration on days preceding the rescheduled visit date.

Prior to the Week 8, 12, 16, 20, and 24 visits, the participant and/or caregiver/guardian should be reminded not to administer BDQ at home on the day of the visit. At these visits, sparse PK sampling must precede observed administration of BDQ by study staff. Otherwise, there is no required sequencing of procedures or specimen collections at these visits.

The final BDQ dose should ideally be administered on day 168 of BDQ dosing, including any non-study BDQ doses taken prior to Entry, and at the site on the day of the Week 24 visit. If the Week 24 visit cannot be scheduled on day 168 of BDQ dosing, it is recommended that the participant still completes BDQ treatment on (or close to) day 168 of BDQ dosing; however, the final BDQ dose may be administered on any day within the Week 24 visit window as per the BDQ TIW dosing schedule (i.e., Days 161–175 on study). If the Week 24 visit is scheduled prior to day 168 of BDQ dosing, BDQ may be dispensed for administration after the visit through 168 days of BDQ dosing.

If the final BDQ dose will not be administered at the site during the Week 24 visit, study staff must contact participants and/or their caregivers/guardians to confirm the date, time, and dose amount of the final BDQ dose administration, ideally on the day the final BDQ dosing is planned. Study staff will need to collect any remaining study drug and dosing supplies within the visit window and as soon as possible after the final BDQ dose is administered.

On Treatment Visit Procedures: Week 8 (Day 56 ± 7 days), Week 12 (Day 84 ±14 days), Week 16 (Day 112 ±14 days), Week 20 (Day 140 ± 14 days) and Week 24 (Day 168 ± 7 days)		
Clinical		• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam (*include height at Weeks 8 and 24, and as clinically indicated*) • Perform ECG • *At Weeks 8, 16, and 24 only in participants with pulmonary TB:* Perform CXR • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated)
Study Drug		*At Weeks 8, 12, 16, and 20:* • Record date, time, and dose amount of the two BDQ doses taken prior to the visit • Prescribe and dispense study drug for in-clinic administration as needed • Provide meal and observe study drug administration following sparse PK sampling • Prescribe and dispense study drug for in-home administration as needed • Provide adherence counseling as needed *At Week 24*: • Confirm date, time, and dose amount of final study drug administration • Collect any remaining study drug and supplies • *Note: For participants who do not take the final BDQ dose at the Week 24 visit, any remaining study drug and supplies should be collected as soon as possible after the final BDQ dose is administered and within the visit window*
Laboratory	**Blood**	Collect blood for*:* • *Prior to observed study drug administration:* Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *At Weeks 8, 16, and 24, for participants taking PAS or ETH:* TSH (and fT4 if TSH is elevated) • *At Week 24 only, if informed consent for storage and future use is obtained:* TB biomarkers • *At Weeks 8, 16, and 24 only, if female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) *If participant is living with HIV, collect additional blood for the following at Weeks 12 and 24 visits only:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages)

		If viral load ≥ 1,000 copies/mL at Weeks 12 and 24 visits only: Perform ARV genotypic resistance testing at the next scheduled visit or earlier as per the site investigator's discretion
	Urine	Collect urine for: • Urinalysis • *At Weeks 8, 16, and 24 only, if female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)
	Respiratory Specimen	*For participants with bacteriologically confirmed RR-TB diagnosis without three consecutive negative culture results following bacteriological confirmation*: Collect sputum or gastric aspirate for TB microbiology testing*
Other	**Audiology**	*At Weeks 8, 16, and 24 only in participants taking an injectable TB medication*: Conduct audiology assessment as per local standard of care

*At least one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) should be collected. Induced sputum or gastric aspirates will be collected in participants 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 participant for the duration of the study. Other types of specimens may be collected if routinely done by the clinical site as per local standard of care, in addition to sputum or gastric aspirate specimens. See Section 8.4 and LPC.

6.8 Off-Treatment Visit Procedures (8, 16, 24, 36, and 48 weeks after BDQ Discontinuation)

The Week 32, 40, 48, 60, and 72 visits are targeted to take place on Days 224, 280, 336, 420, and 504, respectively, counted from the date of enrollment as Day 0, with visit windows as outlined below.

- Week 32 has an allowable window of ± 28 days (i.e., Day 196 – 252)
- Week 40 has an allowable window of ± 28 days (i.e., Day 252 – 308)
- Week 48 has an allowable window of ± 28 days (i.e., Day 308 – 364)
- Week 60 has an allowable window of ± 42 days (i.e., Day 378 – 462)
- Week 72 has an allowable window of ± 42 days (i.e., Day 462 – 546)

For participants that prematurely discontinue BDQ prior to the Week 24 visit and remain on study, study follow-up visits should be scheduled at 8, 16, 24, 36, and 48 weeks after the date of BDQ discontinuation. Visits at 8, 16, and 24 weeks after BDQ discontinuation have an allowable window of ± 28 days from the date of BDQ discontinuation. Visits at 36 and 48 weeks after BDQ discontinuation have an allowable window of ± 42 days from the date of BDQ discontinuation.

Off-Treatment Visit Procedures: Weeks 32, 40, 48, 60, and 72 (8, 16, 24, 36, and 48 weeks after BDQ discontinuation, respectively) ***Visit Windows:*** ***Weeks 32, 40, and 48 (8, 16, and 24 weeks off BDQ): ± 28 days*** ***Weeks 60 and 72 (36 and 48 weeks off BDQ): ± 42 days***		
Clinical		• Obtain interval medical and medication history • Perform targeted physical exam (*include height at Week 48 or 24 weeks off BDQ only*) • *At Week 40 or 16 weeks off BDQ*: Perform ECG • *At Weeks 40 and 72 (16 and 48 weeks off BDQ) only in participants with pulmonary TB*: Perform CXR • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated) • *At Week 48 or 24 weeks off BDQ, for Cohort 3 HIV-exposed participants only*: Determine HIV status (see Section 4.3) • *At the visit following completion of RR-TB treatment:* Classify TB treatment outcome (see Section 8.5)
Laboratory	**Blood**	Collect blood for*:* • Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *At Weeks 32, 48, and 72 (8, 24 and 48 weeks off BDQ), for participants taking PAS or ETH*: TSH (and fT4 if TSH is elevated) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) • *At Week 48 or 24 weeks off BDQ, for Cohort 3 HIV-exposed participants only*: HIV testing, if acceptable documentation is not available (see Section 4.3) *If participant is living with HIV, collect additional blood for:* • *At Weeks 32 and 48 (8 and 24 weeks off BDQ) only:* Lymphocyte subsets (including CD4/CD8 counts and percentages)
	Urine	Collect urine for: • Urinalysis • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)
	Respiratory Specimen	*For participants with bacteriologically confirmed RR-TB diagnosis without three consecutive negative culture results following bacteriological confirmation*: Collect sputum or gastric aspirate for TB microbiology testing*

*At least one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) should be collected. Induced sputum or gastric aspirates will be collected in participants 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 participant for the duration of the study. Other types of specimens may be collected if routinely done by the clinical site as per local standard of care, in addition to sputum or gastric aspirate specimens. See Section 8.4 and LPC.

6.9 Week 96/End of Study Visit

The Week 96/End of Study visit is targeted to take place on Day 672, counted from the date of enrollment as Day 0, with an allowable window of ± 42 days (i.e., Day 630 – 714). For participants who discontinued study drug prior to the Week 24 visit, the End of Study visit should take place 72 weeks or 504 days after the last dose of BDQ, with an allowable window of ± 42 days from the date of the last BDQ dose. There is no required sequencing of procedures at this visit.

Participants exiting the study after this visit will be provided with information about how to contact study staff with any post-study questions and how to learn about the results of the study when available. Arrangements should be made to provide the participant and/or their guardian with clinically meaningful test results from the Week 96/End of Study visit. Information and referrals should be provided as needed to ensure transition to non-study sources of care and treatment for the participant as needed. If a participant has an ongoing grade 3 or higher AE or the outcome of a pregnancy is unknown per protocol Section 8.7 at the Week 96/End of Study visit, additional contacts should occur for study purposes as described in Section 6.10.

Week 96/End of Study Visit Procedures *(± 42 days)* (72 weeks after BDQ discontinuation)		
Administrative and Regulatory		• If participant has an ongoing grade 3 or higher AE at this visit, or the outcome of a pregnancy is unknown per protocol Section 8.7, confirm that informed consent has been obtained for continued contact as per protocol Sections 6.10 and 8
Clinical		• Obtain interval medical and medication history • Perform targeted physical exam (*include height*) • Identify, review, and update AEs • Perform additional evaluations per Section 8 and/or if clinical indicated (consult the Core Team if indicated) • *For Cohort 3 HIV-exposed participants only*: Determine HIV status (see Section 4.3) • Classify TB treatment outcome (see Section 8.5)
Laboratory	**Blood**	Collect blood for*:* • Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *For Cohort 3 HIV-exposed participants only*: HIV testing, if acceptable documentation is not available (see Section 4.3) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) • *If informed consent for storage and future use is obtained:* TB biomarkers *If participant is living with HIV, collect additional blood for:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages) • *If viral load ≥ 1,000 copies/mL*: Perform ARV genotypic resistance testing as per the site investigator's discretion

	Urine	Collect urine for: • Urinalysis • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)

6.10 Participant Contact After End of Study Visit or Early Study Discontinuation

Participants may be contacted after the Week 96/End of Study or Early Study Discontinuation visits:

- To document the outcome of a pregnancy.
- To follow an unresolved grade 3 or higher AE to resolution/stabilization. Follow-up for grades 1 or 2 unresolved AEs may also be done as per site investigator's discretion.
- To follow any unresolved TB treatment outcome.
- To obtain interim medical history, including TB symptoms and AEs, following early withdrawal from the study at 8, 36, and 72 weeks after the last dose of BDQ.
- To perform ARV genotypic resistance testing for participants living with HIV that have a viral load ≥ 1,000 copies/mL at these visits as per the site investigator's discretion.

Consent for this potential continued contact and evaluations will be obtained as part of the informed consent process. The outcome of a pregnancy must be recorded and can be obtained by participant contact at a clinic visit, telephone, and/or from medical documentation. If a female participant or partner of male participant is known to be pregnant at the time of early study withdrawal, the contact will continue until the outcome of the pregnancy is known.

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.

6.11 Unscheduled Visits

Participants may be seen at unscheduled study visits for clinical management evaluation or adherence concerns and education as needed per site investigator discretion. A targeted physical exam should be performed at the visit and interval medical and medication history obtained. Additional evaluations may be performed based on clinical indication.

6.12 Early BDQ Discontinuation

If BDQ is discontinued prior to the Week 24 visit for any reason, the participant should return to the site for an Early BDQ Discontinuation (D/C) visit as soon as possible and within seven days after BDQ discontinuation. Visit procedures for the Early BDQ D/C visit are listed in the table below. For participants who prematurely discontinue the study, see Section 6.13 for procedures that should be performed.

Note: For participants who prematurely discontinue BDQ and the study, procedures at the Early Study D/C visit that overlap with the Early BDQ D/C visit do not need to be repeated.

For participants who confirm continued consent to remain on study, study follow-up visits should be scheduled at 8, 16, 24, 36, and 48 weeks after the date of BDQ discontinuation, with visit procedures conducted per Section 6.8 and the SoE for Off-Treatment visits. Evaluations for the End of Study visit should be conducted at 72 weeks after BDQ discontinuation per Section 6.9.

Early BDQ D/C Visit Procedures *(+ 7 days after BDQ discontinuation)*		
Administrative and Regulatory		• Re-calculate participant's study follow-up visit schedule according to the time of the last BDQ dose
Clinical		• Obtain interval medical and medication history • Assess adherence to study drug • Perform targeted physical exam (*include height*) • Perform ECG • Perform CXR
Study Drug		• Collect any remaining study drug and supplies
Laboratory	**Blood**	Collect blood for*:* • Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *For participants taking PAS or ETH*: TSH (and fT4 if TSH is elevated) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) *If participant is living with HIV, collect additional blood for:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages) • *If viral load ≥ 1,000 copies/mL*: Perform ARV genotypic resistance testing at the next scheduled visit or earlier as per the site investigator's discretion
	Urine	Collect urine for*:* • Urinalysis • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)

6.13 Early Study Discontinuation

Refer to Section 4.7 for criteria for withdrawal from the study. For participants who prematurely discontinue the study prior to the scheduled completion of follow-up, every effort should be made to perform a final series of study evaluations, if possible, according to the table below, as soon as possible and within seven days of site awareness that a participant will discontinue study participation early. There is no required sequencing of procedures at these visits.

As part of the informed consent process, participants are asked for consent to periodic contact if the participant withdraws from the study early. Participants who provide consent for this will be contacted at 8, 36, and 72 weeks after the last BDQ dose to obtain interim history and, if a female participant or partner of male participant is known to be pregnant at the time of early study discontinuation, to document the pregnancy outcome.

Early Study Discontinuation Visit Procedures *(within 7 days of site awareness)*		
Administrative and Regulatory		• Confirm informed consent for continued contact at 8, 36, and 72 weeks after the last BDQ dose, as applicable
Clinical		• Obtain interval medical and medication history • Perform targeted physical exam (*include height*) • Perform ECG • Perform CXR • Classify TB treatment outcome (see Section 8.5) • *For Cohort 3 HIV-exposed participants only*: Determine HIV status (see Section 4.3)
Laboratory	**Blood**	Collect blood for: • Sparse PK sampling (1 mL for Cohorts 1 and 2 and 0.5 mL for Cohort 3) • Hematology: CBC with white cell differential and platelet count • Chemistries: Creatinine, electrolytes (i.e., Na^+, Cl, HCO_3, K^+, Ca^{2+}, Mg^{2+}) and albumin • LFT: ALT, AST, direct bilirubin, total bilirubin (may be done on the same sample collected for chemistries) • *For Cohort 3 HIV-exposed participants only*: HIV testing, if acceptable documentation is not available (see Section 4.3) • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed) *If participant is living with HIV, collect additional blood for:* • HIV-1 RNA PCR • Lymphocyte subsets (including CD4/CD8 counts and percentages) • *If viral load ≥ 1,000 copies/mL*: Perform ARV genotypic resistance testing as per the site investigator's discretion
	Urine	Collect urine for: • Urinalysis • *If female and of reproductive potential*: Pregnancy test (blood or urine test may be performed)
	Respiratory Specimen	*For participants with bacteriologically confirmed RR-TB diagnosis or if clinically indicated*: Collect sputum or gastric aspirate for TB microbiology testing*

*At least one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) should be collected. Induced sputum or gastric aspirates will be collected in participants unable to expectorate sputum spontaneously, as per local standard of care. The choice of procedure will be according to local practice, preferably with the same technique used for each participant for the duration of the study as clinically feasible. Other types of specimens may be collected if routinely done by the clinical site as per local standard of care, in addition to sputum or gastric aspirate specimens. See Section 8.4 and LPC.

6.14 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 Entry visits, 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 caregiver/guardian report), and 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. Relevant dates will be source documented for all conditions and medications; see Section 5.6 for more information on concomitant medications.

At a minimum, the following should be source documented as part of the baseline medical and medication history and entered in eCRFs as applicable per eCRF instructions:

- Date of birth
- RR-TB diagnosis
- TB exposure history
- TB treatment history
- HIV status
- For participants living with HIV: Date of diagnosis, WHO clinical stage, current and prior ARV regimen(s), most recent CD4 count and viral load, and history of immune reconstitution inflammatory syndrome
- Reproductive and obstetrical history (if applicable)
- 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, including signs or symptoms of ongoing or recurrent diarrhea, vomiting, or electrolyte losses
- All medications taken within the 30 days prior to enrollment and/or ongoing at the time of enrollment
- Any other information needed to complete the Screening Case Review during Screening as specified in the P1108 MOP and to determine eligibility for the study

Table 4 specifies the interval medical and medications history elements that must be source documented, as well as associated eCRF entry requirements.

Table 4
Documentation Requirements for Interval Medical and Medication Histories

Assess for and document in Source Documents	Enter into eCRFs
Interval Medical and Medication History Elements	
Any change of guardianship	Yes
Current status of conditions that were ongoing at the previous visit	Any updates of previous entries (e.g., resolution dates)
Occurrence of any new conditions and new TB exposure since the last visit	Any newly identified AEs that meet criteria in Section 7.2
Current status of medications that were ongoing at the previous visit	Any updates of previous entries (e.g., stop dates)
Use of any new medications since the last visit	All ARVs, concomitant medications (including over the counter medicines and herbal remedies), and all TB medications taken from time of enrollment through completion of follow-up

6.15 Physical Examinations

A physical examination is required at each scheduled visit. Complete examinations are required at the Screening and Entry visits; targeted examinations only are required at all other visits.

Complete physical exams should include the following:
- Height measurement (or recumbent length if less than two years of age)
- Weight measurement
- Vital signs, including temperature, blood pressure, pulse, and respiratory rate. *Note: blood pressure does not need to be collected for participants three years of age and under.*
- Examination of respiratory, cardiovascular, and other organ systems

Targeted physical exams should include the following:
- Height measurement (or recumbent length for Cohort 3 participants) at Weeks 8, 24, 48 (or 24 weeks post BDQ), Week 96/End of Study, Early BDQ D/C, and Early Study D/C visits, and as clinically indicated
- Weight measurement
- Vital signs, including temperature, blood pressure, pulse, and respiratory rate. *Note: blood pressure does not need to be collected for participants three years of age and under.*
- Examination of body systems based on prior and new signs, symptoms, and diagnoses

At all visits, additional assessments may be performed at the discretion of the site investigator. All exam findings should be source documented and the following should be entered into eCRFs: height/recumbent length, weight, and vital signs. Abnormal findings identified prior to enrollment will be entered into medical history eCRFs as pre-existing conditions. Abnormal findings identified after enrollment will be entered into AE eCRFs as specified in Section 7.2.

6.16 Additional Considerations for Laboratory Procedures

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for DAIDS Funded and/or Sponsored Laboratories in Clinical Trials Policy, which is available at: https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf

6.16.1 Specimen Collection

Specimens will be collected for this study as indicated in the SoE and per the LPC, available on the study webpage: https://www.impaactnetwork.org/studies/p1108

Consistent with NIH Guidelines for Limits of Blood Drawn for Research Purposes at the NIH Clinical Center, 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 (hematology, chemistries, LFT, TSH, and fT4 if TSH is elevated)
2. PK
3. HIV-1 RNA PCR
4. Lymphocyte subsets
5. Storage for future use

6.16.2 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 6.16, site and local laboratory SOPs, and the LPC. The frequency of specimen collection and testing will be directed by Section 6 and the SoE and specifications for clinical management provided in Section 8. The Laboratory Data Management System (LDMS) will be used to document specimen collection, testing, storage, and shipping as specified in the LPC.

Mycobacterial isolates collected from participants will be shipped and stored centrally for future analysis. Any remaining volume from samples collected for PK analysis will be stored.

Lymphocyte subsets must be performed in a DAIDS Immunology Quality Assessment certified laboratory. HIV PCR tests must be performed in a VQA-certified laboratory, and HIV antibody tests must be performed in a laboratory that operates according to GCLP guidelines and participates in an appropriate external quality assurance program.

6.16.3 Biohazard Containment

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

Respiratory pathogens such as *M.tb* and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are transmitted by inhalation of droplet nuclei. Appropriate precautions will be employed by all personnel in participant 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 CDC and the NIH.

7 SAFETY MONITORING, ASSESSMENT AND REPORTING

Participant safety will be carefully assessed, monitored, and reported at multiple levels throughout this study. Sections 7.1-7.3 describe safety-related roles, responsibilities, and procedures for site investigators. The safety monitoring roles of the Core Team and the SMC are briefly referenced in Section 7.1 and described in greater detail in Section 9.5.

7.1 Safety-Related Roles and Responsibilities

7.1.1 Site Investigators

Site investigators are responsible for continuous monitoring of study participants and for notifying the Core Team if safety concerns arise. Site investigators will enter safety-related data into eCRFs as indicated in Section 7.2 and complete EAE reporting as indicated in Section 7.3.

Site investigators are also responsible for prompt reporting of any unanticipated problems involving risks to participants or others to all applicable IRBs/ECs and other applicable review bodies, per the procedures of each applicable review body.

7.1.2 Core Team

Routine monitoring will be performed by the Core Team, which consists of at a minimum the Protocol Chair, Vice Chair, NIAID and NICHD Medical Officers, Statisticians, Pharmacometricians, Pharmacologists, Data Managers, Laboratory Specialists, Laboratory Data Managers, Cardiologist, Microbiologist, and the Clinical Research Managers or their designees. The Core Team 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 AEs, study drug administration, and other concomitant medications. Refer to Section 8 for more information on participant management.

On behalf of the full Protocol Team, the Core Team will monitor participant safety through routine review of study data reports as described in Section 9.5. The Statistical and Data Management Center (SDMC) will prepare routine safety monitoring and clinical data reports for review by the Core Team, which will meet throughout study implementation to review safety data, discuss study drug management, and address any potential safety concerns.

7.1.3 Study Monitoring Committee (SMC)

The SMC will monitor participant safety through routine and as needed reviews of study data. The frequency of SMC reviews will be determined by the accrual rate and is planned to occur annually. Reports for the annual review may be minimal if accrual rate is slow. The SMC may also be convened upon request of the Core Team. The SMC will be requested to focus on specific study aspects including ECG data review, long-term safety, and other safety measures as needed. Based on any of its reviews, the SMC may recommend that the study proceed as currently designed, be paused, proceed with design modifications, or be discontinued. The SMC will also review Cohort 1 data prior to the opening of Cohorts 2 and 3. Refer to Section 9.5 for more information on the role of the SMC in monitoring this study.

7.2 Safety-Related Data Collection

Note: This section describes eCRF data collection requirements for pre-existing conditions and AEs. As part of this description, reference is made to severity grading and criteria for EAE reporting; refer to Section 7.3 for detailed information on these topics.

The definition of an AE 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 all participants, beginning after administration of the first dose of BDQ. Any untoward medical conditions identified prior to administration of the first dose of BDQ 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 AEs identified will be recorded in eCRFs as described in this section.

Pre-Existing Conditions

All pre-existing conditions (i.e., all grade 1 or higher) identified from 30 days prior to study entry and the time of the first dose of BDQ will be entered into eCRFs. Among other details, the severity of all such conditions will be entered into eCRFs.

Adverse Events

The following AEs – except as specified in the IMPAACT Do Not Report List – identified after the first dose of study drug is administered will be entered into AE eCRFs:

- Grade 3 or higher AEs
- All AEs that lead to a dose modification or discontinuation of study drug
- 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 AE eCRFs, further details for ECGs, including QT intervals, will be entered in designated eCRFs (see Section 8.6). All AEs should be further evaluated as specified in Section 8.1, with additional data recorded on relevant eCRFs.

Note: Suspected, probable, and confirmed diagnoses of infection with SARS-CoV-2 should be reported consistent with WHO case definitions for COVID-19 disease, which are available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-SurveillanceGuidance-2022.2

Laboratory Test Results

All laboratory test results during the study will be entered into relevant eCRFs, regardless of severity grade and whether the test was protocol-specified or ordered by the site investigator for clinical purposes.

7.3 Expedited Adverse Event (EAE) Reporting

7.3.1 EAE Reporting to DAIDS

Requirements, definitions, and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at:
https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at: https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting

For questions about DAERS, please contact NIAID Clinical Research Management System (CRMS) Support at: CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact DAIDS RSC Safety Office at: 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, dated January 2010, will be used for this study. The study drug for which expedited reporting is required is bedaquiline (BDQ).

7.3.3 Grading Severity of Events

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, will be used in this study. This table is available on the RSC website at:
https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables

Exceptions to this are grading for axillary measured fever, ECGs, and cardiac clinical criteria. Axillary measured fever will be graded per Table 5, and ECGs and cardiac clinical criteria will be graded per Appendix V.

Table 5
Axillary Measured Fever Grading

Grade 1	Grade 2	Grade 3	Grade 4
37.4 to < 38.0° C	38.0 to < 38.7° C	38.7 to < 39.4° C	≥ 39.4° C

For creatinine and creatinine clearance, grading should be based on the absolute value only as per the DAIDS AE Grading Table, and not on percentage change from the participant's baseline value. Additionally, underweight events are only required to be graded per the DAIDS AE Grading Table if there is a clinical indication as per the site investigator's discretion (e.g., documented weight-for-age less than the third percentile).

7.3.4 EAE Reporting Period

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

After the protocol-defined EAE reporting period, unless otherwise noted, only suspected, unexpected, serious adverse reactions 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 drug, assessed by the site investigator according to the following categories: definitively related, probably related, possibly related, probably not related, and not related, as outlined below. Further standardized guidance on determining relationship to study drug is available in the DAIDS EAE Manual (referenced in Section 7.3.1).

Relationship categories for AEs are as follows:

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.

As described in detail below, AEs will be managed based on their severity and assessed relationship to study drug (BDQ). AEs will be assessed clinically, through lab or other

investigation, and by caregiver/guardian or participant self-report, where appropriate. Data for AEs will be entered in eCRFs as specified in Section 7.2.

Appendix VIII provides general guidance for management of study drug (BDQ) in response to toxicities. Guidance on BDQ management for specific toxicities is also provided as follows:

- Appendix VI: ECG-determined and clinical cardiac toxicity
- Appendix IX: Bilirubin, AST, ALT, myalgia, and nausea and vomiting

Site investigators will consult the Core Team as directed in Appendices VI, VIII, and IX and otherwise at the site investigator's discretion as needed. **When management of an AE requires consultation with the Core Team, the Core Team should be contacted as soon as possible and within three business days of site awareness of the event, unless otherwise directed below and in Appendices VI, VIII, and IX. The Core Team should be notified as soon as possible of any interruption of study drug (BDQ).**

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 and as specified in Appendices VI, VIII, and IX. The baseline value will be the latest assessment with a non-missing value prior to first study drug exposure at Entry.

Additional evaluations beyond those listed in Appendix I 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 drug. 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 grade 3 or higher AE at the time of the End of Study visit (Week 96 and/or 72 weeks post BDQ), and/or other AEs as per site investigator's discretion, will continue to be followed until resolution or stabilization of the event. The Core Team may request additional follow-up of selected AEs based on the clinical context.

Note: Participants with signs and/or symptoms potentially consistent with COVID-19 should be referred for testing as per local standard of care and the site investigator's discretion.

All participants will ideally remain on study and complete all follow-up visits, even if BDQ is discontinued early due to a toxicity or other reason(s).

8.2 Background RR-TB Therapy

In addition to BDQ, all participants will be on other appropriate TB drugs for RR-TB therapy based on available DST data (of the participant and/or the adult source case), WHO and/or in-country treatment guidelines, and locally available treatment. The RR-TB regimen may be modified according to DST of the participant or the adult source case, as appropriate (see Section 8.4), and available TB therapy. Refer to Appendix IIA for an overview of routine anti-TB drugs used in the management of pediatric RR-TB.

8.3 TB Disease Status and Severity

TB disease status and severity (82) should be assessed at Screening and Entry visits and entered in appropriate eCRFs. Routine screening and investigation for TB disease status and severity will follow local standard of care and procedures in routine locally accredited TB labs including

bacteriology – culture, smear microscopy, molecular testing (e.g., Xpert MTB/RIF Ultra) – in combination with phenotypic or molecular confirmation of RR-TB through DST, clinical history, standard symptom-based questionnaire (83), physical exam, and TB exposure history. TB disease status should be assessed as bacteriologically confirmed RR-TB or probable RR-TB and information collected on disease type (e.g., pulmonary TB, extrapulmonary TB) based on inclusion criterion 4.1.5. TB disease severity should be assessed as severe or non-severe disease; see further guidance in the study MOP.

Standard CXR reading will be done to capture radiological features and assess TB disease status and severity. CXRs will be done as per Section 6 and Appendix I and as clinically indicated. Available CXR results should be reviewed as part of TB disease status and severity assessments. Radiologic assessments should be interpreted per site-specific standard guidelines for CXR review by site investigators with expertise in pediatric TB, using a standard published CXR reading tool (84). The Core Team may be consulted as needed for questions regarding TB disease status and severity.

8.4 Specimens for TB Microbiology

Respiratory specimens for TB microbiology testing (expectorated sputum, induced sputum, or gastric aspirate) will be collected at study visits as specified in Appendix I and Section 6. Additional TB specimens and testing may be performed as clinically indicated at the discretion of the site investigators. All TB specimens collected for the study will be tested in the site's DAIDS-approved TB laboratory. TB microbiology results will be documented and entered in applicable eCRFs. Refer to the P1108 MOP for further guidance on TB specimen collection and LPC for guidance on TB mycobacteriology testing.

Sputum will be collected in older participants who can effectively expectorate sputum. Induced sputum or gastric aspirates will be collected in participants 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 ideally used for a participant for the duration of the study. Fine needle aspiration of peripheral lymphadenopathy may also be collected as clinically indicated. In addition to sputum or gastric aspirate specimens, other types of specimens (e.g., nasopharyngeal aspiration, stools, etc.) may be collected if routinely done by the clinical site.

All participants will have one respiratory specimen (expectorated sputum, induced sputum, or gastric aspirate) collected at Screening. Specimens collected during Screening, and at the Entry visit for bacteriologically confirmed RR-TB participants per Section 6.2, will be sent for concentrated fluorescent smear microscopy, Xpert MTB/RIF Ultra, and TB culture (solid media and automated liquid culture by Mycobacteria Growth Indicator Tube (MGIT)). If the culture is positive for *M.tb*, phenotypic and genotypic DST will be performed for first-line and second-line drugs (see LPC for further guidance).

Note: Xpert MTB/RIF Ultra will only be done at Screening and Entry visit (for bacteriologically confirmed RR-TB participants only) and will not be done at study follow-up visits.

Participants enrolled with bacteriologically confirmed RR-TB per inclusion criterion 4.1.5 will have respiratory specimens collected at study visits as specified in Appendix I and Section 6 for confirmation of microbiological cure of *M.tb*. Following the Week 4 visit, respiratory specimens will only be collected for bacteriologically confirmed RR-TB participants without three consecutive negative culture results from specimens collected after bacteriological confirmation, including any results obtained from routine care testing.

Participants enrolled with probable RR-TB per inclusion criterion 4.1.5 will not have specimens collected for TB microbiology testing after the Screening visit unless positive bacteriology results are obtained thereafter or bacteriologic testing (mycobacterial culture) is clinically indicated (e.g., new symptoms, worsening of symptoms or chest radiographs, or new TB exposure has occurred). Participants enrolled with probable RR-TB who subsequently have a positive TB culture result will be considered to have bacteriologically confirmed RR-TB and respiratory specimens should be collected at study visits as specified in Appendix I and Section 6. For these participants, it is recommended to also contact the TB laboratory where the RR-TB diagnosis was made to request the isolate be sent to the site DAIDS-approved TB lab for microbiology testing if available.

If cultures are negative and subsequently re-convert to positive, or if the participant's response to TB therapy is poor in the opinion of the site investigator, culture and DST should be repeated at follow-up visits as clinically indicated. In addition, *M.tb* isolates, where available, will be stored for gene sequencing for retrospective testing. Sites should make reasonable attempts to source the original *M.tb* isolate, if available.

8.5 TB Treatment Outcome

Site investigator assessments of participants' TB treatment outcomes will be done at the off-treatment visit following completion of the participant's RR-TB treatment regimen (i.e., at 8, 16, 24, 36, and 48 weeks after BDQ discontinuation visits) and at the Week 96/End of Study or Early Study D/C visits. Participants will be assessed through CXR at study visits as specified in Section 6. CXR should also be done as clinically indicated until the end of TB treatment as per local standard of care. Participants will also be assessed by clinical resolution of TB symptoms and mycobacterial culture and smear conversion, in the case of bacteriologically confirmed RR-TB, as appropriate.

At the end of RR-TB treatment, participants' TB treatment outcome should be documented as bacteriological cure, probable cure, treatment failure, death, or lost to follow-up as defined in Table 6 (14). Participants' TB treatment outcome at the Week 96/End of study or Early Study D/C visits should be documented as bacteriological cure without TB recurrence, probable cure without TB recurrence, TB recurrence, treatment failure, death, or lost to follow-up as defined in Table 7. TB treatment outcomes should also be recorded in appropriate eCRFs.

An independent Endpoint Review Committee (ERC), consisting of at least two international TB experts, will assess and determine the final TB treatment outcomes for the study analysis. A third reviewer may be asked to arbitrate if consensus has not been reached. The ERC will review site assessment of participants' TB treatment outcomes, as well as review CXRs and consult the Core Team as needed to evaluate TB treatment outcomes.

Table 6
TB Treatment Outcome at End of RR-TB Treatment Regimen: Classification for Participants with RR-TB*

Bacteriological outcome	And vs. Or	Clinical/radiological outcome	Category
Three consecutive negative respiratory cultures obtained at least one month apart (i.e., at least four study weeks) with no positive culture result after the first negative result until the end of RR-TB treatment**	AND	Completion of RR-TB treatment with clinical/radiological improvement in the assessment of site investigators AND no recrudescence of clinical/ radiological criteria for RR-TB at the end of RR-TB treatment	Bacteriological Cure
Bacteriological Cure criteria above are not met (for those with confirmed RR-TB at Entry and/or at screening), and do not meet bacteriological criteria below for Treatment Failure	AND	Completion of RR-TB treatment with clinical/radiological improvement in the assessment of site investigators AND no recrudescence of clinical/radiological criteria for RR-TB at the end of RR-TB treatment	Probable cure
Culture positivity (positive culture at the end of RR-TB treatment)	OR	Insufficient clinical/radiological improvement at the end of RR-TB treatment or recrudescence of clinical/radiological criteria for RR-TB while on treatment	Treatment failure
Any bacteriological outcome	AND	Death (grade 5 AE) for any reason while on RR-TB treatment or at any point at the end of RR-TB treatment	Death
Any bacteriological outcome	AND	Missed more than two months of consecutive treatment for RR-TB on study. *Note*: If participant returns to study and has completed study with cure/probable cure as treatment outcome despite having initially missed more than two months of RR-TB treatment and subsequently completed RR-TB treatment, the end point review committee may consider treatment outcome as Bacteriological Cure or probable cure.	Lost to follow-up

*For participants with probable RR-TB, only the "Clinical/Radiological Outcome" criteria will be used, and these participants cannot be classified as "Bacteriological cure" but "Probable cure".
**Contaminated samples or indeterminate results will not be counted in determining whether negative results are consecutive (e.g., if two consecutive culture results are both negative, followed by a contaminated results, and then followed by a negative result, then the participant meets this criterion.)

Table 7
TB Treatment Outcome at Week 96/End of Study: Classification for Participants with RR-TB*

Bacteriological outcome	And vs. Or	Clinical/radiological outcome	Category
Three consecutive negative respiratory cultures obtained at least one month apart (i.e., at least four study weeks) with no positive culture result after the first negative result until the end of study follow-up	AND	Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 96/End of Study or Early BDQ D/C visits, AND no recrudescence of clinical/radiological criteria for RR-TB by the end of study follow-up	Bacteriological Cure with no TB Recurrence
Bacteriological Cure criteria above are not met (for those with confirmed RR-TB at Entry and/or at screening), and do not meet bacteriological criteria below for Treatment Failure	AND	Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 96/End of Study or Early BDQ D/C visits AND no recrudescence of clinical/radiological criteria for RR-TB by the end of study follow-up	Probable cure with no TB recurrence
Culture positivity (positive culture at the Week 96/End of Study or Early BDQ D/C visits and after starting treatment until completion of TB treatment)	OR	Insufficient clinical/radiological improvement by the Week 96/End of Study or Early BDQ D/C visits or until end of treatment or recrudescence of clinical/radiological criteria for RR-TB while on treatment	Treatment failure
Three consecutive mycobacterial results from samples taken at least four study weeks apart are negative for mycobacterium TB complex** with no positive culture result thereafter until completion/end of TB treatment, OR Criterion as written above is not met (for those with confirmed RR-TB at baseline), but not meeting bacteriological criteria for treatment failure	AND	Completion of TB treatment with clinical/radiological improvement in the assessment of site investigators by the Week 96/End of Study or Early BDQ D/C visits AND no recrudescence of clinical/radiological criteria for RR-TB by the completion/end of treatment, AND Recurrence of clinical/radiological signs/symptoms consistent with RR-TB, or at least one new positive culture, after treatment is completed and by the end of study follow-up.	TB recurrence
Any bacteriological outcome	AND	Death (grade 5 AE) for any reason while on RR-TB treatment or at any point by the end of study follow-up after start of study regimen	Death
Any bacteriological outcome	AND	Missed more than two months of consecutive treatment for RR-TB on study. Note: If the participant returns to study and has completed the study with cure/probable cure as treatment outcome despite having initially missed more than two months of RR-TB treatment and subsequently completed TB treatment, the end point review committee may consider treatment outcome as Bacteriological Cure with no TB Recurrence or probable cure with no TB recurrence *Note*: Any participant who experienced treatment failure or TB recurrence prior to completion of study will not be considered lost to follow-up. Any participants who showed bacteriological or probable cure at the of TB treatment before premature study discontinuation will be considered as lost to follow-up after TB treatment outcome, as determined by the ERC	Lost to follow-up

*For participants with probable RR-TB, only the "Clinical/Radiological Outcome" criteria will be used, and these participants cannot be classified as "Bacteriological cure with no TB recurrence" but as "Probable cure with no TB recurrence".
**Contaminated samples or indeterminate results will not be counted in determining whether negative results are consecutive (e.g., if two consecutive culture results are both negative, followed by a contaminated results, and then followed by a negative result, then the participant meets this criterion.)

8.6 ECG and Cardiac Safety Monitoring

ECGs will be performed as indicated in the SoE and Section 6. At the intensive PK visit, ECGs will be performed within one hour before or after the pre-dose PK sampling and at 4-6 hours after BDQ administration. Sites should carefully monitor electrolyte levels of participants with diarrhea or vomiting, as low electrolytes can increase cardiac risk, and continue to provide participant education on signs and symptoms of possible BDQ side effects. Consultation with the protocol cardiologist is available and encouraged for any abnormal or equivocal ECG findings and/or questions related to cardiac toxicities and assessment. Further guidance is provided in the P1108 MOP on ECG monitoring, assessment, and eCRF completion.

For each ECG evaluation, ECGs should be immediately transmitted for a centralized review to capture any abnormalities not identified and/or reported by the site. Additionally, mean QT interval should be calculated at sites based on triplicate ECG readings (three consecutive ECGs) at each time point. If it is not possible to obtain a triplicate ECG reading, at a minimum one high quality ECG reading should be obtained at indicated visits in the SoE. Consult the Core Team for any questions on ECG quality.

Appendix V and Appendix VI provide grading and management, respectively, for ECG and clinical cardiac toxicities in P1108. On-site site investigators should review ECGs in real-time and assess for clinical relevance and identification of AEs. Following receipt of the centralized ECG reading, generally within three days of transmission, further clinical management should be performed based on the AE grade from the centralized read. The centralized read should be used for determination of final grading for all protocol-specified ECG evaluations, including ECGs performed as part of study eligibility determination (see exclusion criteria 4.2.5 and 4.2.6).

To ensure appropriate safety monitoring by the Core Team, ECG and cardiac-related AEs that meet eCRF safety-related recording requirements per protocol Section 7.2 should be entered in appropriate eCRFs as AEs upon availability of the relevant clinical findings and test results. For the study analyses, ECG results from the centralized read will be used. Therefore, following receipt of the centralized read, sites should review and confirm that the grade for ECG AEs entered in eCRFs is consistent with the grade based on the centralized read.

All ECG reports will also be reviewed as part of formal data analysis by the protocol cardiologist. This will serve to assist with interpretation of all ECG data analysis in relation to the study hypotheses, including for SMC review, as required.

8.7 Management of Contraception and Pregnancy

Any female participant of reproductive potential and engaging in sexual activity that could lead to pregnancy must agree to use at least two contraceptive methods as specified in inclusion criterion 4.1.11 throughout study participation. Any male participant engaging in sexual activity that could lead to pregnancy of a female partner must agree to use a barrier method of contraception (i.e., male condom) until four weeks after BDQ discontinuation per inclusion criterion 4.1.9. Further guidance is provided in the P1108 MOP on contraceptive counseling.

All initial reports of pregnancy in a participant must be reported to the Core Team and site IRBs/ECs, as required, within four weeks of awareness using the appropriate pregnancy notification form. As the potential effects of BDQ on sperm are unknown, pregnancies in partners of male participants should also be reported to the Core Team and site IRBs/ECs, as required,

within four weeks of awareness using the appropriate pregnancy notification form. For female pregnant participants and pregnancies in partners of male participants, if the pregnancy outcome is unknown at the Week 96/End of Study or Early Study Discontinuation visit, the participant should continue to be contacted until the outcome of the pregnancy is known per Section 6.10.

Any female participant who becomes pregnant during the study while on BDQ should immediately discontinue BDQ; however, the participant may continue to take RR-TB and ARV drugs (if applicable) at the site investigator's discretion and in accordance with local standard of care. Follow-up for pregnant participants will continue as per the SoE.

In the event that a participant living with HIV 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).

8.8 Management of HIV-Exposed Participants and Participants Living With HIV

For all participants determined to be living without HIV at Entry, HIV testing should be repeated during study follow-up as clinically indicated. For Cohort 3 HIV-exposed participants, determination of HIV status as specified in Section 4.3 is required at the Week 48 (24 weeks post BDQ), Week 96/End of Study (72 weeks post BDQ), and early study discontinuation visits.

Participants identified as living with HIV during the study will remain in study follow-up and will be referred to non-study sources for HIV care and treatment as soon as possible. Study visits will be conducted as originally scheduled per the SoE, and evaluations for participants living with HIV should be performed. ARVs should be managed consistent with local standards of care.

At Entry, Weeks 4, 12, 24, and Early BDQ D/C visits: If a participant living with HIV has a viral load result ≥ 1,000 copies/mL, ARV genotypic resistance testing should be performed at the next scheduled visit or earlier as per the site investigator's discretion. At the Week 96/End of Study and Early Study D/C visits, ARV genotypic resistance testing should be performed as per the site investigator's discretion for participants with viral load ≥ 1,000 copies/mL at these visits. ARV resistance test results may be provided to non-study care providers to guide ARV regimen selection.

8.9 Criteria for Premature Discontinuation of Study Drug

- Treatment with disallowed medications as determined by the Core Team.
- Participant experiences an AE that requires permanent discontinuation of BDQ as specified in Section 8.1 or in Appendices VI, VIII, and IX.
- Sustained non-adherence that, in the opinion of the investigator, warrants early BDQ discontinuation.
- The site investigator determines that further administration of BDQ would be detrimental to the participant's health or well-being.
- A participant is unable or unwilling to take study drug or a participant's guardian refuses further administration of study drug.
- Participant diagnosed as having drug-susceptible TB (i.e., INH and RIF susceptible) despite an initial diagnosis of DR-TB. INH resistance is also included as drug-resistant TB but is not RR-TB (and therefore participants with INH monoresistant TB or INH-polydrug resistance are not eligible for participation).
- Female participant who becomes pregnant while taking BDQ.

Note that in the event of early BDQ discontinuation, participants will continue on study and off study drug and complete study visits as outlined in Section 6.12.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a Phase I/II open label, single arm dose-finding study to assess the PK and safety/tolerability of BDQ as part of RR-TB therapy for the treatment of RR-TB in infants, children, and adolescents.

This section describes the methodology and analyses planned for primary and secondary safety outcomes and the secondary TB treatment outcomes only. Please refer to Section 10 for descriptions of the PK outcomes and planned analyses.

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

Up to a maximum of 84 participants will be enrolled to achieve a minimum of 54 evaluable participants (18 participants in each of Cohorts 1, 2, and 3) with appropriate data for PK modeling for BDQ dosing. In Cohort 1, up to 12 participants will be enrolled in each weight band to achieve approximately nine evaluable participants in each weight band. The safety analyses will include the safety data across all study follow-up for all participants who received at least one dose of study drug.

Permitted participant exposure to non-study BDQ prior to study entry (up to seven days) per inclusion criterion 4.1.6 to prevent potential enrollment barriers may exclude potential participants with intolerance to BDQ. This may introduce potential bias in the overall safety profile of study participants. The protocol team will collect information on participant exposure to non-study BDQ prior to enrollment to inform interpretation of study safety data.

Accrual to the study will follow an algorithm in which PK and safety will be initially studied in Cohort 1, with Cohorts 2 and 3 not being allowed to open until sufficient PK data from Cohort 1 have been collected to allow an adequate modeled estimate of starting doses for these younger cohorts. In making dosing decisions, the Core Team will review all safety data as well as the results of PK modeling.

Please see Section 3 and Figure 1 for cohort management of participants on routine RR-TB treatment and BDQ and criteria for evaluation of the first cohort and opening subsequent cohorts.

9.2 Outcome Measures

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

9.2.1 Primary Toxicity Endpoints (evaluated through Week 24)

- Termination from treatment due to a drug-related AE
- AEs of ≥ grade 3 severity
- AEs of ≥ grade 3 severity assessed by the Core Team to be at least possibly related to the study drug
- Absolute QTcF interval ≥ 500 msec
- Unstable dysrhythmias requiring hospitalization and treatment
- Death (grade 5 AE)

9.2.2 Secondary Endpoints and Response Variables (evaluated through Week 96 or 72 weeks post BDQ discontinuation)

- AEs of ≥ grade 3 severity
- AEs of ≥ grade 3 severity assessed by the Core Team to be at least possibly related to the study drug
- Absolute QTcF interval ≥ 500 msec
- Unstable dysrhythmias requiring hospitalization and treatment
- Death (grade 5 AE)

9.2.3 TB Treatment Outcomes Endpoint

- TB treatment outcome (see Section 8.5) at Week 96/End of Study or Early Study D/C visit, classified as bacteriological cure with no TB recurrence, probable cure with no TB recurrence, treatment failure, TB recurrence, death, or lost to follow-up.
- TB treatment outcome (see Section 8.5) at end of RR-TB treatment, classified as bacteriological cure, probable cure, treatment failure, death, or lost to follow-up.

9.3 Randomization and Stratification

There will be no randomization. Participants will be enrolled into one of the three cohorts described in Section 3.

9.4 Sample Size and Accrual

The sample size is primarily based on PK considerations. Clinical trial simulations were performed to ensure a sample size able to provide precise enough estimates of apparent clearance as specified by the FDA criteria for pediatric trials (85). Since BDQ exposure over long-term administration primarily is determined by the apparent clearance, the first point implies that the primary objective of the study (to determine BDQ doses for children that achieve similar weekly exposure as adults taking BDQ at the current standard recommended dose) can be fulfilled. The methods and results of the simulations are described in Appendix X.

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

Participants are considered PK-evaluable if they have completed the intensive PK sampling collection and have at least one sample with measurable BDQ and M2 concentrations. Participants will be assessed by the Core Team for evaluability once PK data from the intensive PK visit are available. Regardless of evaluability, the safety population for this study will include all participants who receive at least one dose of study drug.

Non-evaluable participants will be replaced unless the maximum accrual of 24 participants in Cohort 1 and 30 participants in Cohorts 2 and 3 is already achieved. It is possible for the maximum number of participants to be enrolled in a cohort and not achieve the required 18 evaluable participants; however, the sample size per cohort was determined to accommodate loss of participant data due to non-evaluability or loss to follow-up.

Table 8 presents exact 95% CIs around various potential rates of ≥ grade 3 AEs which might be observed in a total sample of 54 participants who might contribute data to the primary safety analysis, a sample of 18 participants within any age stratum and a potential sample of six participants, which represents the smallest sample on which dosing decisions might be made. This table indicates that CIs will be quite wide around the sample size of 18 participants within a given age cohort but would be considerably more precise around a total sample of 54 participants.

Table 8
Percent of Participants Experiencing ≥ Grade 3 AEs (or ≥ Grade 3 AEs Attributed to the Study Drug) with Exact 95% CIs

N*	n (%) With ≥ Grade 3 AEs	95% CI
6	0 (0%)	0% -- 46%
18	0 (0%)	0% -- 19%
54	0 (0%)	0% -- 7%
6	1 (17%)	.4% -- 64%
18	3 (17%)	4% -- 41%
54	9 (17%)	8% -- 29%
6	2 (33%)	4% -- 78%
18	6 (33%)	13% -- 59%
54	18 (33%)	20% -- 47%

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

9.5 Monitoring

The study will be monitored by the Core Team, which will review safety and PK data regularly as specified in the Study Progress, Data, and Safety Monitoring Plan with the aim of determining a dose per weight scheme for the three cohorts while protecting participant safety. In addition, the IMPAACT Network will appoint an SMC to provide independent reviews, when necessary, to ensure participant safety and to review decisions concerning changes in dosing and/or opening new cohorts.

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

Accrual to this study will be monitored by the Core Team and IMPAACT leadership in accordance with SOPs. The team will monitor feasibility quarterly, first based on site activation and then on accrual. Initially, the team will monitor site registration monthly to ensure that an adequate number of sites will be activated to participate in the study. If relatively few of the eligible sites have been activated after the protocol has been approved for six months (excluding any time the study is paused to accrual), the team will re-assess the feasibility of the protocol and will examine the reasons why sites have not been activated or are not accruing adequately and may amend the protocol accordingly.

The DMC will generate monthly screening and enrollment reports based on the data described in Section 4.5 and accrual reports described below. Using these reports, the Core 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 84 participants will be enrolled to achieve a minimum of 54 evaluable participants, enrollment is projected to be completed within approximately 4.5 years. Each site must establish and implement an SOP to achieve the projected rates of enrollment specified in the accrual plan. Should accrual rates fall below projections, the Core Team will work with study sites to identify operational issues and to take appropriate action as needed.

The Core 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. Team members will similarly review other key indicators of the quality of study conduct (e.g., adherence to study drug 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.

SMC reviews will take place at least annually, as determined by the accrual rate or specific AEs (described in Section 9.5.2). The SMC will be provided with accrual data in addition to safety data as described below.

9.5.2 Participant Safety

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

AEs will be monitored from Entry onwards throughout the follow-up period. If the Core Team identifies any potential treatment-related toxicities which may compromise participant safety, the study may be paused and the Core Team may request the SMC to review all relevant data and make recommendations on whether, and under what conditions, the study would be allowed to proceed.

In addition to routine monitoring of safety data, there will be two interim analyses of PK and safety data for each age cohort, for a particular dosing scheme, during the dose-finding phase. The first will occur when six participants under the current BDQ dosing scheme have completed the intensive PK sampling at the Week 1 or Week 2 visit (see Sections 6.3 and 6.4). If the first six participants have acceptable PK and safety profiles, as evaluated by the Core Team, a second interim analysis will occur when 12 participants under the current BDQ dosing scheme have completed the intensive PK sampling.

The safety data will be considered "unacceptable" if the following conditions are met, as assessed by the Core Team (*only among evaluable participants in the cohort under evaluation for the current dosing scheme*):

1) Any fatal or life-threatening AE assessed by the Core Team to be at least possibly related to study drug occurs.
2) For N=6: At least two participants experience a grade 3 or non-life-threatening grade 4 AE assessed by the Core Team as at least probably related to study drug.
3) For N=12: At least three participants experience a grade 3 or non-life-threatening grade 4 AE assessed by the Core Team to be at least probably related to study drug.
4) For N=18: At least four participants experience a grade 3 or non-life-threatening grade 4 AE assessed by the Core Team to be at least probably related to study drug.

The safety data will be reviewed concurrently with PK data and whether PK criteria are met or not.

Second line regimens for treatment of RR-TB have historically been observed to have many toxicities (86). Some of the drugs in these regimens showed high incidence of AEs leading to permanent discontinuation, such as the second-line injectables (amikacin: 10.2% [6.3 – 16.0], kanamycin: 7.5% [4.6 – 11.9], capreomycin: 8.2% [6.3 – 10.7%] and LZD (14.1% [9.9 – 19.6]). Out of 8,622 patients included in a meta-analysis, 23.5% had at least one TB drug discontinued due to severe AEs. Thresholds for observed number of events were determined so that there would be reasonable high probability of meeting the threshold if the true rate of grade 3 or 4 non-life-threatening AEs at least probably related to BDQ were 25% or higher, and at the same time would have a low probability of meeting the threshold if the true rate were less than 10% (low type I error rate). Table 9 shows the probability that a specific threshold (X = observed number of events) is met for a given sample size and true event probability, assuming that the true rate of drug-related fatal events or life-threatening AEs is very rare and having any drug-related fatal event or life-threatening AE is also a trigger for unacceptable safety. For example, with six participants under a specific dosing scheme, the probability any participant experiences a drug-related fatal event or life-threatening AE, or at least two participants experience drug-related grade 3 or non-life-threatening grade 4 AEs is 47% or higher if the true rate of grades 3 or 4 drug-related non-life-threatening AEs was 25% or higher, and at the same time would have low probability of type I error (≤11%) if the true rate was at most 10%.

Table 9
Probability that safety criteria are met based on number (X) and observed proportion of participants with drug-related grade 3 or 4 non-life-threatening AE for a given sample size (N) and true event probability*

Participants →	N=6		N=12			N=18			
Threshold X: (Obs. %) →	X=1 (17%)	X=2 (33%)	X=1 (8%)	X=2 (17%)	X=3 (25%)	X=2 (11%)	X=3 (17%)	X=4 (22%)	X=5 (28%)
True Prob. Grade 3 or 4 Non-Life Threatening AE									
50%	98%	89%	>99%	>99%	98%	>99%	>99%	>99%	98%
25%	82%	47%	97%	84%	61%	97%	86%	69%	48%
20%	74%	34%	93%	73%	44%	90%	73%	50%	28%
15%	62%	22%	86%	56%	26%	75%	52%	28%	12%
10%	47%	11%	72%	34%	11%	46%	27%	10%	3%
8%	39%	8%	63%	25%	7%	32%	17%	5%	1%
6%	31%	5%	52%	16%	3%	19%	9%	2%	<1%
5%	26%	3%	46%	12%	2%	13%	6%	1%	<1%
4%	22%	2%	39%	8%	1%	8%	3%	<1%	<1%
3%	17%	1%	31%	5%	<1%	4%	2%	<1%	<1%
2%	11%	1%	22%	2%	<1%	1%	1%	<1%	<1%
1%	6%	<1%	11%	1%	<1%	<1%	<1%	<1%	<1%
0%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%

*Assume as well that true probability of drug-related fatal event or life-threatening AE is very rare (almost 0%), and having at least one drug-related fatal event or life-threatening AE is also a safety trigger

Participants who successfully complete 24 weeks of BDQ treatment will be examined for long term safety every eight weeks for the next 24 weeks, and every 12 weeks thereafter until 96 weeks (i.e., 72 weeks post last BDQ dose) have been completed, unless a clinical trigger requires closer follow-up. Sites should refer to the SoE in Appendix I.

During the annual review, the Core Team may request the SMC focus on specific safety aspects, such as ECG data review. Note that SMC reports may be minimal if these types of events are rare and/or if accrual has been slow.

In addition, an *ad hoc* SMC review or consultation will occur, as noted below, by the following:

(1) In the event of **a fatal or life-threatening AE, as assessed by the site in consultation with the Core Team**, the Core Team will review the AE and assess its relationship to study drug.
- If the site investigator and/or the Core Team assesses the AE as **possibly, probably, or definitely related to study drug**, accrual will be paused. The Core Team will discuss how the study should proceed and consult with the SMC.
- If the site investigator and the Core Team assess the AE as **probably not or not related to study drug**, accrual will continue. The SMC will be informed of the AE along with the Core Team's assessment and decision-making.

(2) Within each cohort, and under the current dosing regimen: For N=6, if at least two participants within a cohort experience a grade 3 or non-life-threatening grade 4 AE at least probably related to study drug as assessed by the Core Team; OR for N=12, if at least three participants within a cohort experience a grade 3 or non-life-threatening grade 4 AE at least probably related to study drug as assessed by the Core Team; OR for N=18, if at least four participants within a cohort experience a grade 3 or non-life-threatening grade 4 AE at least probably related to study drug as assessed by the Core Team, then the SMC will be notified of this.

(3) If > 25% of participants within a given cohort experience a QTcF > 500 ms then the SMC will be notified of this.

(4) In the event of any unresolvable disagreement within the Core Team on an issue that would impact decision-making or if the Core Team encounters any other event or trend of concern, an SMC review of the relevant data will be convened.

9.6 Analyses

9.6.1 Primary Safety Analyses

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

Each participant's safety data will be summarized as: (1) the most severe grade of AEs, and (2) the most severe grade of AEs assessed to be at least possibly related to study treatment. Frequency distributions of these safety outcomes will be presented in aggregate and will be broken down by age cohort. Listings of all ≥ grade 3 events will be provided.

The proportions of participants experiencing ≥ grade 3 AEs will be presented in aggregate and broken down by age cohort, with these proportions bounded by exact 95% CIs. Similar analyses will present the proportions of participants exhibiting ≥ grade 3 events which have been assessed to be at least possibly related to study drug, again bounded by exact 95% CIs. Tabulations will also be presented to summarize all AEs, as well as all AEs which have resulted in treatment discontinuation. Summary statistics of QT values at each time point performed will also be presented. Additionally, listings of participants who experience unstable dysrhythmias requiring hospitalization and treatment will be presented.

In addition, if possible, a primary evaluation of safety across the 24 weeks of study treatment will be performed on the data from participants who have been started at the final recommended dose for a given cohort and have remained on that dose for the 24-week period or have left the study or had a dose modification due to safety failure prior to 24 weeks of exposure (in which case the participant will be analyzed as a failure). Note that such an analysis may not be possible, since the

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

Given that the modest sample sizes within cohorts will provide limited power for statistical tests of differences across age cohorts, only very large apparent effects would be statistically significant. Interpretation of differences across cohorts will depend upon whether these differences are great enough to be considered to be clinically significant. If no such differences are observed, then the clearest interpretation of the findings will come from the aggregated data, where analyses will have the greatest statistical precision. However, if results vary across cohorts to a clinically important extent, interpretation of results should consider 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 *ad hoc* SMC review will be presented descriptively. Details concerning the analyses will be included in a separate analysis plan.

9.6.2 Secondary Analyses

9.6.2.1 Safety

The 24-week analyses described above for the primary analysis will be repeated as secondary analyses at 72 weeks after BDQ discontinuation and by HIV status. Of note, precision may be limited for participants living with HIV, particularly if only the required minimum number of participants living with HIV are enrolled. In addition, descriptive and exposure-related analyses will present safety data from participants whose doses have undergone individual adjustment or who were treated on doses other than the final recommended dose for their cohorts.

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

9.6.2.2 TB Treatment Outcomes

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

living with HIV, particularly if only the required minimum number of participants living with HIV are enrolled.

9.6.3 Exploratory Analyses of TB Biomarkers

Specimens for TB biomarkers will be collected, and descriptive analyses will track changes over time in these biomarkers. Descriptive analyses will also be performed to examine whether the TB biomarker data appear to differ between participants who convert bacteriologically during study follow-up compared to those who do not.

9.6.4 Additional Considerations

Special statistical and data analysis considerations may be warranted in the event that the COVID-19 pandemic or other unanticipated occurrences (e.g., natural disasters) affect the conduct of the study and/or the integrity of study data. To the extent possible, any such considerations will be addressed in the study statistical analysis plan. Alternatively, a separate analysis plan focused on these considerations — describing, for example changes of analysis populations, visit windows, outcome measures, and analyses to assess impacts of and account for missing data — may be prepared. All analysis plans will take into consideration applicable regulatory guidance and industry best practices.

10 CLINICAL PHARMACOLOGY PLAN

10.1 Pharmacology Objectives

See primary objective 2.1.1 and secondary objectives 2.2.1 and 2.2.3.

Population PK modeling analysis will be conducted and include all participants who have completed the intensive PK sampling and have at least one sample with measurable BDQ and M2 concentrations to propose dosage regimens for pediatric participants across ranges of body weights and ages.

10.2 Study Design, Modeling and Data Analysis

10.2.1 Number of Participants

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

10.2.2 PK Sampling

PK assessments will be performed for all participants to determine plasma concentrations of BDQ and its M2 metabolite at selected time points. Sampling will be both intensive and sparse; this efficient sampling schema is supported by extensive modeling and will impose the least burden on participants while yielding high quality, clinically relevant data. Bioanalysis of BDQ and its M2 metabolite will be performed centrally at the University of Cape Town Clinical Pharmacology Laboratory using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

BDQ dosing will be directly observed by study staff on the days of PK sampling (both intensive and sparse PK sampling). The time of BDQ doses administered in the clinic at visits with PK sampling and the time of administration for the two BDQ doses preceding PK sampling should be documented and recorded in eCRFs. Other TB and ARV medications administered at PK sampling visits, as applicable, should also be documented and recorded in eCRFs. Food intake, including the start time of the meal and type (i.e., full meal or snack), will also be documented and recorded in eCRFs. Meals provided on PK sampling days are recommended to be standardized as much as possible at each site (see further guidance in the P1108 MOP).

PK sampling may be rescheduled within the study visit window per Section 6 if a participant is clinically unable to undergo PK sampling at the scheduled visit or sampling was not successful. In consultation and with approval from the Core Team, PK sampling may be repeated on participants with a BDQ dose adjustment. Repeat PK sampling should be performed as per the PK sampling schedule indicated for the applicable study visit in Section 6. Whole blood specimens (1.0 mL for Cohorts 1 and 2; 0.5 mL for Cohort 3) will be collected at each PK sampling time point as indicated in Section 6.

If a participant prematurely discontinues BDQ or the study, the participant should return for an Early BDQ or Study Discontinuation visit, respectively, and sparse PK sampling performed at any time during this visit. The date and time the last dose of BDQ was administered should be recorded on eCRFs. Further details regarding the collection, processing, and storage of PK samples are provided in the P1108 MOP and LPC.

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

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

The population PK model will be informed by PK data as available across cohorts, and by potential novel insights from other emerging pediatric data. Based on this model, a dose regimen will be calculated to target a weekly AUC at steady state close to the median in adults (187 µg*h/mL (87)) in Cohorts 2 and 3. The dose will be decided by the Core Team based on the existing dosage strength (100 mg tablet or 20 mg scored tablet) and practical considerations. In younger age groups and for participants unable to swallow tablets, the 100 mg formulation will be

dispersed in water, or the 20 mg pediatric formulation will be used for Cohorts 2 and 3. The 100 mg formulation dissolves once shaken well and is palatable. The dissolved form has been shown to have the same bioavailability as whole tablets (46). In all cohorts as well as in individual participants, doses may be adjusted as appropriate, based on emerging PK and safety data.

10.2.4 PK Data Analysis

PK parameters for BDQ and M2 will be determined using nonlinear mixed effect models developed in NONMEM (88). In all cases, when new data are available, the updated BDQ model will be used. Body weight, race/ethnicity, age, albumin, and other covariates identified or hypothesized to be of PK importance (e.g., nutritional status, TB disease severity, BDQ formulation), will be included in the analysis. Included in the formal covariate analysis will also be HIV status and, if there is sufficient information, interactions with drugs as part of concomitant ARV therapy.

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

The updated population PK model will be used to predict exposures in pediatric populations following long-term BDQ dosing for the following purposes: (i) to propose updated doses if a group or cohort fails to meet PK criteria and/or have unacceptable safety data, (ii) to propose doses for Cohorts 2 and 3, and (iii) for an exposure-safety analysis using data from all evaluable participants. For the purpose of proposing pediatric dosing regimens and the investigation of the effects of HIV status, the PK model will be based on all data available when the last participant of the last cohort has completed the Week 24 or Early BDQ D/C visit. However, given the long half-life of BDQ, sparse PK sampling will continue at off-treatment visits through the remainder of study follow-up. Further details on the population PK analysis are described in the PK Analysis Plan.

10.2.5 PK of ARV Drugs and Second-line TB Therapy

PK of ARVs and TB drugs other than BDQ are beyond the scope of the aims of this study. After all protocol-specified analyses are complete, study samples with informed consent for future research use will be stored for other potential investigator-initiated studies, including studies related to other TB drugs and/or ARVs to assess drug-drug interactions.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

As described in Section 4.5, data on screening and enrollment in this study will be collected using the DMC 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 Site Clinical Operations and Research Essentials (SCORE) Manual, which is available at: https://www.niaid.nih.gov/research/daids-clinical-site-implementation-operations

eCRFs and an eCRF completion guide will be made available to study sites by the DMC. Study 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 timeframes specified by the DMC; queries must also be resolved in a timely manner. Selected laboratory data are transferred electronically to the DMC through the LDMS.

The Protocol Team and/or study oversight bodies (e.g., SMC) may determine that additional source data associated with procedures or evaluations performed per protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

Further information on eCRFs and IMPAACT data management procedures will be provided by the DMC. A User Manual for the SES is available on the DMC portal at: https://www.frontierscience.org

11.2 Essential and Source Documents and Access to Source Data

Study sites must comply with DAIDS requirements for essential documents and source documentation as specified in the DAIDS SCORE Manual. This includes establishing SOPs for maintaining essential and source documents. 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 US Code of Federal Regulations (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, Janssen, IMPAACT, site IRBs/ECs, site drug regulatory authorities, the FDA, the

Office for Human Research Protections, and other US, local, and international regulatory entities. Records must be kept on-site throughout the period of study implementation; thereafter, instructions for off-site storage may be provided by NIAID. No study records may be removed to an off-site location or destroyed prior to receiving approval from NIAID.

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 SCORE Manual.

12 CLINICAL SITE MONITORING

Under contract to NIAID, site monitors will inspect study site facilities and review participant study records — including informed consent and assent forms, paper-based CRFs (if used), 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. 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 monitors.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity (89). Site investigators must make available study documents for site monitors to review utilizing a secure platform that is 21 CFR Part 11 compliant. The DMC has configured Medidata Remote Source Review (RSR) to be available to all sites. If Medidata RSR is not utilized, other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to electronic medical records, and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Board/Ethics Committee Review and Approval

Prior to study initiation, site investigators must obtain IRB/EC review and approval of this protocol and site-specific informed consent and assent forms in accordance with 45 CFR 46; subsequent to initial review and approval, IRBs/ECs must review the study at least annually. Site investigators must promptly report to the IRBs/ECs any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension or termination of IRB approval.

Site investigators are responsible for awareness of and adherence to the policies and procedures of all applicable IRBs/ECs. All IRB/EC policies and procedures must be followed and complete documentation of all correspondence to and from all applicable 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 Section 14.2).

13.2 Vulnerable Participants

It is NIH policy to ensure that children should be included in clinical research conducted or supported by the NIH when appropriate (90, 91). This study complies with that policy and will provide clinical research data to inform RR-TB treatment guidelines for children. In particular, children with RR-TB have been excluded from trials of novel antituberculosis agents — agents with the potential to dramatically shorten and simplify the treatment of RR-TB in children.

Infants, children, and adolescents who take part in this study are considered vulnerable participants per US CFRs, and IRBs/ECs must consider the potential benefits and risks to infant, children, and adolescent participants as described in 45 CFR 46 Subpart D. 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.

The risk category assigned by the IRB/EC determines the parental or guardian 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 for enrolling minors in clinical research as specified in the DAIDS SCORE Manual. In addition to the US regulations cited above, sites must also comply with all applicable local, national, and international guidelines and regulations. In cases where multiple different sets of requirements apply, the most stringent requirements must be followed.

13.3 Informed Consent and Assent

Refer to Section 4.5 and the P1108 MOP for further information on informed consent and assent procedures for this study. Refer to Appendix XIII for the P1108 sample ICF and Appendix XIV for the P1108 sample assent form.

Written informed consent and assent (if applicable) for study participation will be obtained from each potential participant's parent or guardian before any study-specific procedures are performed. It is generally expected that the consent of one parent (or guardian) will be sufficient for the child's participation in this study. However, consenting requirements at each site will depend on the site IRB/EC risk determination as described in Section 13.2; all applicable IRB/EC requirements must be followed. When applicable per site IRB/EC policies and procedures, written assent will also be obtained from each child before any study-specific procedures are performed. If a participant provides assent for the study and later withdraws assent after enrollment, they should be withdrawn from the study. The participant's wishes should be followed even if their parent or guardian wants them to remain on-study.

For participants who do not meet IRB/EC criteria for providing consent or assent at the time of screening and enrollment, if such criteria are met during follow-up, consent or assent should be obtained at the next study visit after the criteria are met and prior to performing study procedures at the visit. If participants do not provide consent or assent for continued study participation, they should be discontinued from the study. Consent or assent signature requirements should comply with site IRB/EC policies and procedures.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. The process will include a description of what is currently known about the safety and efficacy of the study drug and the context of current local standards of care for TB and HIV care and treatment. The assent process will include a similar but age-appropriate discussion. The amount of information and level of detail provided as part of the assent process should be tailored to the age and maturity of the potential participant, guided by applicable IRB/EC policies and procedures. Sites may develop multiple assent forms, if desired, in anticipation of different information needs across the study age range. When preparing site-specific assent forms, sites may remove or modify the wording included in the sample assent forms in order to provide the most appropriate information and level of detail, consistent with applicable IRB/EC policies and procedures.

As part of the informed consent process, participants/parents/guardians will be asked whether they agree to storage and future research testing of biological specimens remaining after all protocol-specified testing has been completed as indicated in Appendix XV. This storage and future research testing are optional and may be declined with no impact on other aspects of study participation. Likewise, genetic testing of residual specimens is optional and may be declined. This informed consent and assent process should ideally be conducted at the study Screening or Entry visit but may be completed at any time through the last study visit.

Should the consenting parent or legal guardian of an enrolled participant die or no longer be available for any reason, or should guardianship otherwise change for any reason, all applicable IRB/EC policies and procedures should be followed. If the participant is doing well on study drug, it is generally expected that they will stay on study drug with safety monitoring evaluations performed consistent with local standard of care. Other study-specific evaluations (outside the standard of care) should not be performed until informed consent for continued study participation is obtained from the participant's new legal guardian. If a new legal guardian cannot be identified, or if the new guardian does not consent to continued study participation, the participant must be withdrawn from the study.

In accordance with the DAIDS requirements for enrolling minors in clinical research (as specified in the DAIDS SCORE Manual), all sites must establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled child, 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 RR-TB have benefited from receiving BDQ as part of RR-TB treatment. 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 receipt of study drug.

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

- Nausea
- Joint pain
- Headache
- Hemoptysis (coughing up blood)
- Chest pain
- Anorexia (loss of appetite)
- Rash
- Increase in blood amylase
- Abdominal pain

Other serious adverse effects include death, QT prolongation (heart rhythm problem) and/or hepatitis.

In children 12 to less than 18 years of age the most common adverse effects include:

- Joint pain
- Nausea
- Abdominal pain

In children five to less than 12 years of age the most common adverse effect is increased liver enzymes.

Refer to Section 1 and the package insert for BDQ for a description of the potential risks associated with the use of BDQ.

Most study procedures are routine medical procedures that are associated with minimal to no risk. 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 very small risk of infection where the needle is inserted. Blood collection may also cause lightheadedness or fainting.

A CXR may be indicated to confirm active TB disease. The radiographic exposure required is minimal and this procedure is associated with minimal risk.

Refer to Section 13.7 for further information on privacy and confidentiality. Despite efforts to maintain confidentiality, participant involvement in this study could become known to others, possibly leading to unfair treatment, discrimination, or other social impacts (e.g., because participants could become known as having HIV). For example, participants could be treated unfairly or discriminated against or could have problems being accepted by their families and/or communities. Every effort will be made to protect participant information, but this cannot be guaranteed.

13.6 Reimbursement/Compensation

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

13.7 Privacy and Confidentiality

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

All study-related information will be stored securely. Participant research records will be stored in locked areas with access limited to study staff. All laboratory specimens, CRFs, and other documents that may be transmitted off-site (e.g., EAE report forms) 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 to store study records that bear participant names or other personal identifiers separately from records identified by PID. All local databases must be secured with password protected access systems. Lists, logbooks, appointment books, and any other documents that link PID numbers to personal identifying information should be stored in a separate, locked location in an area with limited access.

13.8 Communicable Disease Reporting

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

13.9 Management of Incidental Findings

Study clinicians will inform participants and/or their parents/guardians of all clinically meaningful physical exam findings and laboratory test results. When applicable, site clinicians will provide referrals to non-study sources of medical care for further evaluation and/or treatment of these findings.

13.10 Management of New Information Pertinent to Study Participation

Study staff will provide participants and/or their parents/guardians 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.

13.11 Post-Trial Access to Study Drug

The 100 mg oral tablet formulation of BDQ is licensed in adults and is available by prescription at international sites to adults with RR-TB. The 20 mg BDQ formulation is FDA-approved and is licensed for use in children six years of age and older. Post-study access to the 100 mg oral tablet or 20 mg scored tablet is not relevant to participants in P1108 as BDQ is prescribed only during the first 24 weeks of RR-TB therapy. The 20 mg BDQ formulation is available for procurement through the Global Drug Facility.

14 ADMINISTRATIVE PROCEDURES

14.1 Regulatory Oversight

This study is sponsored by the NIAID, NICHD, and National Institute of Mental Health, which are part of the NIH. Janssen will provide study product for this study but is not involved in sponsorship or regulatory oversight of this study.

Within the NIAID, DAIDS is responsible for regulatory oversight of this study. DAIDS will distribute safety-related information pertaining to the study drug prior to and during the conduct of the study, in accordance with its sponsor obligations.

NIAID provides funding to the clinical research sites at which this study will be conducted. The institute contracts with an independent clinical site monitoring group to perform clinical site monitoring as described in Section 12. As part of this activity, monitors will inspect study-related documentation to ensure compliance with all applicable US, local, and international 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 study informed consent and assent forms approved, as appropriate, by applicable IRBs/ECs 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 the required documents have been received.

Site-specific informed consent and assent forms 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 other applicable regulatory entity approvals, sites should implement the amendment immediately, unless instructed otherwise. 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 required documents have been received. Site-specific informed consent and assent forms 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: https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual.

14.3 Study Implementation

This study will be conducted in accordance with the protocol, international good clinical practice guidelines, and all applicable US, local, and international regulations. Study implementation will also be guided by the IMPAACT Network MOP, P1108 MOP, LPC, and other study implementation materials, available on the IMPAACT website: www.impaactnetwork.org

Study implementation at each site will also be guided by site-specific SOPs. The DAIDS SCORE Manual specifies the minimum set of SOPs that must be established at sites conducting DAIDS funded and/or sponsored clinical trials. 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 requirements for source documentation specified in the DAIDS SCORE Manual, 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 applicable 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 Network MOP.

14.5 ClinicalTrials.gov

The NIH Policy on Dissemination of NIH-funded Clinical Trial Information establishes the expectation that clinical trials funded in whole or in part by the NIH will be registered and have summary results information submitted to ClinicalTrials.gov for public posting. The protocol team will comply with this policy as well as the requirements of 42 CFR 11.

15 PUBLICATIONS

All presentations and publications of data collected in this study are governed by IMPAACT policies, which are available in the IMPAACT Network MOP. The Core Team will undertake to disseminate data from each age cohort, as data are available, to inform public health policy and practice.

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

	Screening	On Treatment Visits										Early BDQ D/C[7]
		Entry/ Day 0	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	
CLINICAL EVALUATIONS												
Determination of HIV status[1]	x [0-6 mL]											
Medical and Medication History	x	x	x	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x	x	x	x
BDQ adherence assessment			x	x	x	x	x	x	x	x	x	x
TB disease status and severity	x	x										
ECG[2]	x	x	[x]	[x]	x		x	x	x	x	x	x
CXR	x						x		x		x	x
Audiology assessment (*if on an injectable TB medication*)		[x]					[x]		[x]		[x]	
LABORATORY EVALUATIONS												
Hematology[3]	1 mL	[1 mL]	1 mL	1 mL	1 mL		1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
Chemistries[3]	2 mL	[2 mL]	2 mL	2 mL	2 mL		2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
LFT (ALT, AST, direct bilirubin, total bilirubin)[3]	x	[x]	x	x	x		x	x	x	x	x	x
TSH (*and fT4 if TSH is elevated*)[4]		[2 mL]					[2 mL]		[2 mL]		[2 mL]	[2 mL]
TB biomarkers (storage)[3]	[0.5-1 mL]	[0.5-1 mL]									[0.5-1 mL]	
Pregnancy test[5]	x [1 mL]				x [1 mL]		x [1 mL]		x [1 mL]		x [1 mL]	x [1 mL]
Specimens for TB microbiology[6]	x	x			x		x	x	x	x	x	
Obtain TB isolate from routine lab (*if RR-TB culture positive*)	x											
Urinalysis		x			x		x	x	x	x	x	x
Intensive PK[2]			[2.5-5 mL]	[2.5-5 mL]								
Sparse PK[2]			[0.5-1 mL]	[0.5-1 mL]	0.5-1 mL		0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL
Only in participants living with HIV												
HIV-1 RNA PCR		3 mL			3 mL			3 mL			3 mL	3 mL
Lymphocyte subsets		1 mL			1 mL			1 mL			1 mL	1 mL
ARV genotypic resistance testing		*At Entry, Week 4, Week 12, Week 24, and Early BDQ D/C visits: If the participant's viral load is ≥ 1,000 copies/mL, collect an additional 3-5 mL of blood for ARV genotypic resistance testing at the next scheduled visit or earlier as per the site investigator's discretion. At Early Study D/C visits: 3-5 mL of blood for ARV genotypic resistance testing should be collected as per the site investigator's discretion for participants with viral load ≥ 1,000 copies/mL at this visit. Note: The 3-5 mL additional blood volume does not appear in the total blood volume below as it is collected at an unscheduled visit.*										
TOTAL MAXIMUM BLOOD VOLUMES (*higher volumes for participants living with HIV*)												
Cohort 1	3-11 mL	0-10mL	4-8 mL	4-8 mL	4-9 mL	0 mL	4-7 mL	4-8 mL	4-7 mL	4 mL	4-12 mL	4-11 mL
Cohort 2	3-10 mL	0-10 mL	4-8 mL	4-8 mL	4-8 mL	0 mL	4-6 mL	4-8 mL	4-6 mL	4 mL	4-11 mL	4-10 mL
Cohort 3	3-10 mL	0-10 mL	3.5-5.5 mL	3.5-5.5 mL	3.5-7.5 mL	0 mL	3.5-5.5 mL	3.5-7.5 mL	3.5-5.5 mL	3.5 mL	3.5-10.5 mL	3.5-9.5 mL

Appendix I (cont.): Schedule of Evaluations for All Cohorts (1, 2 and 3)

	Off-Treatment Visits						
	Week 32 (8 wks post BDQ)	**Week 40 (16 wks post BDQ)**	**Week 48 (24 wks post BDQ)**	**Week 60 (36 wks post BDQ)**	**Week 72 (48 wks post BDQ)**	**Week 96/ End of Study (72 wks post BDQ)**	**Early Study D/C[7]**
CLINICAL EVALUATIONS							
Determination of HIV status[1]			x [0-6 mL]			x [0-6 mL]	x [0-6 mL]
Medical and Medication History	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x
TB treatment outcome[8]	[x]	[x]	[x]	[x]	[x]	x	x
ECG		x					x
CXR		x			x		x
LABORATORY EVALUATIONS							
Hematology	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL	1 mL
Chemistries	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL	2 mL
LFT (ALT, AST, direct bilirubin, total bilirubin)	x	x	x	x	x	x	x
TSH (*and fT4 if TSH is elevated*)[4]	[2 mL]		[2 mL]		[2 mL]		
TB biomarkers (storage)						[0.5-1 mL]	
Pregnancy test[5]	x [1 mL]	x [1 mL]	x [1 mL]	x [1 mL]	x [1 mL]	x [1 mL]	x [1 mL]
Specimens for TB microbiology	x	x	x	x	x		x
Urinalysis	x	x	x	x	x	x	x
Sparse PK	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL	0.5-1 mL
Only in participants living with HIV							
HIV-1 RNA PCR						3 mL	3 mL
Lymphocyte subsets	1 mL		1 mL			1 mL	1 mL
ARV genotypic resistance testing	*At Week 96/End of Study and Early Study D/C visits: 3-5 mL of blood for ARV genotypic resistance testing should be collected as per the site investigator's discretion for participants with viral load ≥ 1,000 copies/mL at this visit.* *Note: The 3-5 mL additional blood volume does not appear in the total blood volume below as it is collected at an unscheduled visit.*						
TOTAL MAXIMUM BLOOD VOLUMES (*higher volumes for participants living with HIV*)							
Cohort 1	4-8 mL	4-5 mL	4-8 mL	4-5 mL	4-7 mL	4-10 mL	4-9 mL
Cohort 2	4-7 mL	4 mL	4-7 mL	4 mL	4-6 mL	4-9 mL	4-8 mL
Cohort 3	3.5-6.5 mL	3.5 mL	3.5-12.5 mL	3.5 mL	3.5-5.5 mL	3.5-14.5 mL	3.5-13.5 mL

1. Refer to Section 4.3 for determination of HIV status requirements. If acceptable source documentation is not available as specified in Section 4.3, HIV testing may include collection of up to 6 mL of blood. Determination of HIV status is required at Week 48 (24 weeks post BDQ), Week 96/End of Study, and Early Study D/C visits only for Cohort 3 HIV-exposed participants.
2. Intensive PK sampling will be performed at the Week 1 or Week 2 visit as described in Sections 6.3 and 6.4. Sparse PK sampling should be performed at the Week 1 or Week 2 visit in which intensive PK sampling is not performed. ECG should be performed at the intensive PK visit (Week 1 or Week 2) as specified in Sections 6.3 and 6.4.
3. Hematology, chemistries, and/or LFT are not required at the Entry visit if specimen collection for these tests at the Screening visit is within seven days of the Entry visit. At the Entry visit, TB biomarkers should be collected if the Entry visit is more than 14 days from TB biomarker collection at the Screening visit if consent is obtained for this evaluation.
4. TSH (and fT4 if TSH is elevated) should only be performed for participants taking PAS or ETH.
5. A blood (1 mL) or urine (5 mL) pregnancy test may be performed.
6. All participants will have one specimen for TB microbiology testing collected at Screening. TB microbiology specimens will be collected at Entry and follow-up visits per Section 8.4 for participants with bacteriologically confirmed RR-TB.
7. For participants who discontinue BDQ prior to the Week 24 visit, see Section 6.12 for visit procedures.
8. TB treatment outcome should be done at the off-treatment visit following completion of the RR-TB treatment and at the Week 96/End of Study or Early Study D/C visit.

Appendix IIA: Drug Groups Routinely Used for Drug-Resistant Tuberculosis Treatment in Children

Group	Abbreviation
Group A	
Fluoroquinolones: Levofloxacin or Moxifloxacin	LFX / MXF
Bedaquiline	BDQ
Linezolid	LZD
Group B	
Clofazimine	CFZ
Cycloserine or Terizidone	Cs / Trd
Group C	
Ethambutol	E
Pyrazinamide	Z
Delamanid	DLM
Aminoglycosides: Amikacin (Streptomycin)	Am / Sm
Ethionamide or prothionamide	ETH / Pto
Meropenem (with amoxicillin/clavulanate)	Mpm (with Amc-Clv)
Para-aminosalicylic acid	PAS
Not classified but used	
Isoniazid high-dose	INH-hd

Appendix IIB: Constructing an RR-TB Treatment Regimen in Children

Regimens for RR-TB treatment in children are individualized according to the child or adult source case's *M. tuberculosis* isolate drug susceptibility test results as well as information about previous treatment experience. The WHO divides anti-TB drugs into Groups A-C (as shown in Appendix IIA). This helps to construct a regimen aiming at four to five effective drugs per regimen, depending on severity of disease and extent of drug resistance. Regimens should be constructed consistent with current international WHO and local guidance and practice, which will be updated periodically as WHO and country guidelines for standards of care change. The 2019 and 2022 suggested approach from the WHO is outlined below:

1. In patients with RR-TB or MDR-TB, a regimen with at least four effective TB medicines during the intensive phase is recommended, including four second-line TB medicines from groups A (up to three drugs), group B (two drugs) and if not feasible to build a regimen from groups A and B, drugs from group C. Some first-line drugs are included in group C, but to use these as effective drugs, susceptibility to that drug must be confirmed. High-dose isoniazid, which is not included in the WHO guidance, has shown good early bactericidal activity at high dose against organisms with an *inhA* promoter region mutation conferring isoniazid resistance. As of March 2022, the use of BDQ and DLM is recommended for all children.

2. In patients with RR-TB (which may be mono-resistance), it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.

3. WHO has included shorter (9-12 month) RR/MDR-TB regimens in their guidance for treatment of mainly pulmonary rifampin-mono-resistant or MDR-TB without resistance to any second-line drug or isoniazid resistance conferred by both *inhA* and *katG* mutations. Patients who received more than one month of any second-line drug also do not qualify for the shorter regimen. This regimen can effectively be used at any age.

   If at all possible, use only all-oral injectable-free RR-TB regimens.

Appendix III: Summary of the Adverse Effects of Second-line Drugs Used in the Treatment of Drug Resistant Tuberculosis in Children

Drug	Main Adverse Effects (22)
Levofloxacin	Sleep disturbance, GI disturbance, arthralgia/arthritis, headache, idiopathic raised intracranial pressure, prolongation of QTc interval (less so than moxifloxacin)
Linezolid	Headache, diarrhea, nausea, myelosuppression, peripheral neuritis, optic neuritis, lactic acidosis, pancreatitis
Clofazimine	Skin discoloration, ichthyosis, abdominal pain, QT interval prolongation
Cycloserine/Terizidone	Neurological and psychological effects, severe depression, and suicidal ideation in adolescents
Ethambutol	Optic neuritis
Pyrazinamide	Arthritis/arthralgia (increased risk with fluoroquinolone use), hepatotoxicity, skin rashes
Delamanid	QTc prolongation, dizziness, nausea and vomiting, paraesthesia, anxiety, hallucinations, and night terrors
Amikacin	Ototoxicity, nephrotoxicity
Ethionamide/Prothionamide	GI disturbance, metallic taste, hypothyroidism
Amoxicillin/clavulanate, Imipenem, Meropenem	GI intolerance, hypersensitivity reactions, seizures, liver, and renal dysfunction
Para-aminosalicylic acid (PAS)	GI intolerance, hypothyroidism, hepatitis
Isoniazid high-dose	Hepatotoxicity, peripheral neuropathy

Appendix IV: Potential Interactions and Combined Toxicity Between the Routine Second-line Tuberculosis Drugs and ART in Children

Drug	Pharmacokinetic interactions	Increased risk of adverse effects
Injectables (amikacin or streptomycin)	Unlikely	Nephrotoxicity with tenofovir
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

Appendix V: Supplemental Toxicity Table for Grading ECGs and Cardiac Clinical Criteria

	Grade 1	Grade 2	Grade 3	Grade 4
ECG Grading Criteria: corrected QTc interval *Note*: QTc corrected based on Fridericia method (QTc=QT/cubed root of RR interval).	QTc ≥ 460 msec, but < 480 msec	QTc ≥ 480 msec, but < 500 msec	QTc ≥ 500 msec OR QTc > 60 msec greater than baseline AND QTc ≥480 ms	Life-threatening consequences (e.g., Torsades de pointes, other serious ventricular dysrhythmias)
Cardiac Clinical Event Grading Criteria	NA	Any one of the following clinical symptoms (one event, without clear evidence of non-cardiac etiology): • syncope • chest pain • palpitations • dizziness	Recurrence/ongoing clinical symptoms (without clear evidence of non-cardiac etiology): • syncope • chest pain • palpitations • dizziness	Recurrence/ongoing clinical symptoms – *with evidence of ventricular tachycardia (VT)** • syncope • chest pain • palpitations • dizziness **Note*: Presence of VT *is the adverse outcome* to be identified and avoided to the extent possible. The symptoms above are surrogates for "possible" VT, and if VT is demonstrated, then BDQ should be permanently discontinued irrespective of QTc or symptoms.

Appendix VI: Toxicity Management of ECG-Determined or Clinical Cardiac Toxicities

ECG-determined or clinical cardiac toxicity	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1 ECG or Cardiac Clinical Criteria	Upon initial identification of a grade 1 ECG, consult the Core Team and repeat ECG and/or clinical evaluation of symptoms as soon as possible and within three business days. BDQ may continue while awaiting repeat evaluations. If repeat evaluations and/or ECG do not confirm the initial grade (i.e., grade of repeat ECG and/or clinical evaluations is higher), manage per the grade of the repeat result. If repeat evaluation is grade 1, continue routine monitoring at the next study visit, unless otherwise directed by the Core Team.
Grade 2 ECG or Cardiac Clinical Criteria	Upon initial identification of a grade 2 ECG or cardiac clinical criteria, consult the Core Team and repeat ECG and/or clinical evaluation of symptoms as soon as possible and within two business days. BDQ may continue while awaiting repeat evaluations. If repeat evaluations and/or ECG do not confirm the initial grade (i.e., grade of repeat ECG and/or clinical evaluations is lower or higher), manage per the grade of the repeat result. If repeat evaluation is grade 2, continue close monitoring as determined by the site investigator in consultation with the Core Team.
Grade 3 ECG	Hold BDQ upon initial identification of a grade 3 ECG. Consult the Core Team and repeat ECG and clinical evaluation of symptoms as soon as possible and within two business days. Other medications that may prolong the QT interval should be held at the discretion of the site investigator. Assess K^{+}, Mg^{+2} and Ca^{+2} (corrected for albumin) and correct as necessary. If repeat ECG does not confirm the initial grade (i.e., grade of repeat ECG is lower or higher), manage per the grade of the repeat result. If repeat evaluation is grade 3, continue to hold BDQ and notify the Core Team within one business day of the repeat result. Other QT prolonging medications should continue to be held per the site investigator. BDQ may only be resumed with approval from the Core Team.
Grade 3 or 4 Cardiac Clinical Criteria	Permanently discontinue BDQ upon initial identification of grade 3 or 4 cardiac clinical criteria and notify the Core Team within one business day. Other medications that may prolong the QT interval should be held at the discretion of the site investigator. Repeat ECG and clinical evaluation of symptoms within one business day. Assess K^{+}, Mg^{+2} and Ca^{+2} (corrected for albumin) and correct as necessary.

ECG-determined or clinical cardiac toxicity	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 4 ECG	Permanently discontinue BDQ upon initial identification of a grade 4 ECG and notify the Core Team within one business day. Other medications that may prolong the QT interval should be held at the discretion of the site investigator. Repeat ECG and clinical evaluation of symptoms within one business day. Assess K^{+}, Mg^{+2} and Ca^{+2} (corrected for albumin) and correct as necessary.

Appendix VII: Table to Determine Lower Level of Normal Heart Rate by Age

The table below should be used when evaluating heart rates on ECGs performed for Screening and follow-up visits. This table should be used in conjunction with exclusion criteria 4.2.5 and 4.2.6 and serial ECGs.

Normal Heart Rate Ranges by Age (92)

	Participant's Age								
	0 to <3 Months	**≥ 3 to < 6 Months**	**≥ 6 to < 12 Months**	**≥ 1 to < 3 Years**	**≥ 3 to < 5 Years**	**≥ 5 to < 8 Years**	**≥ 8 to < 12 Years**	**≥ 12 to < 16 Years**	**≥ 16 to ≤ 21 Years**
Normal Heart Rate Range (bpm)	94-179	105-185	108-169	89-152	73-137	65-133	62-130	60-120	50-100*
Mean (bpm)	149**	141	131	119	109	100	91	80	--
	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 VIII: Toxicity Management of General Toxicities

General Toxicities	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1	Continue BDQ and routine monitoring as specified in the SoE; work-up to exclude other causes as determined by the site investigator.
Grade 2	Continue BDQ and routine monitoring as specified in the SoE, with more frequent monitoring if clinically indicated, and work-up to exclude other causes as determined by the site investigator.
Grade 3	Upon initial identification of grade 3 event, hold BDQ if assessed as at least possibly related to BDQ. Notify the Core Team of the assessment of relationship to BDQ and management action taken as soon as possible and within three business days. If the initial grade 3 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. For grade 3 clinical events and confirmed grade 3 laboratory events: • *If assessed as probably or definitely related to BDQ*: Permanently discontinue BDQ • *If assessed as possibly related, probably not, or not related to BDQ*: BDQ may only be resumed with approval from the Core Team. If BDQ is resumed and the grade 3 event recurs – and is confirmed for grade 3 laboratory events per repeat testing as specified above – permanently discontinue BDQ. • Participants should be monitored weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.
Grade 4	Hold BDQ upon initial identification of grade 4 event. Notify the Core Team of the assessment of relationship to BDQ and management action taken as soon as possible and within three business days. If the initial grade 4 event is a laboratory abnormality, the test should be repeated as soon as possible and within three business days. If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. For grade 4 clinical events and confirmed grade 4 laboratory events: • *If assessed as probably or definitely related to BDQ*: Permanently discontinue BDQ • *If assessed as possibly related, probably not, or not related to BDQ*: BDQ may only be resumed with approval from the Core Team. If BDQ is resumed and the event recurs to a grade 3 or 4 event – and is confirmed grade 3 or 4 laboratory event per repeat testing as specified above – permanently discontinue BDQ. • Participants should be monitored weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.

Appendix IX: Toxicity Management of Specific Toxicities

BILIRUBIN	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1	Continue BDQ and routine monitoring as specified in the SoE; work-up to exclude other causes as determined by the site investigator.
Grade 2	Upon initial identification of a grade 2 bilirubin, repeat testing as soon as possible and within three business days. Testing for AST, ALT, and for other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections) should also be done, consistent with local standard of care and as per the site investigator. BDQ may continue while awaiting the repeat test result. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. If the repeat test result is grade 2, consult the Core Team as soon as possible and within three business days. The Core Team should be notified of the assessment of relationship to BDQ and management action taken. The participant should be monitored closely until improvement to baseline or stabilization, as determined by the site investigator in consultation with the Core Team.
Grade 3	Hold BDQ upon initial identification of a grade 3 bilirubin. Repeat testing and notify the Core Team of the assessment of relationship to BDQ and management action taken as soon as possible and within three business days. Testing for AST, ALT, and for other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections) should also be done, consistent with local standard of care and as per the site investigator. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. For confirmed grade 3 bilirubin: • *If assessed as probably or definitely related to BDQ*: Permanently discontinue BDQ and notify the Core Team as soon as possible and within one business day of the repeat result. Participants should be monitored weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team. • *If assessed as possibly related, probably not, or not related to BDQ*: Continue to hold BDQ and consult the Core Team as soon as possible and within three business days. Continue close monitoring and work-up to exclude other causes, as determined by the site investigator in consultation with the Core Team. BDQ may be resumed after resolution to grade 2 or lower, unless otherwise instructed by the Core Team.

BILIRUBIN	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 4	Hold BDQ upon initial identification of a grade 4 bilirubin. Repeat testing as soon as possible and within three business days. Testing for AST, ALT, and for other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections) should also be done, consistent with local standard of care and as per the site investigator. Notify the Core Team of the site assessment of relationship to BDQ and management actions taken while awaiting the repeat test result (i.e., within three business days of awareness of initial event). If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. If the repeat test result is grade 4, BDQ may only be resumed with approval from the Core Team. Participants should be monitored weekly until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.
Meets Hy's law (ALT or AST elevations are 3-fold accompanied by 2-fold elevation in total bilirubin)	Hold BDQ upon initial identification of events meeting Hy's law. Consult the Core Team and repeat testing for elevated AST or ALT and total bilirubin as soon as possible and within three business days. The Core Team should be notified of the assessment of relationship to BDQ and management action taken. Conduct tests for other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections), consistent with local standard of care and as per the site investigator, and within three business days as well. Other potential hepatotoxic medications should be held, as determined by the site investigator. If repeat testing confirms that criteria for Hy's law are met, permanently discontinue BDQ. Participants should be followed until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.

AST and/or ALT	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1	Continue BDQ and routine monitoring as specified in the SoE; work-up to exclude other causes as determined by the site investigator.
Grade 2	Upon initial identification of a grade 2 AST or ALT, repeat testing as soon as possible and within three business days. Testing for bilirubin and other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections) should also be done, consistent with local standard of care and as per the site investigator. BDQ may continue while awaiting the repeat test result. If the repeat test result does not confirm the initial grade (i.e., is lower or higher), manage per the grade of the repeat result. For confirmed grade 2 AST and/or ALT with signs or symptoms of clinical hepatitis (e.g., fatigue, nausea, vomiting, right upper quadrant pain, jaundice), manage as per grade 3 or 4 below. If the repeat test result is grade 2, without signs or symptoms of clinical hepatitis, consult the Core Team as soon as possible and within three business days. The Core Team should be notified of the assessment of relationship to BDQ and management action taken. Consider temporarily discontinuing other potential hepatotoxic medications, as determined by the site investigator. The participant should be monitored weekly until improvement to baseline or stabilization, as determined by the site investigator in consultation with the Core Team.
Grade 3 or 4	Hold BDQ upon initial identification of a grade 3 or 4 AST or ALT. Consult the Core Team and repeat testing as soon as possible and within three business days. Testing for bilirubin and other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections) should also be done, consistent with local standard of care, and as per the site investigator. Other potential hepatotoxic medications should be held, as determined by the site investigator. If the repeat test result does not confirm the initial grade (i.e., is lower), manage per the grade of the repeat result. For confirmed grade 3 or 4 AST and/or ALT: • Continue to hold BDQ and notify the Core Team of the repeat result within one business day. The Core Team should be notified of the assessment of relationship to BDQ and management action taken. • If AST and/or ALT return to baseline within three weeks of the initial event, and other potential causes of hepatotoxicity are excluded as determined by the site investigator in consultation with the Core Team, BDQ may be resumed with approval from the Core Team. • If AST and/or ALT do not return to baseline within three weeks of the initial event and an alternative cause is not identified in consultation with the Core Team, BDQ should be permanently discontinued. • Participants should be monitored weekly until improvement to baseline or until stabilization and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.

Meets Hy's law (ALT or AST elevations are 3-fold accompanied by 2-fold elevation in total bilirubin)	Hold BDQ upon initial identification of events meeting Hy's law. Consult the Core Team and repeat testing for elevated AST or ALT and total bilirubin as soon as possible and within three business days. The Core Team should be notified of the assessment of relationship to BDQ and management action taken. Conduct tests for other possible causes (e.g., viral hepatitis A and B and other clinically relevant infections), consistent with local standard of care and as per the site investigator, and within three business days as well. Other potential hepatotoxic medications should be held, as determined by the site investigator. If repeat testing confirms that criteria for Hy's law are met, permanently discontinue BDQ. Participants should be followed until improvement to baseline or until stabilized and no longer in need of frequent monitoring, as determined by the site investigator in consultation with the Core Team.

Myalgia	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1 or 2	Continue BDQ, with close monitoring as determined by the site investigator.
Grade 3	Hold BDQ upon initial identification of grade 3 myalgia. Notify the Core Team as soon as possible and within three business days. Work-up to exclude other causes and closely monitor participant as determined by the site investigator in consultation with the Core Team. BDQ may only be resumed with approval from the Core Team.
Grade 4	Hold BDQ upon initial identification of grade 4 myalgia. Notify the Core Team as soon as possible and within three business days. Work-up to exclude other causes and closely monitor participant as determined by the site investigator in consultation with the Core Team. BDQ may only be resumed after the event resolves to less than or equal to grade 2 and approval from the Core Team.

Nausea and/or Vomiting *If a participant experiences new onset of vomiting, after being established on a TB regimen, assess for signs and symptoms of clinical hepatitis, potential hepatotoxicity, or raised intracranial pressure. Reinforce participant and/or caregiver/guardian awareness of these signs and symptoms. Instruct participant and/or caregiver/guardian to contact the site investigator should any signs or symptoms occur consistent with clinical hepatitis, potential hepatotoxicity, or raised intracranial pressure.*	
SEVERITY	**STUDY DRUG AND CLINICAL MANAGEMENT**
Grade 1 or 2	Continue BDQ and work-up to exclude other causes as determined by the site investigator. Provide symptomatic management and routine monitoring as specified in the SoE. If new onset of vomiting after being established on a TB regimen, conduct tests for ALT and total bilirubin and, if clinically indicated, evaluate for raised intracranial pressure. • If ALT or total bilirubin are grade 1 or higher, evaluate for clinical hepatitis, following appropriate management in the tables above. • If ALT and/or total bilirubin are normal, continue follow-up as specified in the SoE.
Grade 3	Hold BDQ upon initial identification of grade 3 vomiting. Consult the Core Team as soon as possible and within three business days. Work-up to exclude other causes as determined by the site investigator. BDQ may only be resumed with approval from the Core Team.
Grade 4	Hold BDQ upon initial identification of grade 4 vomiting. Consult the Core Team as soon as possible and within three business days. BDQ may only be resumed after the event resolves to less than or equal to grade 2 and approval from the Core Team.

Appendix X: BDQ Pharmacometric Clinical Trial Simulations to Inform P1108 Study Design

Provided by Elin Svensson and Mats Karlsson, Uppsala University

Objectives

Evaluate PK sampling strategies and samples size for characterization of bedaquiline (BDQ) PK in children. The study design should (i) ensure ability to provide precise enough estimates of apparent clearance as specified by the FDA criteria for pediatric trials (85) and (ii) ensure sufficient power to detect potential differences in PK parameters between children without and with concomitant HIV disease. The first point implies that the primary objective of the study (to determine BDQ doses for children who achieve similar weekly exposure as adults taking BDQ at the current standard recommended dose) can be fulfilled.

Methods

A population PK model of BDQ and the M2 metabolite developed on data from primarily HIV-negative RR-TB adult patients obtained in two Phase II studies (C208 and C209) was used as the basis for these clinical trial simulations. The model includes random effects describing inter-individual variability in bioavailability (F), clearance (CL) of BDQ and M2, central volume of distribution (V) of BDQ and M2, and inter-compartmental clearance for BDQ first distribution compartment. Allometric scaling was applied with the coefficients found to fit the adult data best (0.27 for clearances and 1.0 for volumes). Maturation of the metabolizing enzyme CYP3A4 in the youngest children was modeled with a fixed, previously described function (93). The typical value of clearance of BDQ and M2 was set to that of an individual of black race.

The population characteristics age, sex and weight were simulated simultaneously with the PK. Age was simulated uniformly within each cohort and sex was simulated with a 50/50 probability. Weights were derived for the given age and sex with a simplified LMS method (94) based on WHO growth standards (0-10 years) (95) and the NHANES study (10-18 years) (96).

Initial calculations based on the inter-individual variability in and the body weight relationship with apparent BDQ clearance (CL/F) estimated in adults indicated that 18 participants per cohort should be sufficient to obtain a narrow enough 95% confidence interval (CI) to fit within 60 to 140% of the geometric mean as stated in the FDA criteria (85). This sample size was then further evaluated in the clinical trial simulations. It was assumed that six children living with HIV would be included in each age cohort of 18. The dosing regimen for Cohort 1 was implemented as described in the protocol. For Cohorts 2 and 3 doses predicted to result in concentrations comparable to those seen in adults were used (8-15 kg: 150 mg QD and thereafter 100 mg TIW, below 8 kg: 100 mg QD and thereafter 50 mg TIW). PK sampling was implemented as outlined in Appendix I.

The analysis was performed in NONMEM (88), aided by the stochastic simulation and estimation (SSE) functionality in PsN (97). 100 virtual trials were simulated assuming (i) no difference in PK between children living with and without HIV, (ii) 30% lower BDQ and M2 CL in children living with HIV or (iii) 30% lower BDQ bioavailability in children living with HIV. Parameters were re-estimated on the simulated data including or not including a parameter describing a difference in CL or bioavailability in patients living with and without HIV. The parameter precision, the power to detect a true effect of HIV and, the risk of finding a significant effect of HIV when data were simulated without (type 1 error) were evaluated. The parameter precision in CL/F was described by 95% parametric CIs at the tails of the expected weight distribution (5 kg and 50 kg respectively, assuming that when precision is acceptable at the extremes it will also be acceptable at weights between those values). The CIs were based on the mean and standard error of the estimates of CL/F for a 5 kg and 50 kg child respectively, obtained in the re-

estimation of the 100 simulated trials. Hypothesis testing was conducted with likelihood ratio test based on the objective function value (OFV, equivalent to –2 ln likelihood) which is approximately chi-square distributed. The degrees of freedom are equal to the difference in number of parameters between the two nested models compared. The likelihood was determined with the first-order conditional estimation as implemented in NONMEN. The significance level used was 5%.

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

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: $SE_{LCL} = \sqrt{\sigma_1^2 + \left(log\left(\frac{WT}{33.5}\right)\right)^2 \sigma_2^2 + 2\sigma_{12} log\left(\frac{WT}{33.5}\right)}$

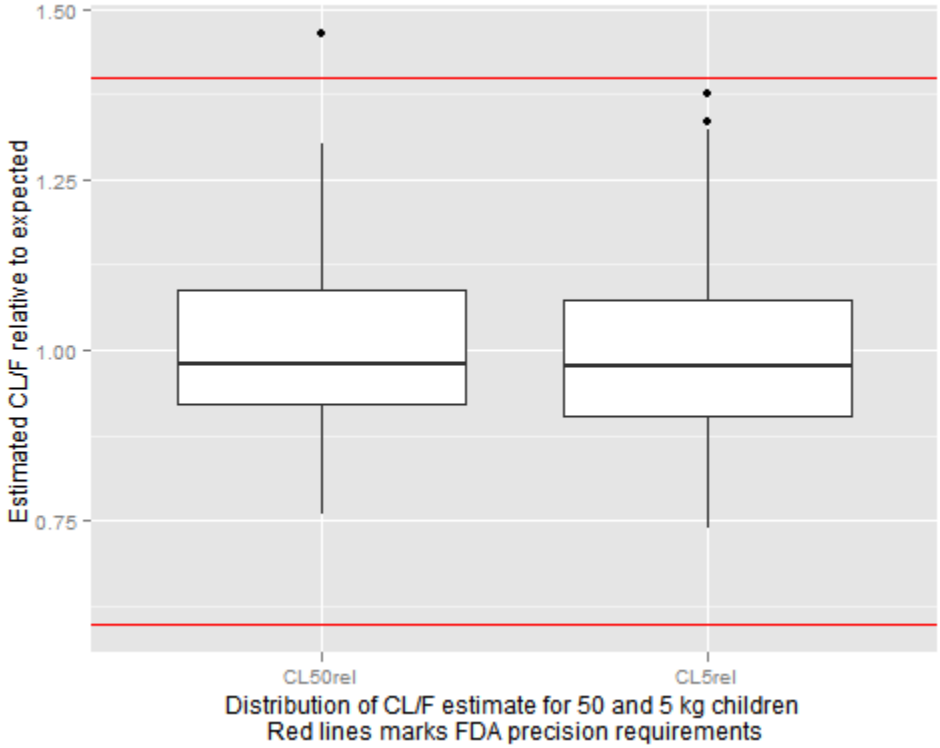
The percentage of the 100 simulated trials where the 95% parametric CI of CL based on the point estimate and SE_{LCL} fell within the limits (60-140% of expected) were calculated for 5 kg and 50 kg and visualized with plots.

Results

(i) Fulfilling FDA precision criteria

The precision in CL/F was generally good. For a 5 kg child the mean of the estimates was 2.79 L/h and the 95% CI 2.06 to 3.50 L/h, which falls well within 60%-140% of the expected value (1.68 to 3.92 L/h) and hence fulfills the FDA criteria (1). For a 50 kg child the mean of the estimates was 5.26 L/h and the 95% CI 3.98 to 6.53 L/h, which also fall within the stipulated interval (3.15 L/h to 7.34 L/h). The distribution of the estimated CL/F values (N=100) relative to the expected for a 5 kg and a 50 kg child is illustrated in Figure 9.

Figure 9
The Distribution of Estimated CL/F Relative to the Expected Value (used in simulation) for a 5 kg and a 50 kg Child.



When attempting to estimate all model parameters on only the data from the first 12 participants in Cohort 1 followed until Week 8, the parameter precision was not satisfactory. The 95% CI for CL/F (50 kg participant) was 1.01 L/h to 8.21 L/h which falls outside the 60%-140% interval of the expected value.

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

The estimated power to detect a 30% change in CL or bioavailability and the type 1 error rates are listed in Table 10. With small studies like this, the reference distribution deviates from the expected chi-square distribution, resulting in a somewhat inflated type 1 error. In the analysis of the real data, type 1 error control can be achieved through permutation tests.

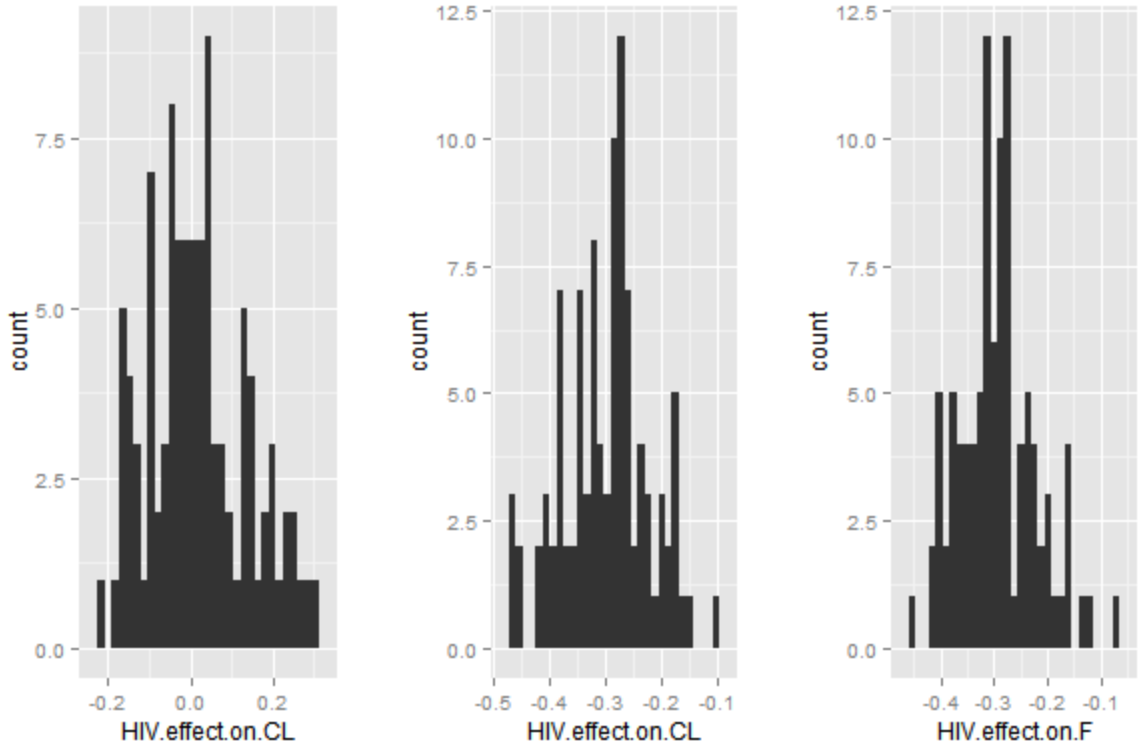
Table 10
Power and type 1 error rate for detection of an effect of HIV, all cohorts combined

Scenario	Power	Type 1 error
No effect of HIV		8%
CL -30% in participants living with HIV	88%	
F -30% in participants living with HIV	92%	
No effect of HIV, cohort 1 data		10%
CL -30% in participants living with HIV, Cohort 1 data	43%	

When data were simulated without an effect of HIV but an effect was allowed on CL in the re-estimations, this effect was on average estimated to 1.8% (95% CI -21.8% to 25.4%). The -30% effect on

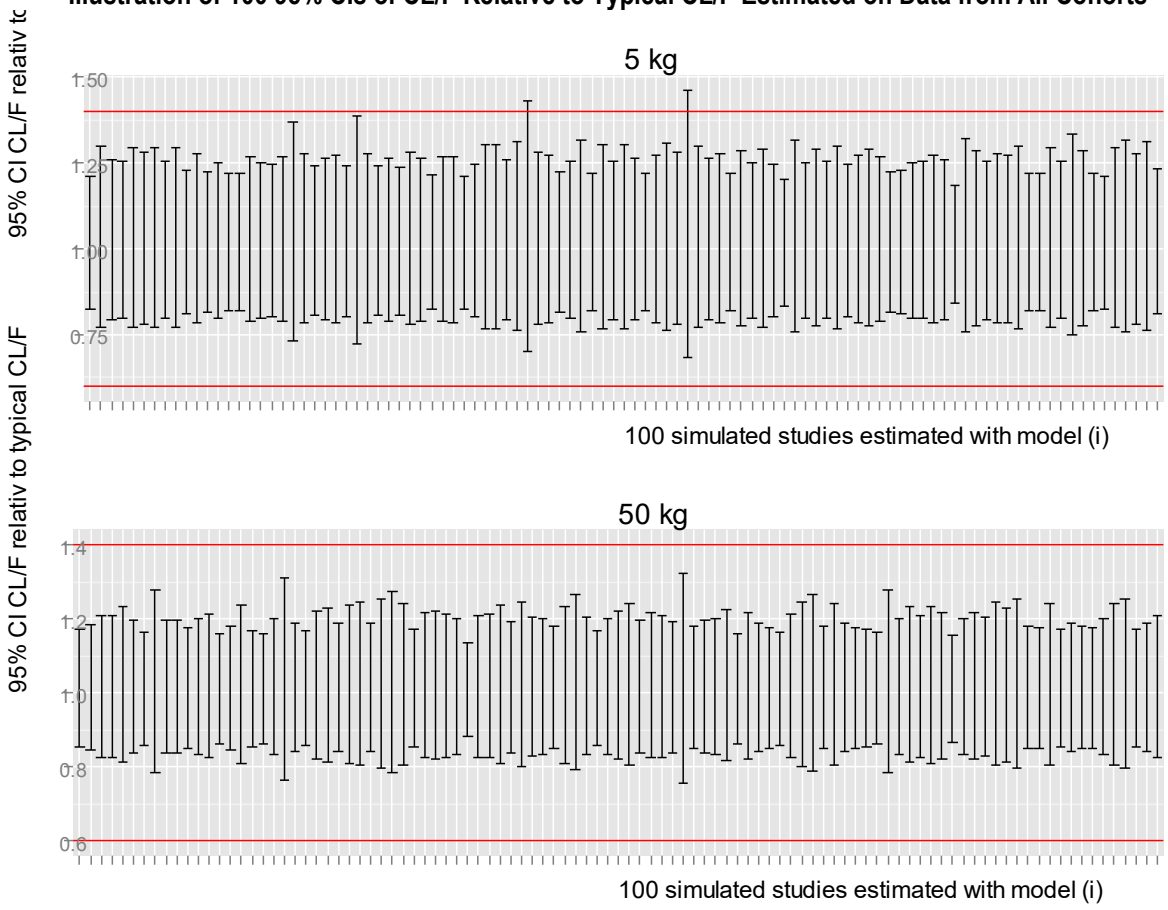
CL or bioavailability was re-estimated to -30.0% (95% CI -44.7% to -15.0%) and -29.1% (95% CI -43.1% to -15.1%), respectively. The distributions of the estimates are illustrated in Figure 10.

Figure 10
Distribution of Estimated Effect if HIV When Data Were Simulated Without Any Effect (left), With -30% in CL (middle) or -30% in Bioavailability (right).



The power calculations for model (i) showed high power to achieve precise enough CIs as defined by Wang et al. The power for apparent clearance in 5 kg and 50 kg children were 98% and 100% respectively. The obtained CIs are illustrated in Figure 11.

Figure 11
Illustration of 100 95% CIs of CL/F Relative to Typical CL/F Estimated on Data from All Cohorts



Conclusions and Discussion

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

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

Appendix XI: Bedaquiline Dosing Tables for Cohorts 2 and 3

If the Core Team determines that a BDQ dose regimen adjustment is needed during the study, the selected table below will be communicated to sites as per Section 5.2. Tables A and B correspond to optimized BDQ dosing given an allometric coefficient of 0.5 and 0.75, respectively. If the Core Team determines that a dose adjustment is required and the appropriate dose is not included in the tables below, an updated dosing table will be provided through the appropriate mechanism.

Table A

Weight	Entry through the Intensive PK visit	After the Intensive PK visit and through the Week 24 visit
> 11 kg to ≤ 30 kg	BDQ 140 mg once daily, every day Given as seven ***20 mg tablets*** to equal 140 mg per dose Total weekly dose of 980 mg	BDQ 60 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses. Given as three ***20 mg tablets*** to equal 60 mg per dose Total weekly dose of 180 mg
> 7 kg to ≤ 11 kg	BDQ 100 mg once daily, every day Given as one ***100 mg tablet*** *or* Given as five ***20 mg tablets*** to equal 200 mg per dose Total weekly dose of 700 mg	BDQ 40 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses. Given as two ***20 mg tablets*** to equal 40 mg per dose Total weekly dose of 120 mg
≥ 3 kg to ≤ 7 kg	BDQ 60 mg once daily, every day Given as three ***20 mg tablets*** to equal 60 mg per dose Total weekly dose of 420 mg	BDQ 20 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses Given as one ***20 mg tablet*** to equal 20 mg per dose Total weekly dose of 60 mg

Table B

Weight	Entry through the Intensive PK visit	After the Intensive PK visit and through the Week 24 visit
> 11 kg to ≤ 30 kg	BDQ 100 mg once daily, every day Given as <u>one</u> ***100 mg tablet*** *or* Given as <u>five</u> ***20 mg tablets*** to equal 100 mg per dose Total weekly dose of 700 mg	BDQ 40 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses. Given as <u>two</u> ***20 mg tablets*** to equal 40 mg per dose Total weekly dose of 120 mg
> 7 kg to ≤ 11 kg	BDQ 80 mg once daily, every day Given as <u>four</u> ***20 mg tablets*** to equal 80 mg per dose Total weekly dose of 560 mg	BDQ 20 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses. Given as <u>one</u> ***20 mg tablet*** to equal 20 mg per dose Total weekly dose of 60 mg
≥ 3 kg to ≤ 7 kg	BDQ 40 mg once daily, every day Given as <u>two</u> ***20 mg tablets*** to equal 40 mg per dose Total weekly dose of 280 mg	BDQ 10 mg once a day *only on Monday, Wednesday, and Friday* with at least 48 hours between doses Given as <u>one half</u> of a ***20 mg tablet*** to equal 10 mg per dose Total weekly dose of 30 mg

Appendix XII: Operational Guidance for Study Implementation at Sites Experiencing Operational Disruptions Due to COVID-19

To safeguard the health and well-being of study participants and study staff in the context of circulating SARS-CoV-2 and the associated coronavirus disease 2019 (COVID-19), the guidance provided in this appendix may be implemented at sites experiencing disruptions due to COVID-19.

The extent to which site operations may be disrupted by COVID-19 may vary across sites and over time. **All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff.** All sites must also comply with any directives received from the study sponsor, the IMPAACT Network, and/or the P1108 Core Team. Should a determination be made in the future that the guidance provided in this appendix is no longer applicable, sites will be formally notified and instructed to inform their IRBs/ECs and other applicable regulatory entities.

Visit Scheduling

- Sites are advised that potential participants who are screened for the study should be enrolled only if the site investigator has confidence that local conditions will allow for, at a minimum, the intensive PK visit to be conducted in-person at the study site. The site investigator should also have confidence that intensive PK samples can be collected, processed, and shipped consistent with Section 6 and relevant sections of the study-specific Manual of Procedures and Laboratory Processing Chart. In the absence of such confidence, screening and enrollment should not proceed.
- Sites are advised to optimize the visit windows specified in Section 6 when scheduling study visits during periods of operational disruption. Sites that anticipate operational disruptions or closures are advised to conduct study visits early in the visit window before the disruption occurs. Sites that are currently experiencing operational disruptions or closures are advised to conduct study visits late in the visit window.
- Sites should utilize the protocol-specified visit windows to schedule study visits in-person, when possible, in full compliance with the protocol. Visits conducted outside of the protocol-specified windows are preferred to missed visits. Sites that anticipate a visit may need to be conducted prior to or after closing of the protocol-specified visit window, due to operational disruptions or closures, should contact the P1108 Core Team (impaact.p1108core@fstrf.org) for guidance on visit completion on a case-by-case basis.
- When visits must be delayed or missed, sites should make every effort to avoid gaps in BDQ supply (see further guidance for study drug supply below).

Prioritization of Study Visit Procedures

- If it is not possible to conduct study visits in-person at the study site, visit procedures may be performed off-site or remotely (e.g., by telephone) as described below. Site investigators must ensure that standard operating procedures are in place for off-site and remote procedures.

- *In-person off-site visits*: Sites may conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. Where this option is permitted, study staff should communicate with participants and/or their caregivers/guardians to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality.

  Off-site visit procedures should be conducted by designated study staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR) or

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

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

1. Clinical procedures and evaluations:
   - Update medical and medication history since the last study visit, including new TB exposure history, AEs, and all concomitant medications
   - ECGs
   - Physical exam and vitals as per the protocol and as clinically indicated
   - Chest x-ray
   - Assess TB treatment outcome (at the off-treatment visit following completion of the participant's RR-TB treatment regimen and at the Week 96/End of Study visit)
   - Audiology assessments, if applicable
2. Laboratory procedures and evaluations (in order of prioritization). *Note: If it is not possible to perform these tests consistent with the site's Protocol Analyte List, tests may be performed in alternate laboratories using alternate assays (alternate laboratories must adhere to local regulations for clinical laboratory testing).*
   - Liver function tests, Chemistries, Hematology
   - Intensive or Sparse PK
   - HIV-1 RNA PCR and lymphocyte subsets (only in participants living with HIV)
   - TSH (and fT4 if TSH is elevated)
   - Pregnancy test
   - Urinalysis
   - ARV genotypic resistance testing if participant's viral load ≥ 1,000 copies/mL and as per the site investigator's discretion
   - TB biomarkers collected only per site capacity and if informed consent obtained for future storage
3. Provide contraceptive counseling, as applicable

At off-site visits when specimen collection is required, the procedures specified in protocol Section 6.16 must be followed. Blood and urine may be collected at off-site visits. Further invasive specimen collection, such as for sputum or gastric aspirate, should NOT be attempted in non-medical site settings due to infection control concerns.

- *Remote visits (e.g., via telephone)*: Sites with no ability to conduct in-person visits (either at the clinic or off-site) may perform the following study procedures remotely, per the respective scheduled study visit, prioritized in the order outlined below:
  - Update medical and medication history since last visit, including new TB exposure history, AEs, and all concomitant medications
  - Assess TB treatment outcome (at the off-treatment visit following completion of the participant's RR-TB treatment regimen and at the Week 96/End of Study visit)
  - Provide contraceptive counseling, as applicable

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

Study Drug Supply

- Sites are advised to dispense study drug supplies in quantities sufficient through the Week 24 visit.
- Sites are advised to maintain frequent communication with participants and/or their caregiver/guardian (e.g., by telephone) to inquire about each participant's health, use of study drug, and study drug supplies.
- Sites are encouraged to implement study drug dispensing and delivery options involving outdoor pick-up or drop-off. Sites are also advised that, when other options are not feasible, the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* permit shipment or courier of study drug from the site directly to participants. This method should only be used in the short-term and if permissible per local institutional and IRB/EC policies. Refer to the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for additional details on this method. Sites must ensure that study product storage conditions are maintained in accordance with the protocol and documented until dispensed to the participant.
- Sites are encouraged to provide adherence assessment, counseling, and support remotely (e.g., by telephone).
- Sites are permitted to utilize rapid urine pregnancy test kits (either performed by study staff or given to and performed by participants themselves) in the context of these study drug pick-up or drop-off options. Sites should carefully consider how to maintain privacy and confidentiality of discussions related to sexual activity and the need for and results of pregnancy testing.
- If pregnancy testing or any other procedures cannot be performed for any reason, however, study drug supplies should still be provided.

Documentation

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for IMPAACT P1108.
- Documentation should be entered in participant study charts in real-time (or close to real-time) should any of the following occur:
  - Missed visits
  - Out-of-window visits
  - Off-site visits (document the location of the visit)
  - Incomplete or partial visits (document which procedures were performed, and which were not)
  - Remote contacts performed in lieu of in-person visits (document method used to complete the contact and which procedures were performed)
  - Any other participant contacts
  - Use of alternate laboratories or alternate laboratory assays
  - Alternate provision of study drug
- In consultation with the Division of AIDS, the IMPAACT Network has developed and disseminated guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures due to COVID-19. Please contact the IMPAACT Operations Center Clinical Research Managers with any questions related to documentation and reporting requirements.

Appendix XIII: Sample Informed Consent Form for Study Participation

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

Protocol Version 2.0, Dated 21 September 2022

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.

Introduction

This form is for the participant or the parent or guardian of the baby, child, or adolescent who is being asked to participate in the research study named above.

Participants in this study may be babies, children, or adolescents less than 18 years. In this form, participants are referred to as "children" even though they may be babies or older teenagers. For most participants, the parent or guardian will provide informed consent for participation in the study. This form refers to "your child" with the expectation that parents or guardians will be reading the form. However, some adolescents may qualify to provide informed consent for themselves. For these adolescents, when reading this form, "your child" refers to the adolescent who is providing informed consent.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. We will take as much time as needed for you to fully understand the study. We will ask you questions to see if we have explained the study clearly.

Here is a summary of important information about the study:

- The medicines usually given to treat tuberculosis or "TB" are called "first-line" medicines (or drugs). First-line drugs include rifampin (RIF). When RIF no longer works to treat TB, this is called rifampin-resistant TB or "RR-TB".
- This study is testing a medicine called Bedaquiline (or "BDQ"). BDQ is used to treat RR-TB.
- BDQ has been tested and approved for adults and children five years and older with multidrug-resistant TB (MDR-TB).
- This study will look at whether BDQ can be safely used without any bad side effects when given to babies, children, and adolescents. It will also look for the best amount of BDQ to give to babies, children, and adolescents for treatment of RR-TB.
- Children will be in the study for approximately two years.
- At study visits, children will have physical exams, urine collection, and blood draws for laboratory tests. Tests will be done to check children's health, including their heart and lungs and the amount of BDQ in their blood.
- Children will take BDQ every day for approximately two weeks, and then take BDQ once a day on Monday, Wednesday, and Friday through the Week 24 visit.
- There are possible risks for children in the study. One possible risk is that BDQ could cause side effects, including heart and liver damage, which could lead to death. These side effects are rare.

- There are possible benefits for children in the study. Possible benefits are that BDQ may help treat RR-TB in your child and reduce the risk of death from RR-TB in children.

More information about the study is given in this form. You should feel that you understand the study before deciding whether your child will participate. If you decide that your child will participate, you will be asked to sign or make your mark on this form. You will be offered a copy to keep.

About the study

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[sites: insert name of site]* are doing this study. The person in charge of the study at this clinic is *[sites: insert name of Investigator of Record]*.

This study is testing a medicine called Bedaquiline or "BDQ" to treat RR-TB in children. The study will include up to 84 children from Haiti, India, and South Africa. The children will be 0-17 years old.

The United States National Institutes of Health is paying for the study.

1. The study is testing BDQ in babies, children, and adolescents with RR-TB.

TB is a very important health problem in many countries. Children with RR-TB usually take a combination of TB medicines (four or more) for a long time. Current RR-TB medicines can have bad side effects and children often need to be in the hospital for treatment. For these reasons, TB medicines that are safe to use in children with RR-TB are needed.

This study is testing the use of BDQ to treat RR-TB with other TB drugs. BDQ is also called "Sirturo". BDQ is made by Janssen Research & Development. The US Food and Drug Administration (FDA) approved BDQ in adults and children five years and older and weighing at least 15 kg for MDR-TB in the lungs. BDQ is approved to be used with other TB drugs and not by itself. BDQ is recommended by the World Health Organization (WHO) for adults and children with MDR/RR-TB. More data on BDQ doses in children are needed. [*Sites: add information on local approvals, if applicable*]

BDQ will be given to participants in this study to help find the best dose (amount) of BDQ for babies, children, and adolescents with RR-TB, when taken with other RR-TB medicines. This study will also look at whether BDQ can be safely used without any bad side effects when given to babies, children, and adolescents.

In this study, children will take BDQ once a day, every day for approximately two weeks. Children will then take BDQ once a day on Monday, Wednesday, and Friday for approximately 22 weeks. Children will continue to take the TB and HIV medicines, if applicable, given by their health care provider.

As part of this study, your child will be assigned to a group based on their age. There are three groups in this study, each with at least 18 children. The three groups are as follows:

- Group 1: Children 6 to less than 18 years of age
- Group 2: Children 2 to less than 6 years of age
- Group 3: Babies 0 months to less than 2 years of age

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

2. Only children who qualify can participate.

If you decide to have your child join this study, we will first do some tests to see if your child qualifies. More information about the tests is given in #4. If your child qualifies, your child will be entered in the study. If your child does not qualify, your child cannot be entered in the study.

3. It is your decision whether to have your child participate in the study.

Deciding to have your child join the study is voluntary (your choice). You are free to have your child join or not join. If you decide to have your child join, you can change your mind and take your child off the study at any time. Your decisions will have no effect on the medical care your child receives. Your child's access to services, and your child's normal benefits and rights, will not be affected.

Take your time and consider your decision carefully. If you wish, you can talk to other people about the study before you decide. You can bring other people here to learn about the study with you.

No matter what you decide about the study, it is important for your child to receive medical care and take TB medicines as instructed by their health care provider. If your child is living with HIV, your child should also keep taking anti-HIV medicines (ARVs). We will discuss your options with you.

Your child does not need to join this study to receive medical care, TB medicines, or ARVs. Your child can keep receiving medical care, TB medicines, and ARVs from outside the study. Your child may also qualify for other studies. Please ask any questions you may have about these types of alternatives.

Finding out if your child qualifies for this study

4. We will ask questions, review your child's medical records, examine your child, and test your child's blood.

To find out if your child qualifies for the study, we will:

- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical exam.
- Give your child an electrocardiogram (ECG). This is a test of how well your child's heart is working.
- Collect sputum from your child. See #10 below.
- Give your child a chest x-ray. This takes a picture of your child's lungs. See #11 below.
- If your child has RR-TB that has been confirmed in a laboratory, we will try to find this sample (a TB culture) so we can compare the type of TB from this sample with other TB samples taken from your child during the study.
- Draw your child's blood (up to 9 mL or about 2 teaspoons) for tests. The tests will check:
  - Your child's blood cells, liver, and kidneys.
  - Your child's blood for HIV. Certain HIV tests are required for the study. If the required tests are not in your child's medical records, we will do the tests that are needed.
- If your child can become pregnant, we will collect blood (1 mL or less than ¼ teaspoon) or urine for a pregnancy test. If your child is pregnant, they will not qualify for the study. See #12 below.
- If you agree, we will draw your child's blood (up to 1 mL or less than ¼ teaspoon) for later TB testing. The later tests will look at how the body responds to TB and RR-TB treatment. We will ask you about collecting and saving these samples in a separate form.
- Talk with you about the study requirements and if your child is able to meet these requirements.

These procedures will take up to four hours *[sites: modify how much time these procedures will take as appropriate]*.

Some test results will be ready quickly. Others may take about one week or more. We will schedule your child to come back when the results are ready. We may ask you to bring your child back for more tests if needed to find out if your child qualifies for the study.

We will also ask your child about sexual activity. If your child is a female and having sex that could lead to pregnancy, to qualify for the study, they will be required to use contraception throughout the study. More information is provided in #12 below. If your child is a male and having sex that could lead to pregnancy of a female, they will be required to use contraception until four weeks after stopping BDQ to qualify for the study. We will talk with you and your child about the importance of avoiding pregnancy and about the contraception methods that can be used in this study.

5. We will tell you if your child qualifies for the study.

We will review the results and all other information to determine if your child qualifies for the study.

- If your child does not qualify for the study, we will tell you this and give you information on where your child can receive medical care and other services your child may need. We will still use some information collected about your child (for example, age, sex, and race). We will use this information to look at patterns or common reasons for not entering the study. We will destroy any of your child's samples remaining after testing.

- If your child does qualify for the study, we will ask you to confirm your decision for your child to join the study. With your confirmation, your child will be entered into the study.

If your child joins the study, your child will receive BDQ as part of the study.

If your child is living with HIV, your doctor will talk to you about ARVs that may be taken with BDQ. Your child's ARVs may need to be adjusted while your child is taking BDQ. ARVs and other TB medicines your child may take will not be provided by the study.

BDQ is available as a tablet that can be swallowed whole or can be crushed. BDQ is also available in a smaller tablet form for young children. Children in Groups 2 and 3 may take the smaller BDQ tablet. The formulation your child receives and how they take it, either swallowed whole or crushed, will depend on your child's age and whether your child can swallow pills.

Entering the study

6. If your child qualifies, your child will enter the study.

On the day your child enters the study, we will:
- Review your child's medical records.
- Ask about your child's health and medicines.
- Give your child a physical exam.
- Give your child an ECG.
- Collect sputum from your child if your child's TB was confirmed by a positive TB lab test. See #10 below.
- Collect urine from your child to test how your child's kidneys are working.

- If you agree, we will draw your child's blood (up to 1 mL or less than ¼ teaspoon) for later TB testing. The later tests will look at how the body responds to TB and RR-TB treatment.
- If your child is taking an injectable medicine for RR-TB, we will check your child's hearing abilities.
- If your child is living with HIV, we will draw 4 mL (less than 1 teaspoon) to look at the amount of HIV in your child's blood (called viral load) and check the number of cells that fight against HIV (called a CD4 count). Based on the results of these tests and how long your child has been taking ARVs, we may collect an additional 3-5 mL (about 1 teaspoon) of blood to check for resistance to ARVs. Resistance means that ARVs may not work against the HIV in your child's body.

During this visit we may also draw your child's blood (up to 3 mL or less than 1 teaspoon) to check your child's blood cells, liver, and kidneys if it has been more than seven days since these tests were done to see if your child qualifies for the study. If your child is taking TB medicines called ethionamide or para-aminosalicylic acid (PAS), we will also collect blood from your child (2 mL or less than ½ teaspoon) to check your child's thyroid.

At this visit we will give your child their first dose of BDQ provided by the study. We will give you BDQ tablets and show you and your child how to take the tablets. It is very important for your child to take BDQ as instructed. Your child will take BDQ every day until the intensive PK visit. We will take as much time as needed for you and your child to understand the instructions. We will talk with you about strategies to help your child take BDQ as instructed.

This visit will take about four hours. [*sites: modify how much time this visit will take as needed*]

During the study

7. Your child will have nine study visits while taking BDQ over approximately six months.

After your child has entered the study, your child will have nine visits while taking BDQ over the first six months in the study. These visits will take place at approximately 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks after entering the study. Your child may have more visits if they are sick or if we need to do more tests to check on their health.

Most visits will take up to 2-3 hours [*sites: modify general visit time as* needed]. For some study visits, the visit may take place over more than one day.

At every visit, we will:
- Review your child's medical records.
- Ask about your child's health and medicines.
- Review if your child took BDQ since the last visit as instructed.
- Give your child a physical exam.
- Give you medicines for your child to take until the next visit, as needed.

At some visits, we will:
- Give your child an ECG.
- Give your child a chest x-ray. See #11 below.
- Draw your child's blood (3 mL or less than 1 teaspoon) to check your child's blood cells, liver, and kidneys. If your child is taking TB medicines called ethionamide or PAS, we will also collect blood from your child (2 mL or less than ½ teaspoon) to check your child's thyroid.
- Collect sputum from your child if your child's TB was confirmed by a positive TB lab test. See #10 below.

- Collect urine from your child to test how your child's kidneys are working.
- Draw your child's blood to look at the amount of BDQ in your child's blood. The amount drawn will range from 0.5 mL to 5 mL (less than ⅛ to 1 teaspoon). More information on this is given in #9 below.
- If your child is taking an injectable medicine for RR-TB, we will check your child's hearing abilities.
- If your child is living with HIV, we will draw 4 mL (less than 1 teaspoon) to check your child's viral load and CD4 count. Based on the results of these tests and how long your child has been taking ARVs, we may collect an additional 3-5 mL (about 1 teaspoon) of blood to check for resistance to ARVs.
- If you agree, we will draw your child's blood (up to 1 mL or less than ¼ teaspoon) for later TB testing. The later tests will look at how the body responds to TB and RR-TB treatment.
- If your child can become pregnant, we will ask about their sexual activity and collect blood (1 mL or less than ¼ teaspoon) or urine for a pregnancy test. See #12 below.

8. Your child will have six visits after your child stops taking BDQ.

After your child stops taking BDQ, your child will have six study visits over one and a half years. These visits will take place at approximately 2, 4, 6, 9, 12, and 18 months after your child stops taking BDQ. Your child will finish the study about two years after entering the study. Your child may have more visits if they are sick or if we need to do more tests to check on their health.

Each visit will take up to 1-2 hours *[sites: modify how much time visits will take as needed]*.

At each of these visits, we will:
- Ask about your child's health and medicines.
- Give your child a physical exam.
- Draw your child's blood (3 mL or less than 1 teaspoon) to check your child's blood cells, liver, and kidneys.
- Collect urine from your child to test how your child's kidneys are working.
- Draw your child's blood (0.5-1 mL or less than ¼ teaspoon) to look at the amount of BDQ that may be in your child's blood. See #9 below.
- If your child can become pregnant, we will ask about their sexual activity and collect blood (1 mL or less than ¼ teaspoon) or urine for a pregnancy test. See #12 below.

At some visits, we will:
- Give your child an ECG.
- Give your child a chest x-ray. See #11 below.
- Draw your child's blood (2 mL or less than ½ teaspoon) to check your child's thyroid.
- Collect sputum from your child. See #10 below.
- If your child is in Group 3 and may have the HIV virus in their blood, we will draw your child's blood (up to 6 mL or less than 1¼ teaspoon) to check for HIV in their body. Certain HIV tests are required for the study. If the required tests are not in your child's medical records, we will do the tests that are needed.
- If you agree, we will draw your child's blood (up to 1 mL or less than ¼ teaspoon) for later TB testing at your child's last study visit. The later tests will look at how the body responds to TB and RR-TB treatment.
- If your child is living with HIV, we will draw up to 4 mL (less than 1 teaspoon) to check your child's viral load and CD4 count. Based on the results of these tests and how long your child has been taking ARVs, we may collect an additional 3-5 mL (about 1 teaspoon) of blood to check for resistance to ARVs.

9. At some visits, we will closely measure the amount of BDQ in your child's blood.

One reason for doing this study is to find out the best dose (amount) of BDQ for babies, children, and adolescents. To do this, we need to closely measure the amount of BDQ in the blood after your child takes BDQ. This is called a pharmacokinetic or "PK" test. Blood for PK tests will be drawn in the same way that other blood for the study is drawn.

While your child is taking BDQ, it is very important that you give your child the doses of BDQ exactly as instructed and not miss any doses, except on the days of study visits with PK tests. On the days of study visits with a PK test, we will ask that you not give your child BDQ at home before coming to the clinic. At visits with a PK test, your child will take BDQ at the clinic. This is important so that we know exactly what time BDQ is given to your child on the day of the PK test. At and/or before visits with a PK test, we will ask you when your child took BDQ for the two doses before the visit date. For the two BDQ doses before a PK visit, it is very important your child takes BDQ on time. We will help you remember this before each visit.

There will be two types of PK tests done in this study. One test is called a "sparse PK". For this test, we will draw 0.5 mL – 1 mL (less than ¼ teaspoon) of your child's blood at one time during the study visit. Your child will have blood collected for the first sparse PK test at one or two weeks after they enter the study based on when your child started taking BDQ every day. Blood for sparse PK tests will then be collected at approximately 1, 2, 3, 4, 5, and 6 months after your child enters the study and is taking BDQ. While your child is taking BDQ, blood for the sparse PK test will be drawn before your child takes BDQ at the clinic on the day of the PK visit. Blood for sparse PK tests will also be collected at each study visit after your child stops taking BDQ. A sparse PK test will also be done if your child leaves the study earlier than planned.

The second type of PK test is called an "intensive PK". An intensive PK test will be done after your child receives at least 14 daily doses of BDQ. For most children, the intensive PK test will be done at the Week 2 visit. If your child took some BDQ before entering the study, the intensive PK test may be scheduled at the Week 1 visit. For the intensive PK test, your child will have one sample collected before your child takes BDQ at the clinic. Your child will then have four samples collected for up to eight hours after your child takes BDQ at the clinic. We will draw 0.5 mL – 1 mL (less than ¼ teaspoon) of your child's blood at each time point during the intensive PK test (a total of 2.5– 5 mL or ½-1 teaspoon).

10. We will test for TB and check for what kinds of medicines do not work for the type of TB your child has.

To find out if your child qualifies for the study, we will collect sputum from your child to check their TB status. We will also use the sputum to see which TB medicines may not work for the type of TB your child has.

Sputum is a thick fluid that the body produces in the lungs and airways. There are a few different ways that we can collect sputum. The ways to collect sputum from children are routine in most places with TB. We will talk with you and your child about the best way to collect sputum for your child.

One way that we may collect sputum is asking your child to cough deeply and to spit out mucus, or sputum, from your child's lungs.

Some children may not be able to cough deeply enough to spit out sputum. Another way that we can collect sputum is called "induced sputum collection." This will help your child cough up sputum from the lungs more easily. We will ask your child to breathe in a solution that includes salt through a breathing mask (called a nebulizer). The solution helps people cough more easily.

Some children may not cough at all. They may swallow the sputum. If your child cannot cough up sputum, we will collect sputum using a way called "gastric aspiration." We will insert a small tube in your child's nose to collect sputum from your child's stomach.

If your child enters the study and your child's TB was confirmed by a positive TB lab test, we will collect sputum at some visits to check your child's TB status.

11. At some visits, we will perform a chest x-ray.

A chest x-ray takes pictures of your child's lungs in your child's chest. Chest x-rays can help check your child's lungs and TB status. During a chest x-ray, your child may be asked to remove their clothes and wear a gown. Your child will need to sit, stand, or lie very still to take a clear x-ray picture. Your child may be asked to hold their breath for a few seconds while the x-ray is being taken.

12. Additional requirements and pregnancy testing for the study.

Children should not join this study if they are pregnant or want to become pregnant within the next two years. If your child has had their period or your child is sexually active, we will do extra procedures.

If your child can become pregnant, we will collect blood (1 mL or less than ¼ teaspoon) or urine for a pregnancy test to see if your child qualifies for the study. The pregnancy test must show that your child is not pregnant to qualify for the study.

We will also ask your child about sexual activity. If your child is having sex that could lead to pregnancy, they will be required to use two methods of contraception to qualify for the study. We will talk with you and your child about the importance of avoiding pregnancy and about the contraception methods that can be used in this study. We will help you and your child choose the best contraceptive methods for your child.

If your child is a female and joins the study, we will collect blood (1 mL or less than ¼ teaspoon) or urine for a pregnancy test during study visits. *[Sites may modify the following sentences to include locally appropriate language regarding disclosure of pregnancy results to parents or legal guardians:* We will talk over the test result as soon as it is available with your child in private without you or other parents/guardians present. Your child must give us permission before we can share these results with you or other parents/guardians.*]*

At each visit, we will talk with you about contraception and to see how your child is doing with their chosen methods. We will ask you and your child to tell us if you want to stop or change methods. We will ask you and your child to tell us if your child (or their partner) may be pregnant at any time. If you or your child do not want your child to use contraception, your child will leave the study.

If your child (or their partner) becomes pregnant during the study, please let us know right away. If your child becomes pregnant, your child will stop taking BDQ, but continue to come to the clinic for study visits as originally planned. We will tell you if your child can get other TB medicines at this clinic or if you must go to another clinic. We will also tell you where you can take your child for health care related to the pregnancy.

If the outcome of a pregnancy for your child or your child's partner is not known at the last scheduled study visit, then the study staff will contact you for information about the outcome of the pregnancy after the last study visit. If your child is living with HIV and becomes pregnant, information about your child's

pregnancy may be registered in the "Antiretroviral Pregnancy Registry" by the study staff. All information reported would be kept private with no links to identify your child.

13. Tests will be done at different laboratories.

We will do most tests of your child's specimens 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 results show that your child may need medical care or treatment that cannot be provided by the study, we will tell you where your child can go for this care.

The tests to measure the amount of BDQ and the later TB tests to look at other factors related to TB in your child's blood will be done at laboratories in South Africa or other countries. If any of the results may be important for your child's health, we will tell you about them. Otherwise, the results will not be given to you or your child.

14. Some children may need to stop taking BDQ.

This may happen for children who:

- Are not able to take BDQ tablets as instructed
- Have bad effects from BDQ tablets
- Need to take other medicines that cannot be taken with BDQ
- Are identified as having TB that responds to first-line TB medicines
- Become pregnant

If your child stops taking BDQ before the Week 24 visit, your child will stay in the study and have follow-up visits at 8, 16, 24, 36, 48, and 72 weeks after your child stops BDQ to continue checking your child's health.

15. We may take your child off the study.

All children are expected to stay in the study for about two years. However, we may take your child off the study early. This may happen if:

- The study is stopped for any reason.
- 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.
- Your child is having sex that might lead to a pregnancy and is not willing to use contraception methods required by the study.
- Your child is in another clinical trial not approved by the P1108 Protocol Team while your child is in the P1108 study.

If your child must leave the study early, we will explain this and tell you where your child can go for any care and treatment your child may need. We will talk with you about your child's options and help make sure your child can get TB medicines from outside the study.

16. Please tell us if you want your child to leave the study.

You are free to take your child off the study at any time for any reason. The care your child receives will not be affected, but it is important that we know your decision. We will ask you to bring your child to the clinic for one last visit. At this visit, we will do the same types of procedures listed in #7 or #8 (see

above). We will answer any questions you may have and give you information on how to contact us in the future, if you wish.

If your child leaves the study early, we will still use the information and samples already collected from your child. If you do not want these samples and information to be used, we will not use them.

17. We may contact you after your child's last visit.

We may ask to be in contact with your child after your child's last study visit for the following:

- If your child (or their partner) becomes pregnant while in the study, we will arrange to be in contact with your child until the outcome of the pregnancy is known.
- If your child is sick or injured at the last study visit, we may ask your child to come to the clinic for additional visits until your child's health improves.
- If your child leaves the study earlier than planned, we will plan to contact you and your child to check on your child's health at 2, 9, and 18 months after your child's last dose of BDQ.

Risks of the study

18. There are some risks from the study procedures.

Most procedures done in this study are routine medical procedures, with little risk to your child. Your child may feel nervous or embarrassed when answering questions for the study. Other risks are described below.

Blood Draws
Drawing blood can cause pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause fainting or infection.

HIV Tests
Your child will be tested for HIV before entering the study and may be tested while in the study. You and your child may become worried or anxious about your child's test results. We will explain all tests to you and your child and provide counseling to help with feelings you may have about the tests and your child's results.

Chest X-Rays
Chest x-rays use radiation to take a picture of the lungs. Radiation is energy in the form of waves. All people are exposed to a low level of natural radiation from the sun. This is called background radiation. High levels of radiation can cause cancer. However, the level of radiation from a chest x-ray is much lower than the level that causes cancer. The level from one chest x-ray is also about the same as the background radiation every person normally has over 12 days.

Sputum Collection
Depending on how sputum is collected for your child, the risks may be different. See #10 above for the different ways we might collect sputum. For children who can cough deeply to spit out sputum or children who get induced sputum collection, there are no extra risks. It can be uncomfortable to cough and children might get tired or dizzy from coughing.

For children who have gastric aspiration to collect sputum, the tube might be uncomfortable for the child's nose or stomach. The tube may also make your child feel like gagging. Collecting the specimen from the stomach is a common and safe medical procedure. The study staff have been trained to do these procedures to limit these side effects.

ECG
Small sticky patches will be put on your child's skin to do an ECG to check your child's heart. ECG patches may cause a skin reaction such as redness or itching. A small amount of hair may also be removed with the placement of ECG patches.

19. There are some risks in taking BDQ.

BDQ is developed to treat RR-TB. All TB medicines can cause side effects. This includes TB medicines your child would receive outside the study. Some side effects are minor. Others can be more severe. Not all possible side effects of BDQ in humans are known.

What is known about using BDQ in adults?
More than 5,000 volunteers in clinical trials have received BDQ. More than 200 participants (without TB) received at least one dose of BDQ. Based on these trials, BDQ was found as generally safe and well tolerated. In some of these studies, volunteers received only BDQ. In some studies, the volunteers may have received BDQ or a "placebo." A "placebo" is a pill that looks the same as BDQ but has no medical effect. Using a placebo allows studies to better see the benefits and risks of BDQ.

In one of the studies of BDQ that compared BDQ and a placebo in adults, there was very little difference between the number of side effects experienced by people taking BDQ and people taking the placebo:

	BDQ/Background regimen	**Placebo/Background regimen**
	79 people were on the BDQ	81 people were on the placebo
Nausea	30 (less than half of the people)	26 (about a third of the people)
Joint pains	26 (about a third of the people)	18 (less than a quarter of the people)
Headache	22 (less than a third of the people)	10 (only an eighth of the people)
Coughing blood (Hemoptysis)	14 (less than a quarter of the people)	9 (less than an eighth of the people)
Chest Pain	9 (less than an eighth of the people)	6 (less than an eighth of the people)
Loss of appetite (Anorexia)	7 (less than an eighth of the people)	3 (less than an eighth of the people)
Increased liver enzymes	7 (less than an eighth of the people)	1 (less than an eighth of the people)
Rash	6 (less than an eighth of the people)	3 (less than an eighth of the people)
Increased blood amylase	2 (less than an eighth of the people)	1 (less than an eighth of the people)

The most common side effects of BDQ in adult studies were:
- Nausea
- Joint pain
- Headache
- Hemoptysis or coughing up blood or blood-stained mucus from the lungs and body airways.
- Chest pain
- Anorexia (loss of appetite)
- Rash
- Abdominal pain
- Increase in blood amylase. Amylase is a substance in the body that helps digest and break down food.

Other severe side effects of BDQ that are less common include:
- QT prolongation or possible problem with the rhythm of the heartbeat
- Liver damage
- Death

In children 12 to less than 18 years of age, the most common side effects are:
- Joint pain
- Nausea
- Abdominal pain

In children five to less than 12 years of age, the most common side effect is increased liver enzymes. No serious side effects or significant changes to pulse rate, blood pressure, or breathing related to BDQ were seen in prior studies. More information about the more severe but less common side effects is provided below.

Changes in regular heart rhythm
BDQ can cause a specific kind of side effect to the heart called an increased "QT interval." An increased QT interval might put a person at greater risk of having a problem with the rhythm of the heartbeat. In very rare cases, this can be fatal. An ECG allows health providers to see the "QT interval".
An increase in the "QT interval" may be seen in people taking BDQ and other TB drugs at the same time. In one study, 79 people were taking BDQ and 81 people were taking a placebo. Three of the people on BDQ (3.8%) and four of the people not on BDQ (4.9%) had an increase in their QT interval. Some people had increases in their QT interval that were much larger than the average increase. However, no side effects related to heart rhythm problems were seen in these patients. If your child's doctor finds that the QT interval is longer than normal for your child's 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 the level of certain substances ("electrolytes") in your child's blood are normal, because low levels of these substances can increase the QT interval. Your child's doctor will also ensure that your child is not on other medications known to cause a lengthening of the QT interval.

Liver damage
The liver is an organ near the stomach. In some studies, people who took BDQ with other TB drugs had a rise in substances in the liver called "transaminases", compared to people not taking BDQ. These substances can be measured in the blood, and we will check your child for them during the study. In one study, 79 people were on BDQ and 81 people were on placebo. Seven people on BDQ (8.9%) and one person not on BDQ (1.2%) had an increase in these liver substances. Some of the other TB medicines your child may take may also cause increases in these liver substances. If the levels of these substances become too high, your child's TB medicines may be changed. If your child gets liver problems, your child 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.

Deaths
In previous studies, no deaths have been reported in adults without TB who received BDQ. In a study of adults with TB, more deaths were seen in participants who received BDQ compared to participants who did not receive BDQ. The doctors working on that study could not find a reason for this difference. Most of the deaths occurred several months after the participants stopped taking BDQ. However, doctors are not able to determine if the deaths were related to BDQ or not.

This study is being done because information from research and routine care indicates that BDQ may reduce the risk of death in adults and adolescents with RR-TB. If RR-TB is not treated well, RR-TB

disease may worsen and cause death. One participant in this study has died. This participant was very sick from RR-TB and other illnesses and was in the hospital for several weeks before entering this study. On the day the child died, the child was resting when he started having trouble breathing. The child then died before he could be seen by a doctor and the cause of his death is unknown. All available information about this child has been carefully reviewed. As this child's TB improved while in the study, it seems most likely that his death was due to his health problems other than TB and his death was not due to BDQ.

As the study continues, the study doctors will continue to closely monitor all participants in the study and potential risks of any bad effects. This will be done while participants are taking BDQ and for about one and half years after stopping BDQ.

Other information about BDQ
At this time, possible effects of BDQ in pregnancy are unknown.

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

Most TB drugs that your child may have taken in the past or will take with BDQ to treat TB can cause rashes or skin changes, nausea, or vomiting. In studies in healthy volunteers and TB patients taking both BDQ and other anti-TB drugs, a higher-than-normal amount of uric acid in the blood has been observed. Uric acid is a body waste product. It forms when substances called "purines" break down.

As described above, although TB germs were no longer found in the one child who died in this study, it seemed that this child died due to other illnesses. While BDQ can help improve RR-TB disease, it is important for children on this study to also receive treatment for any other illnesses they have.

20. There may 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 samples will be kept in secure locations. All samples and most records will be labeled only with a code number. However, your and your child's name will be written on some records.

The information we collect about your child for this study will be combined with information collected about all other children in the study. This will be done at an organization called a statistical and data management center. The IMPAACT Network statistical and data management center is in the United States. We will send your child's information to this center. The information will be sent securely, following applicable laws and policies. Your child's name and other information that could personally identify your child will not be sent.

Despite our best efforts to keep your child's information private, it is possible that your child's information could be obtained by someone who should not have it. If this were to happen, your child could be treated badly or unfairly.

Information collected for this study may be used for other research in the future. For example, researchers may use information from this study to try to answer different questions about children with RR-TB or HIV. Any future research done with the information from this study must be approved by the IMPAACT Network; additional consent for this is not required. If any future research is done, information about your child may be used. Your child's information will be labeled with a code number, and the only link

between the code number and your child's name will be kept here at this clinic. Your child's name and other information that could personally identify your child will not be given to other researchers.

Benefits of the study

21. There may be benefits to your child from being in the study.

By joining the study, your child will be part of the search for new medicines for children with RR-TB. BDQ has been shown to be safe and effective for adults and is approved by the US FDA for use in children at least five years old. Therefore, taking BDQ may be of benefit to your child.

Your child will have regular visits here and we will be frequently checking on their health. It is possible that the examinations and tests done in the study may help your child stay healthy. If these procedures show that your child may need medical care that cannot be provided through the study, we will tell you where you can go for the care your child needs.

Although the benefits described above are possible for all children in the study, there is no guarantee that your child will directly benefit from being in the study.

Other information about the study

22. We will take precautions against COVID-19.

During this study, we will follow all applicable guidelines related to COVID-19. This may include asking you and your child about symptoms of COVID-19 or doing procedures like taking your child's temperature before study visits. If your child needs to quarantine because of COVID-19, we will work with you to determine how best to schedule your child's study visits.

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

There are no costs to you or your child for study visits or procedures or BDQ given in the study.

[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).]*

24. 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 drug regulatory authority]*
- *[insert name of other site regulatory entities]*
- The United States National Institutes of Health and its study monitors
- The United States Food and Drug Administration
- The United States Office for Human Research Protections
- Other US, local, and international regulatory entities
- The IMPAACT Network that is coordinating the study
- The company that makes BDQ tablets, Janssen Research and Development

The study staff and these groups are required 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 clinical trial will be available on ClinicalTrials.gov. This website will not include information that can identify your child. At most, the website will include a summary of the clinical trial results. You can search this website at any time.

Your child's study information may be disclosed to other authorities if required by law. *[Site: add more specific detail here describing local laws that may be applicable.]*

25. 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. It is possible, however, that your child could have an illness or injury that is study-related. This means the illness or injury occurred as a direct result of being in the study.

[Sites may modify this paragraph to reflect local institutional policies; information regarding coverage available through clinical trial insurance obtained by the site should be included if applicable; the statement regarding no program for compensation through the NIH may not be removed.] 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 health insurance. There is no program to pay money or give other forms of compensation for study-related illness or injury through *[site name]* or the United States National Institutes of Health.

Who to Contact

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

- If you have questions about the study:
  [insert name and telephone number of investigator or other study staff]

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

- If your child has any health or other problems that may be related to study participation:
  [insert name and telephone number of investigator or other study staff]

- If your child wants to leave the study:
  [insert name and telephone number of investigator or other study staff]

Signatures

If you decide to have your child join this study, sign or make your mark below.

Before deciding whether you want your child to join 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 your child if they 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 can ask questions or request more information at any time.

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

[Insert signature blocks as required by site IRB/EC policies.]

Name of Participant (print)	Participant Signature *(Only if of legal age or circumstance to provide independent consent)*	Date
Name of Parent or Guardian (print)	Parent or Guardian Signature	Date
Name of Witness (if applicable, print)	Witness Signature	Date
Study Staff Conducting Consent Process Name (print)	Study Staff Signature	Date

Appendix XIV: Sample Assent Form for Study Participation

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

Protocol Version 2.0, Dated 21 September 2022

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 assent 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.

Introduction

You are being asked to take part in a research study on tuberculosis (TB). To take part in this study, you must agree to participate. Your parent/guardian must also give permission for you to participate. For this reason, it is important that you talk to your parents/guardian about the study before you make your decision to participate.

This form gives information about the study. Please read it or have it read to you. Ask any questions you may have. After we talk with you about this, if you decide to take part in the study, you will record your decision at the end of this form. You will be offered a copy to keep.

About the study

This study is testing a medicine called bedaquiline or "BDQ". BDQ is used to treat rifampin-resistant TB or "RR-TB". The medicines usually given to treat TB are called "first-line" TB medicines (or drugs). First-line TB drugs include rifampin (RIF). When RIF does not work to treat TB, this is called rifampin-resistant TB or "RR-TB".

The United States (US) Food and Drug Administration (FDA) approved BDQ in adults and children five years and older and weighing at least 15 kg for MDR-TB in the lungs. MDR-TB means that the TB in the body does not respond to RIF and one other first-line TB drug called isoniazid. BDQ is approved to be used with other TB drugs and not by itself. BDQ is also recommended by the World Health Organization (WHO) for adults and children with MDR/RR-TB. More data on BDQ doses in children are needed. [*Sites: add information on local approvals, if applicable*]

The study will include up to 84 children from Haiti, India, and South Africa. This study will look at whether BDQ can be safely used without any bad side effects when given to babies, children, and adolescents. It will also look for the best amount of BDQ to give to babies, children, and adolescents for treatment of RR-TB.

The International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) and *[sites: insert name of site]* are doing this study. This study is sponsored by the US National Institutes of Health (NIH). The person in charge of the study at this clinic is *[Sites: insert name of Investigator of Record]*.

Your rights

It is up to you and your parent/guardian to decide if you will take part in this study. You can say yes or no. If you say yes now, you can change your mind later. Your decision will have no effect on the medical care you receive. You can keep receiving medical care and medicines from outside the study. Please ask any questions you may have about other types of medical care and medicines for TB.

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*].

What happens in the study

If you decide to take part in the study, we will first examine you (check your body), draw blood, and do some tests to see if you qualify.

[Sites may remove or modify the following paragraph, as needed, to describe procedures, privacy, and disclosures related to HIV and pregnancy testing as applicable per local standards of care and procedures] Some of the tests done to see if you qualify for the study include tests for HIV and pregnancy. If you enter the study and could get pregnant, you may have urine or blood collected for pregnancy tests during the study. We will tell you the results of these tests. We will ask if you want your parent or guardian to be present when we tell you the results.

If you qualify and enter the study, you will have about 16 study visits over approximately two years. Most of these visits will last about *[Sites please include expected duration]*. At these visits, we will ask you and your parent or guardian about your health and BDQ and other medicines you are taking. We will also examine you. At some visits, we will also:

- Draw blood and collect urine for testing.
- Perform an electrocardiogram (ECG) test to check your heart.
- Perform an X-ray of your chest (take a picture of your lungs).
- Collect sputum to check the TB in your body. Sputum is a thick liquid that comes up when you cough. We will ask you to cough or spit in a cup to collect sputum.
- Depending on the TB medicines you take, we may do hearing tests.

After you enter the study and have taken BDQ every day for approximately two weeks, you will have a visit called the "intensive pharmacokinetic (PK)" visit. During this visit, you will be asked to come to the clinic to have your blood drawn five times over eight hours. This is done to closely measure the amount of BDQ in the blood at each time. We will need to know the specific times that you took BDQ for the two days before the PK visit. We will tell you more about how we will contact you and your parent or guardian to find out these times.

You will take BDQ once a day, every day for approximately two weeks. After your intensive PK visit, you will take BDQ once a day on Monday, Wednesday, and Friday (three times per week) for approximately 22 weeks. BDQ is available as a tablet that can be swallowed whole or can be crushed. BDQ is also available in a smaller tablet form for young children. The formulation you receive and how you take it, either swallowed whole or crushed, will depend on your age and if you can swallow the BDQ tablet. The study doctor will help determine which BDQ tablet you will take and provide instructions on how to take BDQ. BDQ will be provided for you by the study, at no cost.

We will tell you as much information as you want about the study and what will happen when you come here for visits. Please ask any questions you may have. Please tell us if anything bothers you or scares you. We will do our best to explain the study and help you feel more comfortable.

We may ask to be in contact with you after your Week 96 or End of Study Visit if the following occurs:
- You leave the study early. If you leave the study early (stop the study), we will continue to contact you by telephone to collect information at 2, 9, and 18 months after you last took BDQ.
- If you (or your partner) are pregnant at the End of Study Visit, we will continue to contact you by telephone until the outcome of the pregnancy is known.
- If you are sick or injured at the last study visit, we may ask you to come to the clinic for more visits until your health improves.

What good and bad effects could happen

By taking part in this study, you will be helping us test a TB medicine (BDQ) for babies, children, and adolescents with RR-TB. Some good effects could happen from being in the study. For example, BDQ could help you stay healthy and treat the TB in your body.

However, we do not know this for sure. All drugs can cause unwanted or bad effects, including BDQ. For example, they could make you feel sick. We will ask you to tell your parent or guardian any time that you do not feel well. You and your parent or guardian should also tell us if you do not feel well. We will ask you to come to the clinic so we can check on you and try to help you feel better.

Not all potential bad effects of BDQ in humans are known. Based on studies that tested BDQ in adults, we have learned that BDQ is generally safe. This study is being done because research and TB care show that BDQ can decrease death because of TB in adults and adolescents with RR-TB. If RR-TB is not treated well, RR-TB disease may worsen and cause death.

In a study of adults with TB, more deaths were seen in participants who received BDQ compared to participants who did not receive BDQ. Most of the deaths occurred several months after the participants stopped taking BDQ. The doctors working on that study were not able to determine if the deaths were related to BDQ or not. One child in this study has died. This child was very sick from RR-TB and other serious health problems and was in the hospital for several weeks before starting the study. All available information about this child has been carefully reviewed. It seems likely that this child's death was due to health problems other than TB, which improved while in the study, and not due to BDQ.

As the study continues, the study doctors will continue to closely monitor all participants in the study and potential risks of bad effects from BDQ. The most common bad effects observed in adults and children 12 to less than 18 years of age are:
- Headache
- Nausea
- Joint pain
- Chest pain
- Abdominal pain
- Hemoptysis or coughing up blood or blood-stained mucus from the lungs and body airways
- Anorexia or loss of appetite
- Rash
- Increase in blood amylase. Amylase is a substance in the body that helps digest and break down food.

Having your blood drawn may cause pain, bleeding, bruising, swelling, or infection where the needle goes in your arm. You may feel uncomfortable, or your throat may feel sore when we collect sputum. For the ECG test, we will put small, sticky patches on your chest. This may make your skin itchy.

The X-ray of your chest may expose you to radiation. Radiation is energy in the form of waves. High levels of radiation can make you very sick. The level of radiation from a chest X-ray in this study is much lower than the level that causes sickness.

You may feel nervous or embarrassed when answering questions for the study or talking about your answers with your parent or guardian.

Another possible risk is to your privacy. For example, other people could find out that you are in the study or learn other information about you. If this were to happen, you could be treated badly or unfairly. You could feel stressed or embarrassed. We will make every effort to avoid this. For example, most of the records we keep here for the study will be labeled with a code number (not your name).

Please ask any questions you may have

We will tell you as much information as you want about the study. Please tell us if anything bothers you or scares you, or if there is anything you do not understand. We will do our best to explain the study and help you feel more comfortable.

Who to contact about this study

If you have any questions about the study you can contact *[insert name, telephone number, and other relevant contact details of investigator or other study staff]*, or if you have problems, or have questions about how you are treated in the study you can contact *[insert name and telephone number of IRB/EC contact person or other appropriate person/organization].*

During the study, if you have any bad effects, or have questions about the study, you and your parent/guardian can contact *[insert name, telephone number, and other relevant contact details of investigator or other study staff].*

If you need emergency care, or hospitalization is required, tell the doctor that you are participating in this research study.

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)*.

Signatures

Before deciding whether to take part in this study, make sure you have read this form. Make sure all your questions have been answered.

Please write your initials or make your mark next to your choices:

_____ I agree to take part in this study.

_____ I do not agree to take part in this study.

_____	_____	_____
Name of Participant (print)	Signature of Participant	Date
_____	_____	_____
Name of Study Staff Conducting Consent Process (print)	Signature of Study Staff Conducting Consent Process	Date

Appendix XV: Sample Informed Consent Form for Specimen Storage and Future Use

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

Protocol Version 2.0, Dated 21 September 2022

You have decided [to allow your child] to join the study named above. As part of the study, [you/your child] will have blood, urine, and sputum collected. After study testing is completed, there may be some samples that are left over. These are called extra samples. Samples of blood and other body fluids (such as sputum) may also be collected and stored for tuberculosis (TB) future research. These are called stored samples. The IMPAACT Network would like to keep these extra and stored samples and use them for other future IMPAACT Network approved research.

This form gives information about the use of extra and stored samples. Please read it, or have it read to you, and ask any questions you may have. After we discuss the information with you, you will record your decisions on use of extra and stored samples at the end of the form.

1. It is your decision whether or not to allow the extra and stored samples to be used.

You are free to say yes or no, or to change your mind at any time. Your decision will not affect your [child's] participation in the study. If you say no, we will not collect stored samples for TB research and all extra samples will be destroyed after [you/your child] completes the study. You will record your decision at the end of this form.

2. If you agree, your [child's] extra and stored samples will be kept in a repository.

[Sites should insert one of the two options shown below. Choose/adapt the second option if local regulations do not permit storage of samples for future research use in the United States.]

If you agree to have extra and stored samples stored, the samples will be kept at the testing lab or in a repository. A repository is a secure facility that is used to store samples. The IMPAACT Network repository is in the United States. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

A repository is a secure facility that is used to store samples. The IMPAACT Network has a repository in the United States. However, our local regulations require that extra samples be stored in our country. Therefore, we will keep the samples here at our laboratory. There is no limit on how long the samples will be kept *[sites may insert time limits or additional site-specific requirements here if required by local authorities]*.

3. Extra samples and stored samples could be used for different types of research.

Extra samples may be used for research on HIV, TB, the immune system, and other diseases. Stored samples may be used for TB research. The research may be done in the United States or in other places.

If you agree, the extra and/or stored samples could also be used for research that looks at your [child's] genes. Genes are passed to children from their birth parents. They affect how people look and how their bodies work. Differences in people's genes can help explain why some people get a disease while others do not. Your [child's] samples would only be used to look at genes related to HIV, TB, and the immune system. For example, in some children, the body may process BDQ differently.

Any research done with the extra and stored samples must be reviewed and approved by the IMPAACT Network. The research must also be approved by an ethics committee. The role of an ethics committee is to review the research plan and protect the rights and well-being of the people whose samples will be used.

The research done with extra and stored samples is not expected to give any information relevant to your [child's] health. Therefore, the results will not be given to the study staff or to you. The results also will not be placed in your [child's] study records.

4. There is little risk to [you/your child].

When extra or stored samples are used for research, they are labeled with a code number only. To protect your [child's] privacy, no names are used. However, information such as age, gender, HIV status, TB disease severity, and other health information may be linked to the samples. Information on the TB and/or HIV medicines [you/your child] took while in the study may also be linked to the samples.

There may be some risks from tests of your [child's] genes. If others found out the results of these tests, they could treat [you/your child] badly or unfairly. However, this is almost impossible, because the results will not be given to the study staff, or to you, [or to your child] and will not be in your [child's] study records.

5. There may be no benefit to [you/your child].

By allowing extra and stored samples to be used for research, [you/your child] will be part of the search for new information that may benefit people with TB and/or HIV in the future. However, the research done with the extra and stored samples will not directly benefit [you/your child] in any way.

6. You will not be paid for use of [your/your child's] samples.

There is no cost to you for use of your [child's] extra or stored samples. The samples will not be sold, and you will not be paid for use of the samples. It is possible that research done with the samples could lead to a new discovery or a new product. If this happens, there is no plan to share any money with [you/your child].

7. Information from research using extra and stored samples may be reviewed by groups that oversee the research.

These groups include:
- The IMPAACT Network
- The ethics committees that review and approve the research
- Government and other agencies that pay for the research
- Government and other agencies that monitor the research
- Other US, local, and international regulatory entities

The people who do research with the extra and/or stored samples and the groups listed above are required to make efforts to keep information private and confidential.

The results of research done with the extra and/or stored samples may be presented publicly or published. However, no presentation or publication will use your [child's] name or identify [you/your child] personally.

8. If you have any questions, concerns, or problems, use these contacts.

- If you have questions about use of your [child's] extra samples or stored samples:
  [insert name and telephone number of investigator or other study staff].

- If you later change your mind about use of your [child's] extra samples or stored samples:
  [insert name and telephone number of investigator or other study staff].

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

Signatures

Before deciding whether to allow your [child's] extra samples or stored samples to be used for research, make sure you have read this form, or had it read to you. Make sure all your questions have been answered. You should feel that you understand your options and the possible risks and benefits before making your decision.

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

[Insert initial and signature blocks as required by site IRB/EC policies and the IRB/EC determination of the level of risk to children in the categories specified in 45 CFR 46.404-407. Separate consent decisions must be documented for genetic testing].

For your [child's] extra samples, write your initials or make your mark next to one of the choices below.

_____ I agree to the storage and use of my [child's] extra samples to be used for future research. I also allow my [child's] samples to be used for tests of my [child's] genes.

_____ I agree to the storage and use of my [child's] extra samples to be used for future research. I do not allow my [child's] samples to be used for tests of my [child's] genes.

_____ I do not allow my [child's] extra samples to be used for any future research.

For your [child's] stored samples, write your initials or make your mark next to one of the choices below.

_____ I agree to the collection of stored samples and storage and use of my [child's] stored samples for future research. I also allow my [child's] stored samples to be used for tests of my [child's] genes.

_____ I agree to the collection of stored samples and storage and use of my [child's] stored samples for future research I do not allow my [child's] stored samples to be used for tests of my [child's] genes.

_____ I do not allow collection of stored samples from [myself/my child] for future research.

Signature blocks for participants below legal age to provide independent informed consent

Participant Assent

_____	_____
Participant's Name (print)	Participant's Signature and Date

Parent/Guardian Consent

_____	_____
Parent/Guardian Name (print)	Parent/Guardian Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date

Signature blocks for participants of legal age to provide independent informed consent

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date