A5343

A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis

A Limited-Center Trial of the AIDS Clinical Trials Group (ACTG)

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The ACTG Tuberculosis Transformative Science Group	**Gavin Churchyard, MBBCh, MMED, FCP, PhD, Chair**
Protocol Co-Chairs:	**Kelly Dooley, MD, PhD** **Gary Maartens, MBChB, MMed**
Protocol Vice Chair:	**Francesca Conradie, MD, DTM&H**
DAIDS Clinical Representatives:	**Richard Hafner, MD** **Roxana Rustomjee MbChB, MMed, FCPhM, FRCP, PhD**
Clinical Trials Specialists:	**Laura E. Moran, MPH** **Chanelle Houston, BS**

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ACTG
AIDS CLINICAL TRIALS GROUP

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SIGNATURE PAGE

I will conduct the 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 U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (eg, US National Institutes of Health, Division of AIDS) and institutional policies.

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

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SITES PARTICIPATING IN THE STUDY

This is a limited site study open to select non-US sites. The sites that are eligible for participation in the study can be found on the A5343 protocol-specific web page (PSWP).

PROTOCOL TEAM ROSTER

Co-Chairs
Kelly Dooley, MD, PhD
Johns Hopkins Adult AIDS CRS
600 N. Wolfe Street, Osler 527
Baltimore, MD 21287
Phone: 410-955-3100
Fax: 410-614-9978
E-mail: kdooley1@jhmi.edu

Gary Maartens, MBChB, MMed
University of Cape Town
Division of Clinical Pharmacology
Observatory
Anzio Road
Cape Town, 7925
SOUTH AFRICA
Phone: 27-21-4066286
E-mail: gary.maartens@uct.ac.za

Vice Chair
Francesca Conradie, MD, DTM&H
University of Witwatersrand
Clinical HIV Research Unit
Postnet Suite 176
Private Bag X2600
Houghton
Johannesburg, Gauteng, 2041
SOUTH AFRICA
Phone: 0027-11-2768800
Phone: 27 11 2768814
Fax: 27 11 4822130
E-mail: fconradie@witshealth.co.za

DAIDS Clinical Representative**s**
**Roxana Rustomjee MbChB, MMed,
FCPhM, FRCP, PhD
Senior Scientist
Tuberculosis Clinical Research Branch
Therapeutics Research Program
Division of AIDS/NIAID/NIH/DHHS
5601 Fishers Lane, Rm 9E31A
Rockville, MD 20852
Phone: 240-627-3536
Mobile: 301-204-9917
Email: roxana.rustomjee@nih.gov**

DAIDS Clinical Representative (Cont'd)
Richard Hafner, MD
TRP, DAIDS, NIAID, NIH
5601 Fishers Lane
Room 9E30
Rockville, MD 20852
Phone: 301-435-3766
E-mail: rhafner@niaid.nih.gov

Clinical Trials Specialists
Laura Moran, MPH
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
Phone: 301-628-3373
Fax: 301-628-3302
E-mail: lmoran@s-3.com

Chanelle Houston, BS
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
Phone: 301-628-3367
Fax: 301-628-3302
E-mail: chouston@s-3.com

Senior Statistician
Susan L. Rosenkranz, PhD
Statistical and Data Analysis Center
Harvard School of Public Health
900 Commonwealth Avenue, 2nd Floor
Boston, MA 02215
Phone: 617-632-5915
Phone: 617-432-7525
Fax: 617-632-2001
E-mail: sue@sdac.harvard.edu

Protocol Statistician
Yoninah Cramer, MS
Statistical and Data Analysis Center
Harvard School of Public Health
900 Commonwealth Avenue, 2nd Floor
Boston, MA 02215
Phone: 617-632-5901
Fax: 617-632-2001
E-mail: cramer@sdac.harvard.edu

Data Manager
Kathleen Donahue, MA
Frontier Science & Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 Ext.7329
Fax: 716-834-8432
E-mail: donahue@fstrf.org

DAIDS Pharmacist
Oladapo Alli, PharmD
Pharmaceutical Affairs Branch
DAIDS/OCSO/NIAID/NIH
5601 Fishers Lane
Room 9E16 MSC #9832
Rockville, MD **20852**
Phone: 240-627-3593
Fax: 240-627-3112
E-mail: oladapo.alli@nih.gov

Pharmacologist
Helen McIlleron, MD
University of Cape Town
Division of Clinical Pharmacology
K45-Old Main Building
Groote Schuur Hospital
7925 Observatory, Rondebosch
SOUTH AFRICA
Phone: 27-21-4066292
Fax: 27-21-4481989
E-mail: helen.mcilleron@uct.ac.za

Pharmacometrician
Mats Karlsson, PhD
Uppsala University
Box 591
75124 Uppsala
SWEDEN
Phone: +46 18 4714105
Fax + 46 18 4714003
E-mail: mats.karlsson@farmbio.uu.se

Cardiologist Consultant
Joel Morganroth, MD
ERT, Inc.
1818 Market Street #1000
Philadelphia PA 19103
Phone: 215-840-4961
E-mail: jmorganroth@ert.com

Investigators
Andreas Diacon MD, PhD
Karl Bremer Hospital
Mike Pienaar Boulevard
Bellville 7531
SOUTH AFRICA
Phone: 27-219-497-751
Fax: 27-219-181378
E-mail: ahd@sun.ac.za

Justin Shenje MB ChB, MSc
South African Tuberculosis Vaccine
Initiative (SATVI)
Haarlem Street
Brewelskloof Hospital
Worcester, Western Province 6850
SOUTH AFRICA
Phone: 27-233-46570
E-mail: justin.shenje@uct.ac.za

Investigators (Cont'd)
Florian von Groote-Bidlingmaier, Dr med
(GER)
TASK Clinical Research Center
Karl Bremer Hospital
Belleville, 7530
Cape Town, 7530
SOUTH AFRICA
Phone: 27-21-9497751
Fax: 27-21-9181378
E-mail: florianv@sun.ac.za

Field Representative
Joan Gottesman RN, CCRP
Vanderbilt Therapeutics (VT) CRS
One Hundred Oaks
719 Thompson Lane, Suite 47183
Nashville, TN 37204
Phone: 615-936-2664
Fax: 615-936-2644
E-mail: joan.gottesman@vanderbilt.edu

Laboratory Technologist
Gerald L. Tegha, BSc, MSc
Kamuzu Central Hospital/Tidziwe Centre
P.O. Box A-104
100 Mzimba Road
Kamzu Central Hospital
Lilongwe
MALAWI
Phone: 265-999200668
Fax: 265-1755954
E-mail: gtegha@unclilongwe.org

Community Scientific Subcommittee (CSS)
Representative
Jacob Tenai
AMPATH Center and MTRH
P.O. Box 4606
Nandi Road
Eldoret, 30100
KENYA
Phone: 254-712285540
E-mail: jacob.ktenai@gmail.com

International Site Specialist
Akbar Shahkolahi, PhD
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
Phone: 301-628-3318
Fax: 301-628-3302
E-mail: ashahkolahi@s-3.com

Industry Representatives
Janssen Pharmaceuticals, Inc.:
Chrispin Kambili, MD
Janssen Pharmaceutical Inc.
700 US Highway 202 South
Raritan, NJ 08869
Phone: 908-927-5713
E-mail: ckambili@its.jnj.com

R. Bruce Simonson, BS
Janssen Pharmaceutical Inc.
1125 Trenton-Harbourton Road
Titusville, NJ 08560
Phone: 609-730-4498
E-mail: bsimonso@its.jnj.com

Jaylene Allred
Janssen Pharmaceutical Inc.
7220 E 157th St.
Belton, MO 64012
Phone: 816-425-6033
E-mail: jallred@its.jnj.com

Manish Doshi, MD
Janssen Scientific Affairs, LLC
1125 Trenton-Harbourton Rd
Titusville, NJ 08560
Phone: 609-730-6589
E-mail: mdoshi2@its.jnj.com

Industry Representatives (Cont'd)

Otsuka Pharmaceutical Company, Ltd
Jeffrey Hafkin, MD
Otsuka Pharmaceutical Development and
Commercialization, Inc.
Otsuka Novel Products
2440 Research Boulevard
Rockville, MD 20850
Phone: 240-683-3281
Fax: 301-721-7281
E-mail: jeffrey.hafkin@otsuka-us.com

Otsuka Pharmaceutical Company, Ltd.:
Suresh Mallikaarjun, PhD, FCP
Otsuka Novel Products, OPDC
2440 Research Boulevard
Rockville, MD 20879
Phone: 240-683-3221
Fax: 301-721-7221
E-mail: suresh.mallikaarjun@otsuka-us.com

Charles Wells, MD
Otsuka Pharmaceutical Development and
Commercialization, Inc.
Otsuka Novel Products
2440 Research Boulevard
Rockville, MD 20850
Phone: 240-683-3243
Fax: 301-721-7243
E-mail: charles.wells@otsuka-us.com

ViiV Healthcare, Ltd.:
Wendy Snowden, PhD
ViiV Healthcare UK Limited
Mailstop CN12,
GSK House, 980 Great West Road
Brentford
Middlesex
TW8 9GS, UK
Phone: +44 (0)208 380 6311
E-mail:
wendy.x.snowden@viivhealthcare.com

ViiV Healthcare ,Ltd (Cont'd)
Chris Stainsby, BSc
ViiV Healthcare
980 Great West Road
GSK House CN12
Brentford TW8 9GS
United Kingdom
Phone: +44 07880-179182
E-mail:
chris.m.stainsby@viivhealthcare.com

Navdeep Thoofer, PhD
ViiV Healthcare
HIV ViiV CSMO
980 Great West Road
Brentford, Middlesex TW8 9GS
United Kingdom
Phone: +44-20-83086124
Fax: +44-20-83806201
E-mail:
navdeep.k.thoofer@viivhealthcare.com

Laboratory Data Manager
Laura Hovind, BS, MS
Frontier Science & Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716 834 0900 x 7468
Fax: 716 833 0655
E-mail: hovind@fstrf.org

Laboratory Specialist
Kim Banks, MS, MBA, MT (AMT)
ACTG Network Coordinating Center
Social & Scientific Systems, Inc.
Laboratory Science Group
8757 Georgia Avenue, 12th Floor
Silver Spring MD 20910
Phone: 301-628-3404
Fax: 301-628-3304
E-mail: kbanks2@s-3.com

STUDY MANAGEMENT

All questions concerning this protocol should be sent to actg.coreA5343@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.coreA5343@fstrf.org. A response should generally be received within 24 hours (Monday-Friday).

Protocol E-mail Group
Sites should contact the Computer Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5343 e-mail group. Include the protocol number in the e-mail subject line.
• Send an e-mail message to actg.user.support@fstrf.org

Clinical Management
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the protocol team. Send an e-mail message to actg.coreA5343@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to pharmacologic laboratory tests, contact the protocol pharmacologist. Send an e-mail message to actg.coreA5343@fstrf.org (ATTN: Helen McIlleron).

Data Management
For nonclinical questions about transfers, inclusion/exclusion criteria, case report forms (CRFs), the CRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact the data manager. CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
• For transfers, reference the Patient Transfer from Site to Site SOP 119, and contact Kathleen Donahue directly.
• For other questions, send an e-mail message to actg.coreA5343@fstrf.org (ATTN: Kathleen Donahue).
• Include the protocol number, PID, and a detailed question.

Randomization
For randomization questions or problems and study identification number SID lists.
• Send an e-mail message to rando.support@fstrf.org. Call the Statistical and Data Analysis Center (SDAC)/DMC Randomization Desk at 716-834-0900 x7301.

Computer and Screen Problems
Contact the SDAC/DMC programmers.
• Send an e-mail message to actg.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the clinical trials specialists. Send an e-mail message to actg.coreA5343@fstrf.org (ATTN: Laura Moran and Chanelle Houston).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@s-3.com (ATTN: Diane Delgado) via e-mail. Electronic copies can be downloaded from the ACTG Web site (https://www.actgnetwork.org).

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the clinical trials specialists (Laura Moran and Chanelle Houston) or ACTG Site Coordination group at actgsitecoordination@s-3.com.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Oladapo Alli, protocol pharmacist, at 240-627-3593.

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Phone Calls
Sites are responsible for documenting any phone calls made to A5343 team members.
• Send an e-mail to actg.coreA5343@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

BDQ   bedaquiline

CMC   Clinical Management Committee

CNS   **central nervous system**

CSF   **cerebrospinal fluid**

CBC   **complete blood count**

DLM   delamanid

DR-TB   drug-resistant tuberculosis

DTG   dolutegravir

ECG   electrocardiogram

GCLP   Good Clinical Laboratory Practices

INH   isoniazid

INR   **international normalized ratio**

LP   **lumbar puncture**

MBT   multidrug background treatment

MDR-TB   multidrug-resistant tuberculosis

ms   milliseconds

MTB   *Mycobacterium tuberculosis*

NRT   nucleoside reverse transcriptor inhibitor

NTP   National Tuberculosis Program

OBR   optimized background regimen

PK   pharmacokinetic

PD   pharmacodynamic

QTcF   corrected QT based on the Fridericia correction method

QT Interval   measure between Q wave and T wave in the heart's electrical cycle

RIF   rifampin

RR-TB   rifampin-monoresistant tuberculosis

SMOR   single molecule-overlapping reads

TB   tuberculosis

TBM   tuberculous meningitis

TDR-TB   totally drug-resistant tuberculosis

TDS   targeted deep sequencing

TEAE   treatment-emergent adverse event

XDR-TB   extensively drug-resistant tuberculosis

SCHEMA

A5343

A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis

DESIGN   This is a phase II, randomized, open-label, three-arm pharmacokinetic and safety trial of the anti-tuberculosis (TB) drugs bedaquiline and delamanid. Participants will be randomized to one of three arms. Participants in arms 1, 2, and 3 will receive bedaquiline, delamanid, or both drugs in combination, respectively, for 24 weeks together with multidrug background treatment.

                  At any visit prior to and including week 22, participants may be asked to take part in an optional nested cerebrospinal fluid (CSF) sampling study that will entail a lumbar puncture (LP), to be done at weeks 8 or 24.

DURATION   24 weeks on study TB treatment, followed by 104 weeks of follow-up, for a total duration of 128 weeks

SAMPLE SIZE   84 participants**; up to 16 participants will be asked to have an optional LP done**

POPULATION   Men and women age 18 or older, with pulmonary multidrug-resistant or rifampin-monoresistant TB, with or without HIV co-infection.

STRATIFICATION   Randomization will be stratified by HIV status, with institutional balancing.

TB REGIMEN   Arm 1: Bedaquiline 400 mg once daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks

                  Arm 2: Delamanid 100 mg twice daily for 24 weeks

                  Arm 3: Both bedaquiline and delamanid (same doses and duration as in Arms 1 and 2)

HIV REGIMEN   Participants with HIV infection will be offered dolutegravir-based antiretroviral treatment. Dolutegravir will be given at a dose of 50 mg once daily and must be accompanied by two nucleoside reverse transcriptase inhibitors.

1.0   HYPOTHESES AND STUDY OBJECTIVES

1.1   Hypotheses

1.1.1   Primary Hypothesis

Co-administration of delamanid (DLM) and bedaquiline (BDQ) (with multidrug background treatment [MBT] for multidrug resistant TB infection [MDR-TB] or rifampin-monoresistant TB [RR-TB]) will increase the duration of the QT interval (QTcF, as measured on electrocardiogram (ECG), adjusted for heart rate using the Fridericia correction formula) compared to administration of either drug alone (with MBT), but the combined effects on the QT interval will be no greater than additive.

1.1.2   Secondary Hypotheses

1.1.2.1 When DLM and BDQ are co-administered with MBT for TB infection, clinically significant QTcF prolongation (see section 7.1.1 for definition) will be uncommon.

1.1.2.2 Co-administration of BDQ and DLM (in the context of MBT) for MDR-TB or RR-TB will not significantly affect concentrations (area under the concentration-time curve, or AUC) of either drug (or their main metabolites, M2 and DM-6705, respectively).

1.1.3   Exploratory Hypotheses

1.1.3.1 Administration of BDQ and/or DLM for a minimum of 8 weeks in patients with RR or MDR pulmonary TB, without TB meningitis, will result in measurable drug concentrations (total and unbound) in the CSF.

1.1.3.2 BDQ and/or DLM CSF levels will follow a similar concentration curve to that found in plasma.

1.2   Primary Objectives

1.2.1   To estimate the mean changes from baseline (averaged over weeks 8-24) in QTcF when DLM and BDQ are co-administered (along with MBT; Arm 3), when BDQ is administered without DLM (along with MBT; Arm 1) and when DLM is administered without BDQ (along with MBT; Arm 2).

1.2.2   To compare the mean change from baseline (averaged over weeks 8-24) in QTcF when BDQ and DLM are co-administered (with MBT) to the mean change observed when each drug is administered alone (with MBT) (separate comparisons of Arm 3 to Arm 1 and Arm 3 to Arm 2).

1.3   Secondary Objectives

1.3.1   To estimate the proportion of participants who exhibit QTcF >500 ms at any time during study treatment, by arm.

1.3.2   To estimate the proportion of participants who exhibit an increase from baseline in QTcF of greater than 60 ms at any time during study treatment, by arm.

1.3.3   To describe visit-specific QTcF changes from baseline while on study drug treatment and following completion of study treatment (at week 28), for participants in Arm 1 (BDQ), Arm 2 (DLM), and Arm 3 (BDQ and DLM)

1.3.4   To estimate, by arm, the proportion of participants for whom the following occurs: (a) absolute QTcF >480 and ≤500 ms and (b) (separate measure) QTcF increase from baseline of >30 and ≤60 ms.

1.3.5   To compare the pharmacokinetics (PK) of BDQ when given together with DLM with MBT for MDR-TB or RR-TB (Arm 3) versus when given alone with MBR for MDR-TB or RR-TB (Arm 1).

1.3.6   To compare the PK of DLM when given together with BDQ with MBT for MDR-TB or RR-TB (Arm 3) versus when given alone (Arm 2).

1.3.7   To describe the safety and tolerability of study treatment, by arm.

1.4   Exploratory Objectives

1.4.1   To examine the relationships between plasma concentrations of DLM, its DM-6705 metabolite, BDQ, its M2 metabolite and QTcF changes from baseline, on treatment and post-treatment, using a population pharmacokinetic-pharmacodynamic (PK-PD) model.

1.4.2   To estimate the proportion of participants with a positive sputum culture at baseline who convert their sputum culture to negative by 2 months of study treatment and by 6 months of study treatment, by Arm; to report the time-to-culture conversion, by arm, over 6 months of study treatment.

1.4.3   To measure concentrations of DLM and BDQ and key second-line MBT drugs in hair over time.

1.4.4   Among participants with MDR-TB or RR-TB and HIV co-infection initiating dolutegravir (DTG) within ±4 weeks of study entry (as part of their antiretroviral treatment [ART] regimen), to estimate the proportion of participants with suppressed viral load 24 (±6) weeks and 48 (±6) weeks after start of co-treatment.

1.4.5　To describe the safety and tolerability of dolutegravir-based ART and TB treatment among participants co-infected with HIV and MDR-TB or RR-TB.

1.4.6　To estimate the proportion of participants with a favorable TB outcome at week 128, by arm.

1.4.7　To examine the relationships between plasma and hair concentrations of DLM, its DM-6705 metabolite, BDQ, its M2 metabolite, and emergence of drug-resistant subpopulations during intervention and follow-up phases as characterized by targeted deep sequencing (TDS).

1.4.8　To measure plasma and lumbar CSF concentrations of DLM and/or BDQ (total and unbound) in up to 16 participants who are receiving one or both drugs for treatment of MDR-TB or RR-TB.

2.0　INTRODUCTION

2.1　Background

Among bacteria, *Mycobacterium tuberculosis* is the single greatest killer on the planet. The World Health Organization (WHO) [1] estimates that over 9 million new cases and 1.54 million deaths due to tuberculosis (TB) occurred in 2013 (http://www.who.int/mediacentre/factsheets/fs104/en/) [2]. Multidrug-resistant (MDR) TB, TB resistant to isoniazid (INH) and rifampin (RIF), is a growing public health threat, with an estimated 480,000 cases in 2013. RR-TB is also on the rise, and, per WHO, must be treated with second-line agents, similar to MDR-TB [3]. Extensively drug-resistant (XDR) TB, TB resistant to INH, RIF, fluoroquinolones, and injectable anti-TB drugs, has been found in every country in which it has been sought [2]. TB resistant to all currently available anti-TB drugs is now a reality and threatens a return to the pre-antibiotic era [4-7]. Therapeutic options for drug-resistant TB are limited in availability, acceptability and efficacy. For example, only 1 in 5 patients diagnosed with MDR-TB is started on treatment [2]. Current standard treatment for MDR-TB requires 18-24 months of multidrug therapy, including at least 6 months of an injectable agent [8], and yet is successful in only 48% of patients [9]. Due to inappropriate and/or ineffective MDR-TB treatment, nearly 10% of MDR-TB cases now harbor XDR-TB (extensively drug resistant TB). Fortunately, for the first time in decades, new drugs are being registered for treatment of TB, and there are multiple drugs in the development pipeline. Improved treatment of MDR-TB, both to improve clinical outcomes for current patients and to prevent XDR- and TDR-TB, is critical.

The WHO recommends two possibilities for treatment of MDR-TB. Patients with RR-TB are, per WHO guidelines, also eligible for these regimens. Standard-duration treatment regimens must contain at least four drugs to which the organism is likely to be sensitive, and these regimens are typically given for 18-24 months [8]. New in 2016, based on observational studies [10-13], WHO also provides an option for an alternative short-course (9-12 month) MDR-TB treatment regimen for those patients with MDR-TB that is

sensitive to fluoroquinolones and injectable agents [3]. In this regimen, seven drugs, including an injectable, are given during the intensive phase, and four drugs are given during the continuation phase.

It is expected that South Africa will be introducing the WHO shorter-duration MDR-TB regimen in 2017. The regimen will include high-dose INH, prothionamide or ethionamide, kanamycin or amikacin, moxifloxacin, ethambutol, pyrazinamide, and clofazimine (given for 4-6 months, the 'intensive phase') followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol (given for 5-7 months, the 'continuation phase').

Current MDR-TB treatment regimens (both standard- and short-course regimens), however, are poorly-tolerated and have significant toxicities. Regimens, for example, may include kanamycin (ototoxicity, which can be irreversible, and poor bactericidal activity), a fluoroquinolone, ethionamide or prothionamide (dose-limiting GI toxicity), pyrazinamide (risk of resistance, as this drug is a standard part of first-line regimens), cycloserine/terizidone (central nervous system [CNS] toxicity), and ethambutol (ophthalmologic toxicity risk and risk of resistance, as this drug is a standard part of first-line regimens).

The evidence base for the treatment of MDR-TB is limited. The guidelines for both regimens are based largely on expert opinion and observational cohorts. The first randomized controlled trial for an MDR-TB regimen, STREAM 1, is comparing the 18-24 month regimen to the 9-month regimen. Results will be available in 2018.

Having effective new anti-TB drugs and regimens is, thus, not only important to improve cure rates and reduce risk of acquired resistance but also to reduce suffering related to common and severe side effects of standard current MDR-TB regimens. As new drugs are evaluated and registered, ensuring that they can be used together safely and effectively, will build the evidence base needed to test injectable-sparing regimens or regimens that do not include highly toxic drugs.

BDQ and DLM are newly registered anti-TB drugs with novel, and distinct mechanisms of action. BDQ is a diarylquinoline that inhibits *Mycobacterium tuberculosis'* ATP synthase [14]. DLM is a nitroimidazole antibiotic with a mechanism of action that primarily involves inhibition of mycolic acid synthesis [15]. Separately, BDQ and DLM have each been shown to improve sputum culture conversion rates when added to MBT compared to MBT alone [16-19]. In phase II clinical trials of BDQ, adding BDQ to MBT for 8 weeks (at a dose of 400 mg once daily for 2 weeks followed by 200 mg thrice-weekly) increased 2-month sputum culture conversion from 9% to 48% compared to MBT alone [16], and improved culture conversion was sustained at 6 months [17]. When given for 6 months, 24-week culture conversion was improved compared to MBT for 6 months without BDQ [20]. Among patients with MDR-TB given MBT alone, MBT plus DLM 100 mg twice daily, or MBT plus DLM 200 mg twice daily, 2-month culture conversion proportions were 29.6%, 45.4%, and 41.9%, respectively [18]. Long-term outcomes with DLM added to MBT for 6 months were favorable in a nonrandomized comparison to shorter duration DLM use or MBT alone [19]. Based on these phase II trial results showing highly favorable microbiologic outcomes, both BDQ and DLM

have received regulatory approvals in several countries. Combining these two compounds, together with other anti-TB drugs, may improve outcomes for drug-resistant TB, as there will not be cross-resistance with other anti-TB drugs. It is also possible that use of these drugs together may eventually allow for one or more second-line TB drugs in the DR-TB regimen to be dropped. Both have the added benefit of being oral agents. It is expected that both BDQ and DLM will be increasingly available globally now that both drugs have initial regulatory approvals. The combination of BDQ and DLM, though, has not yet been studied in humans.

BDQ is a diarylquinoline with interesting PK properties. It is metabolized by liver cytochrome P450 enzyme 3A (CYP3A) to its main metabolite, M2, and it has triphasic elimination with an effective half-life of 24 hours, but a prolonged terminal elimination half-life of about 5 months. In in vitro human hepatocyte studies, BDQ neither induces nor inhibits drug metabolizing enzymes appreciably. M2 is less active than the parent drug against *M. tuberculosis*. DLM's main route of metabolism is by albumin, and it is only partially metabolized by P450 enzymes (CYP3A4); several metabolites have been identified in human plasma, including, most prominently, DM-6705 (18%) and DM-6706 (7%). While the elimination half-life of DLM is 30-38 hours, its metabolites have longer terminal half-lives, 121-425 hours. Both BDQ and DLM are relatively well-tolerated (see Drug Information below). Each drug modestly increases the QT interval. The combined effects of the two drugs on QT have not been studied [BDQ Investigator Brochure Janssen Pharmaceuticals, Inc., 2015].

Nested study of BDQ and DLM CSF penetration
Tuberculous meningitis (TBM) is a disseminated form of TB most commonly affecting children under 5 years and HIV-positive adults [21-24]. Current treatment for TBM and multidrug-resistant (MDR) TBM is based on treatment regimens for pulmonary TB with many drugs achieving poor CSF penetration and consequently poor outcomes. Among patients treated for drug-sensitive (DS) TBM, adults have a mortality of 30-50% with 20% mortality in children; among those who survive, serious neurologic sequelae are common [25]. MDR TBM confers a 12-fold higher risk of death in children [26] and adults [27] with almost 100% mortality in patients co-infected with MDR-TB and HIV [28, 29].

With the view to create more effective regimens for the treatment of both DS and DR TBM in the future, CSF penetration of new drugs should be evaluated. The A5343 study provides a unique opportunity to study the CSF penetration of its two novel medications, bedaquiline and delamanid. A5343 participants who consent to participate will form part of a nested study to evaluate the CSF penetration of these agents. The participants will not have meningitis; thus, CSF concentrations will most meaningfully reflect those achieved later in TBM treatment when treatment has largely restored the integrity of the blood-brain barrier. This nested study will maximize the contribution of the PK data accumulated in A5343 to advance what is known about bedaquiline and delamanid CSF penetration.

Further details about the LP for CSF collection are included in Appendix I.

Drug Information
Bedaquiline
BDQ is a methoxyquinoline that was FDA-approved in December of 2012 for the treatment of MDR-TB. It inhibits the proton pump of *Mycobacterium tuberculosis (M. tuberculosis)* ATP synthase, a novel mechanism of action for an anti-mycobacterial drug. It is active in vitro against both replicating and non-replicating bacilli, and it has significant bactericidal and sterilizing activity in the murine model of TB infection. In vitro, it is equally active against drug-sensitive, MDR, Pre-XDR, and XDR strains of *M. tuberculosis*. The distinct target and mode of action of BDQ minimizes the potential for cross-resistance with existing anti-TB drugs [BDQ Investigator Brochure, Janssen Pharmaceuticals, Inc., 2015].

Dose and indications
BDQ is FDA-approved for the treatment of MDR-TB in combination with MBT. It is also approved in South Africa and other countries. For the treatment of TB infection, a dose of 400 mg daily (four 100 mg tablets) for 2 weeks, followed by 200 mg three times per week (with at least 48 hours between the doses) to complete 6 months of treatment is recommended.

Pharmacokinetics
BDQ is well-absorbed with a T_{max} of 5 h. Dose-proportionality of C_{max} and AUC was 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 increased bioavailability by 95%. BDQ is metabolized by oxidative metabolism via the CYP3A4 isoenzyme to its N-desmethyl metabolite, M2. The M2 metabolite has activity against *M. tuberculosis*, but it is 3- to 6-fold less potent [BDQ Investigator Brochure Janssen Pharmaceuticals, Inc., 2015].

Drug-drug interactions
Based on studies in human hepatocytes, BDQ is likely an inducer of CYP2E1 and a weak inducer of CYP2C9 but does not appear to induce other isoenzymes, and it demonstrated no inhibition of CYP activity. A drug-drug interaction study of RIF, a CYP3A4 inducer, coadministered with BDQ in healthy participants resulted in reduced BDQ and M2 concentrations by 52% and 25%, respectively, but reductions in BDQ and M2 metabolite concentrations at steady state are expected to be substantially larger [30]. Coadministration of BDQ with ketoconazole, a CYP3A4 inhibitor, increased BDQ concentrations by 22%. Therefore, coadministration of BDQ with a CYP3A4 inducer or inhibitor is likely to affect BDQ exposure. BDQ concentrations are reduced an estimated 20-50% when given together with efavirenz (EFV); with lopinavir-boosted ritonavir, single-dose concentrations are increased 22%, but at steady state, BDQ and M2 metabolite concentrations are likely to be substantially higher [31]. Nevirapine does not appear to have a meaningful impact on BDQ concentrations [31]. Integrase inhibitors like raltegravir or dolutegravir have not been tested with BDQ, but given the metabolic pathways of these drugs, a clinically significant metabolic drug interaction is unlikely.

Toxicities
A total of 173 healthy participants participated in six phase I trials with BDQ. In phase I

trials, BDQ was safe and well tolerated. The most common adverse events (AEs) were headache, nasopharyngitis, postural dizziness, and hyperuricemia (the latter a known side effect of the coadministered pyrazinamide). Three participants withdrew due to: a urinary tract infection, pharyngolaryngeal pain and pyrexia, and increased lipase. In the phase IIa trial, the drug-related AEs were diarrhea and rash (two participants) and somnolence (one participant). In this study, in which TB patients received 400 mg daily, after 7 days, a mean 10 ms increase in QT was seen. In the phase II MDR treatment trial, nausea was the only AE seen more frequently in patients in the BDQ arm than in patients in the placebo arm (Package Insert, IB). In this study involving prolonged use of BDQ at 400 mg daily for 2 weeks followed by 200 mg thrice weekly for 6 weeks in participants with TB, a 5-10 ms increase in the QTcF interval compared to placebo recipients was seen. There were no clinically relevant changes in laboratory tests. However, with prolonged follow-up, an increased risk of death was seen in the BDQ treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%), based on the 120-week visit window. One death occurred during the 24 weeks of administration of BDQ. The imbalance in deaths is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other drugs used to treat TB, HIV status, or severity of disease was observed.

Combining the phase I and IIa trials, another AE that occurred in three or more people was erythema. While ophthalmological findings of conjunctival hyperemia, photophobia, or superficial corneal staining were found in some dogs in preclinical studies after 5 months of daily dosing (though not in other species), there have been no ophthalmological side effects related to BDQ in phase I or phase II trials in humans to date (IB). More hepatic-related adverse drug reactions were also reported with the use of BDQ plus other drugs used to treat TB compared to other drugs used to treat TB without the addition of BDQ.

QT effects
With regard to effects on the QT interval, the proportion of study participants experiencing treatment emergent QT abnormalities during study treatment in the phase II trial are as follows:

n (%)	BDQ/MBT	Placebo/MBT
	Treatment Phase	Treatment Phase
QTcF absolute value, N	79	81
[450 ms – 479 ms]	23 (29.1)	10 (12.3)
[480 ms – 499 ms]	1 (1.3)	1 (1.2)
≥500 ms	1 (1.3)	0
QTcF change in QT, N	77	79
Increase by <30 ms	22 (28.6)	48 (60.8)
Increase by 30-60 ms	45 (58.4)	29 (36.7)

| Increase by >60 ms | 10 (13.0) | 2 (2.5) |

In Trial C208 Stage 2, the largest mean increase from reference in QTcF during the 24-week BDQ treatment was 15.7 ms in week 18, compared to 6.2 ms in the comparator group at the same time point. This difference persisted, likely because of BDQ and M2's long terminal half-lives. Mean increases in QTcF of ≥10 ms were seen from week 5 onwards and decreased after week 24 (when study drug was discontinued). Of note, mean QTcF changes from baseline at the 5-hour time point (T_{max}), were similar to those at predose time points, suggesting lack of a direct correlation between plasma concentrations and QTcF prolongation, though a delayed effect is possible. The time course of QTcF change from baseline with standard BDQ dosing over the 6 months of treatment followed by continuation of MBT is summarized in the figure below, from the FDA NDA filing:

Of note, many patients participating in the phase II trials of BDQ were also receiving other QT prolonging drugs (like moxifloxacin or clofazimine). The following summarizes the effects of having BDQ alone versus BDQ with other QT-prolonging drugs from Study

C209. Maximum QTcF for BDQ alone (without other QT-prolonging drugs) was 480 ms.

QT Correction Number of QT Prolonging Drugs	TMC207/BR							
	n	Mean	SE	Min	1st Quartile	Median	3rd Quartile	Max
QTC BAZETT (calculated) (ms)								
0	132	443.2	1.94	384	428.0	444.0	457.5	510*
1	65	447.5	2.82	403	431.0	445.0	462.0	519^
2	25	458.3	4.38	417	447.0	461.0	465.0	519#
3	7	462.4	5.78	436	456.0	460.0	479.0	480
QTC FRIDERICIA (calculated) (ms)								
0	130	427.4	1.66	386	413.0	427.5	442.0	480
1	67	429.1	2.42	390	414.0	429.0	439.0	496
2	25	441.6	4.69	393	433.0	438.0	445.0	516#
3	7	442.1	4.34	428	430.0	443.0	450.0	461

Delamanid
DLM is a nitro-dihydro-imidazooxazole derivative that inhibits mycolic acid synthesis and enhances killing by generating nitric oxide in MTB in anaerobic conditions. It is active in vitro against actively dividing and dormant mycobacteria with similar MICs against drug-sensitive and MDR-TB strains. The distinct target and mode of action of DLM minimizes the potential for cross-resistance with existing anti-TB drugs [DLM Investigator Brochure, Otsuka Pharmaceutical Company, Ltd., 2016].

Dose and indications
DLM has been approved by the European Medicines Agency and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan at a dose of 100 mg twice daily with food for 6 months for the treatment of MDR-TB.

Pharmacokinetics
DLM absorption is enhanced by food (and even more so with a high-fat meal), and its maximum concentration is reached approximately 4 hours post-dose. DLM exposures increase less than proportionally for doses ranging from 50 to 400 mg. DLM is extensively protein-bound (>99.5%), as are its primary metabolites DM-6704, DM-6705, and DM-6706. DLM is metabolized by albumin. CYP3A4 and CYP1A1 are involved in the subsequent metabolism of DLM metabolites. The main circulating metabolites are DM-6705 and DM-6706. Following DLM 100 and 200 mg BID for 10 days, all metabolites were measurable in plasma and represented <1% to 12% of DLM exposure. The elimination half-life of DLM is 30-38 hours; terminal half-life of the metabolites is longer, 121 to 425 hours. DLM steady state is reached at 10-14 days while DM-6705 steady state is reached at 10-14 weeks. Only a small fraction of DLM (3-8%) is eliminated renally; the majority of the drug is excreted in feces. Gender, race, age, and renal impairment do not affect DLM PK. DLM exposures among patients with MDR-TB were similar to those in healthy participants [DLM Investigator Brochure, Otsuka Pharmaceutical Company, Ltd., 2016].

Drug-drug interactions

DLM and its major metabolites do not show meaningful inhibition of CYP isoenzyme activity, including CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4. DLM is not an inducer of CYP1A2, CYP2C9, CYP3A4/5. Co-administration of DLM with a combination of first-line anti-TB drugs (INH, RIF, pyrazinamide, ethambutol) resulted in a 45% reduction in the concentrations of DLM and all its metabolites (likely related to the impaired solubility of DLM in the presence of additional drugs and to a much lesser extent due to induction of CYP3A4 and CYP1A1 by RIF). To enhance drug solubility and absorption, DLM dosing should be separated from dosing of other MDR-TB drugs by at least one hour. Ethambutol plasma concentrations increased by about 25% when coadministered with DLM. Co-administration of DLM with lopinavir/ritonavir increased DLM and DM-6705 by about 25%. DLM did not affect tenofovir, lopinavir, or ritonavir exposures. Coadministration with EFV did not affect concentrations of either DLM or EFV. MDR1 (Pgp) inhibition or induction does did not appear to affect DLM exposures. No drug interaction studies of DLM together with integrase inhibitors have been performed, but based on knowledge of metabolic pathways, the risk of metabolic drug interaction potential is expected to be low [DLM Investigator Brochure, Otsuka Pharmaceutical Company, Ltd., 2016].

Toxicities

As of 31 Jan 2016, 949 adult participants had been exposed to oral doses of DLM in 19 completed trials in the United Kingdom, Japan, China, South Africa, Peru, Korea, Philippines, Egypt, European Union (EU), and United States (US). The safety data for patients with TB are provided here.

In a 14-day early bactericidal activity (EBA) trial in participants with drug-sensitive (DS-) TB, five treatment-emergent adverse events (TEAEs) considered serious were reported: three participants with QT interval prolongation on ECG and two participants with increased hepatic transaminases in the DLM 300 mg and 400 mg groups, respectively. All five events were mild in severity. Note that additional QT-related information is provided in a separate section directly following this.

Trial 204 was a randomized, double-blind trial evaluating DLM 100 mg or 200 mg BID orally in combination with an optimized background regimen (OBR) versus placebo with OBR for 56 days [18]. Treatment-emergent AEs were reported for >90% of patients in all treatment groups (including the placebo + OBR group). Most TEAEs were mild or moderate in intensity. In this trial, the incidences of most TEAEs were similar (difference <5 percentage points) between the DLM 100 mg BID + OBR group and the placebo + OBR group. In Trial 204, there appeared to be a dose response for the following TEAEs (>5 percentage points lower in the DLM 100 mg BID + OBR group compared with the DLM 200 mg BID + OBR group): vomiting (29.8% vs 36.3%), dyspepsia (3.7% vs 8.8%), pyrexia (5.6% vs 11.3%), decreased appetite (14.9% vs 23.1%), hypokalemia (12.4% vs 19.4%), arthralgia (19.9% vs 26.9%), neck pain (0.6% vs 6.9%), insomnia (26.1% vs 32.5%), and depression (2.5% vs 8.1%). Chest pain (9.9% vs 4.4%) incidence was greater in the DLM 100 mg BID + OBR group and the 200 mg BID + OBR group (8.8% vs. 4.4%) compared to placebo + OBR group.

Trial 208 served as a treatment extension trial to provide safety and tolerability data for longer-term exposure to DLM for up to 6 additional months beyond the exposure in Trial 204 [19]. Although DLM was administered for 6 months in this open-label trial (at least 4 months longer than in previous DLM trials), no new safety concerns were identified when the data were compared with previous trials. The incidence of the following TEAEs were increased in Trial 208 relative to Trial 204 (>5 percentage points higher in Trial 208 than in Trial 204 for the DLM 100 mg BID + OBR group): hyperbilirubinemia (6.6% vs 0.6%), nasopharyngitis (8.8% vs 2.5%), upper respiratory infection (URI; 8.0% vs 1.2%), increased blood cortisol (8.8% vs 2.5%), and headache (30.7% vs 23.6%).

Trial 210 was designed to evaluate the safety, tolerability, and PK of orally administered DLM BID given in sequentially escalated doses for up to 196 days (28 weeks) at each dose to individual cohorts of MDR-TB participants refractory to treatment with OBR (9 months of previous treatment with second-line drugs without achieving sputum culture conversion) and to determine the potential dose-limiting factors and, potentially, the maximum tolerated dose (MTD) in participants treated with DLM. Drug exposure did not increase with these higher doses, apparently due to lack of further absorption. Ten participants were enrolled in Trial 210, and all participants reported at least one TEAE. Most TEAEs were mild to moderate in severity. The most frequently reported TEAEs (>2 participants) were hyperglycemia (6/10 participants; 60%), tuberculosis (i.e., progressive tuberculosis, 5/10 participants; 50%), viral upper respiratory tract infection (4/10 participants; 40%), nausea (4/10 participants; 40%), vomiting (3/10 participants; 30%), hepatomegaly (3/10 participants; 30%), decreased appetite (3/10 participants; 30%), and cough (3/10 participants; 30%).

In trials involving healthy participants without TB or HIV infection, moderate to severe psychiatric side effects were seen in some individuals receiving concomitant EFV and DLM, including one case of acute delirium in one study participant; one case of severe hepatic enzyme elevation was seen in a participant receiving EFV and DLM. In addition, the following AEs were reported but were rare: ischemic colitis (occurring more than 2 weeks after study drug administration ended), hematochezia, and hematemesis.

In summary, DLM at doses of 100 mg BID and 200 mg BID is well-tolerated among participants with TB. The most common toxicities among participants with TB included gastrointestinal side effects (dyspepsia, nausea, vomiting), fever, headache, chest pain, central nervous system side effects, hyperbilirubinemia, and QT prolongation.

QT effect
In the 14-day early bactericidal activity (EBA) trial in patients with drug-sensitive (DS-) TB, 3 patients had ECG QT interval prolongation corrected by Bazett's formula (i.e., QTcB interval ≥450 ms [male] or ≥470 ms [female]) in the DLM 100 mg, 200 mg, and 300 mg groups, respectively; the concomitant QTcF interval with each of these events remained <460 ms. These events were considered mild in severity.

Trial 204, which incorporated specific features of a thorough QT study, assessed serial, time-matched ECGs on Days 1, 14, 28, and 56 at 2, 3, 4, 10, 12, and 24 hours post-dosing along with periodic safety ECGs throughout the course of the trial. By day 56, the

largest effect on time-averaged change in QTcF (relative to baseline and the placebo arm) reached 12.1 ms in the 100 mg DLM BID arm and 14.8 ms in the 200 mg DLM BID arm. (Note, participants randomized to receive placebo plus OBR (placebo + OBR) had a mean increase from baseline of 3 ms).

In terms of categorical ECG assessment, prolonged QT interval incidence—as assessed by the local investigator—was greater in the DLM 100 mg BID + OBR group versus the placebo + OBR group (9.9% vs 3.8%) and in the 200 mg BID + OBR group compared to placebo + OBR group (13.1% vs. 3.8%). The incidence of any QT outliers, though, was low: 1 of 161 patients receiving 100 mg BID DLM and 1 of 160 receiving 200 mg BID exhibited a QTcF interval >500 ms. Of note, both participants were asymptomatic. In addition, there were no cases of torsades de pointes or any clinical events suggestive of a proarrhythmia state attributable to DLM. Finally, 3% of participants in the DLM 100 mg BID + OBR group and 4% in the DLM 200 mg BID + OBR group had QTcF >60 ms change from baseline compared with 0% in the placebo group.

In Trial 208, QTcF data were not calculated from time-matched samples as in Trial 204, so caution is necessary when interpreting comparative results. Overall, over 6 months of dosing, the mean QTcF interval increased over the first 6 weeks and then stabilized after week 6-8; differences from time point to time point were minor and not clinically relevant. Only 6 (2.8%) participants had reported TEAEs related to prolonged QT. A low percentage of participants (3.8%, 8/213) had a change in QTcF of >60 ms. These data suggest that further increases in QTcF duration are not likely to occur with longer-term (e.g., 6 months, 26 weeks) dosing of DLM beyond the 2-month (56 days) period in Trial 204, using the same dose regimen.

QTc interval prolongation appears to be associated with DM-6705 plasma concentrations and to a lesser extent with DLM, DM-6704, and DM-6720 plasma concentrations. DM-6705 accumulates slowly over time to reach maximal concentrations after 2 months of treatment. Key elements of a thorough QTc trial were therefore incorporated into Trial 204 to clearly establish a PK/PD relationship for QTc interval prolongation. Placebo-corrected mean change from baseline in Fridericia's corrected QT interval [ΔΔQTcF] on Day 56 estimated using the linear PK/PD model was 14.24 ms with DLM 100 mg BID + OBR at the DM-6705 mean Cmax of 151 ng/mL and 21.98 ms with DLM 200 mg BID + OBR at the DM-6705 mean Cmax of 233 ng/mL (Trial 204). A slightly (0.5 to 3 ms) lower effect in QTcF prolongation was predicted using an Emax model that seemed to fit the data better. The highest DM-6705 concentrations (Cmax) and QTc effect were observed on day 56. The QT interval prolongation reversed after treatment was discontinued (Trial 204).

Finally, a post hoc multivariate analysis of Trial 204 data suggested that—in addition to DLM exposure—hypoalbuminemia (albumin <3.4 mg/dL) hypokalemia, female sex, lower heart rate, and older age were each independent risk factors for QTcF prolongation.

Dolutegravir
DTG is an integrase strand transfer inhibitor (INSTI) that is used for the treatment of
HIV-1 infection.

Dose and indications
DTG is approved for use in combination with other antiretrovirals in treatment-naïve and
treatment-experienced HIV-1 infected adults and children aged 12 years and older and
weighing at least 40 kg. The recommended dose of DTG in treatment naïve or
treatment-experienced, integrase-naïve patients is 50 mg QD for most patients (for
exceptions, see Drug interactions section below). The recommended dose of DTG in
integrase-experienced patients with certain integrase-associated resistance substitutions
(L74I/M, E138A/D/K/T, G140A/S, Y143H/R, E157Q, G163E/K/Q/R/S, or G193E/R) or
clinically suspected integrase resistance is 50 mg BID. Additionally, in these patients,
alternative combinations that do not include metabolic inducers should be considered
when possible.

Pharmacokinetics
DTG is metabolized by the UGT1A1 metabolic pathway with minor contributions by
CYP3A4, UGT1A3, and UGT1A9. DTG has a terminal half-life of approximately 14
hours, and Cmax occurs approximately 2-3 hours postdose. DTG tablets may be taken
with or without food. DTG is highly protein-bound (approximately 99%) based on in vitro
data, and in healthy participants, DTG has a mean unbound fraction of approximately
0.23% [32].

Drug interactions
In vitro, DTG does not inhibit or induce cytochrome P450 enzymes. DTG is therefore not
expected to affect the PK of drugs that are substrates of CYP450. Given that DTG is
metabolized by UGT1A and CYP3A, when coadministered with potent UGT1A/CYP3A
inducers such as EFV, fosamprenavir/ritonavir (FPV/r), tipranavir/ritonavir (TPV/r), or
RIF, a dose adjustment of DTG to 50 mg BID is needed. In treatment-experienced
participants with HIV-1 that has integrase resistance mutations as described above, ART
combinations that do not include metabolic inducers should be considered when
possible. DTG should not be used with etravirine (ETR) without coadministration of
atazanavir/ritonavir (ATZ/r), darunavir/ritonavir (DRV/r), or lopinavir/ritonavir (LPV/r,
Kaletra). Coadministration with nevirapine (NVP) should be avoided because there are
insufficient data to make dosing recommendations. Coadministration with metabolic
inducers such as oxcarbazepine, phenytoin, phenobarbital, carbamazepine, and St.
John's wort should be avoided because there are insufficient data to make dosing
recommendations. DTG should be taken 2 hours before or 6 hours after taking cation-
containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium
supplements, or buffered medications.

In vitro, DTG inhibited the renal organic cation transporter, OCT2 (IC50 = 1.93 µM). In
vivo, DTG inhibits tubular secretion of creatinine by inhibiting OCT2. Thus,
coadministration of DTG with dofetilide is contraindicated due to the potential for
increased dofetilide plasma concentrations and the risk for serious and/or life-
threatening events. In addition, monitoring of glucose levels is recommended when

starting or stopping DTG and metformin together as a dose adjustment may be needed for metformin.

Efficacy and toxicity data
The efficacy of DTG in HIV-1 infected treatment naïve participants was based on 48-week data from two randomized, international, multicenter, double-blind, active-controlled trials, SPRING 2 (ING113086) and SINGLE (ING114467). In SPRING 2, 822 participants were randomized and received either DTG 50 mg QD or raltegravir (RAL) 400 mg BID, both in combination with fixed-dose dual nucleoside reverse transcriptor inhibitor (NRTI) backbone (either abacavir [ABC]/3TC or TDF/FTC) [33]. At 48 weeks, the proportion of participants with HIV-1 RNA <50 copies/mL was 88% in the DTG group compared with 85% in the RAL group (adjusted difference 2·5%; 95% confidence interval (CI) –2·2 to 7·1). The median increase from baseline to week 48 in CD4+ cell count was 230 cells/mm^3 in both groups. The most common (≥10%) AEs (all grades) for DTG vs. RAL groups were nausea (14% vs. 13%), headache (12% vs 12%), nasopharyngitis (11% vs 12%), and diarrhea (11% in each group). Few participants had drug-related serious AEs (3 [<1%] vs. 5 [1%]), and few discontinued due to AEs (2% in each group). Rates of laboratory abnormalities were similar between treatment groups, and no clinically significant changes in the fasting lipid profile were noted in either group. Nonpathologic inhibition of the organic cation transporter, OCT2, in the proximal renal tubules [34] resulted in small, non-progressive increases in serum creatinine early in treatment with DTG (weeks 2–4) and then remained stable to week 48, consistent with previous findings [35]. No participants on the DTG or the RAL arm discontinued ART due to renal AEs. No evidence of treatment-emergent resistance was observed in participants with virologic failure on DTG, whereas among RAL-treated participants, one had integrase treatment-emergent resistance and four had NRTI treatment-emergent resistance.

In SINGLE, 833 participants were randomized and received either DTG 50 mg QD with fixed-dose ABC/3TC or fixed-dose TDF/FTC/EFV [36]. At 48 weeks, the proportion of participants with HIV-1 RNA <50 copies/mL was 88% on DTG compared with 81% on TDF/FTC/EFV (adjusted difference 7.4%; 95% CI 2.5% to 12.3%; p=0.003). The adjusted median increase from baseline in CD4+ cell count was 267 cells/mm^3 for DTG+ABC/3TC vs. 208 cells/mm^3 for TDF/FTC/EFV at 48 weeks (adjusted difference 59; 95% CI 33% to 84%). The most common (≥10%) AEs for DTG+ABC/3TC vs. TDF/FTC/EFV groups were dizziness (7% vs. 32%), nausea (10% vs. 12%), abnormal dreams (6% vs. 15%), and insomnia (10% vs. 5%). The number of participants who discontinued study due to AEs for DTG+ABC/3TC was 10 (2%) compared with 41 (10%) on TDF/FTC/EFV groups. Few participants had drug-related serious AEs (1 [<1%] vs. 8 [2%]). Renal AEs leading to discontinuation occurred in one participant on DTG+ABC/3TC and two participants on TDF/FTC/EFV. At 48 weeks, small increases were noted in total, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol in both groups but total cholesterol/HDL ratio remained stable; comparable increases in triglycerides were observed in both groups. No evidence of treatment-emergent resistance was observed in participants with virologic failure on DTG, whereas among TDF/FTC/EFV-treated participants, four had non-NRTI (NNRTI) treatment-emergent resistance and one had major NRTI treatment-emergent resistance.

In May 2018, ViiV Healthcare became aware of a potential safety issue related to neural tube defects (NTD) in infants born to women with exposure to dolutegravir at the time of conception that was identified from a preliminary unscheduled analysis of a study conducted among pregnant women in Botswana (Tsepamo study, 4 NTD among 426 pregnancies on dolutegravir). This represented an incidence of about 0.9% with an expected background rate of about 0.1%. In the reproductive toxicology studies, including embryofetal development studies performed in animals prior to drug licensure, there were no adverse development outcomes, including NTD, but dolutegravir was found to cross the placenta. Up to now, data from the Antiretroviral Pregnancy Registry (APR), clinical trials, and post marketing use have not indicated a potential safety issue, but data from these sources are limited. The FDA recommends that women of reproductive potential have a pregnancy test before starting dolutegravir and that women of childbearing age who decide to take a dolutegravir-containing regimen consistently use effective contraception while on HIV treatment (www.fda.gov).

2.2   Rationale

Rationale for the study: The risk of PK drug interactions between BDQ and DLM is anticipated to be low. However, these drugs are likely to be used together commonly, and, importantly, both drugs have metabolites (M2 for BDQ and DM6705 for DLM) that have preliminary associations (in vitro or in vivo) with specific toxicities (phospholipidosis, QT prolongation) that may be of clinical concern. Most importantly, there is a potential for pharmacodynamic interaction, as both drugs prolong the QT interval (individually by around 12-15 ms). It is unknown if the combination will show less than additive, additive, or synergistic QTc prolongation and if QT prolongation when the drugs are coadministered will be of sufficient frequency and magnitude to be of clinical importance. It is therefore necessary to evaluate for potential interactions before proceeding to large clinical trials using the combination of BDQ and DLM.

The combination of BDQ and DLM is not FDA-approved. There are several reasons why the combination of BDQ and DLM should be tested in participants with TB rather than healthy participants: the safety profiles of the drugs, the fact that QTc prolongation may increase with accumulation of the drugs/metabolites necessitating observations during extended dosing, and the need for multiple dosing to assess PK interaction effects because of the long half-lives of BDQ and the DLM metabolite (DM-6705); finally, the disease state and concomitant drugs may influence safety and PK.

Rationale for the long period of follow-up. The later time points in the study are primarily to detect safety signals following the 24-week course of BDQ, as there was higher mortality in participants randomized to BDQ than placebo in the phase II study, resulting in a black box warning by the FDA on the label. These deaths generally occurred late, after BDQ discontinuation, and this mortality imbalance, thus, remains unexplained.

Rationale for offering DTG for HIV treatment to participants with HIV/MDR-TB co-infection. DTG will be offered for both naïve and treatment-experienced HIV patients.

Among patients with MDR-TB in South Africa where this study will be conducted, about 30-50% are coinfected with HIV and will require concurrent MDR-TB and HIV treatment. However, ART options are limited. Specifically, because BDQ is metabolized by CYP3A and its therapeutic window is not well-defined, it cannot be used with EFV or pharmacoenhancers like ritonavir or cobicistat because these medications may reduce or increase BDQ and M2 exposures substantially. Triple or quadruple NRTI regimens are available, but are therapeutically inferior to first-line ART regimens. Nevirapine 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. DTG does not induce or inhibit CYP3A and its metabolism is not expected to be affected by BDQ or DLM. Further, it is under review by the Medicines Control Council in South Africa for registration and may be available locally in the near future. This study provides an opportunity to use DTG-based ART together with the newest, most promising anti-TB drugs for patients with MDR-TB and HIV coinfection, thus addressing an important unmet medical need. We will be able to assess HIV virologic suppression and safety among coinfected participants taking DTG-based ART and MDR-TB treatment. DTG will be offered to participants with HIV infection and will be continued throughout their study participation, even after study TB drugs have been discontinued.

Rationale for longitudinal characterization of drug resistance. Molecular characterization of TB resistance to BDQ and DLM is both challenging and important. Both drugs possess potentially large numbers of unique mutations conferring resistance (within any one of five coenzyme F_{420} genes, a 7.5kb region, for nitroimidazoles, and within the *atpE* [37] and *Rv0678* [38] genes for BDQ) not currently amenable to standard molecular TB diagnostic platforms due to target size and poorly characterized resistance-conferring "hot spots." Both agents possess unique susceptibilities that may increase the likelihood of resistance development. While DLM has a relatively high stochastic spontaneous mutation rate of 6.44×10^{-6} to 4.19×10^{-5} [39], BDQ and its M2 metabolite have an average terminal elimination half-life of 132 and 112 days, respectively. This prolonged half-life may generate potentially long durations of sub-therapeutic drug concentrations with variable amounts of companion drug "protection," depending on how the drug is incorporated into future MDR-TB [35] or MDR-latent TB infection (LTBI) [36] regimens. This is concerning given the frequency of TB resistance in the setting of monotherapy [40-42], the association of low drug concentrations with acquired drug resistance [43-47], and the clinical settings of salvage treatment in which these drugs are likely to be used.

Drug resistance amplification during treatment is an important driver of the drug-resistant TB epidemic [48, 49], and we hypothesize that selection of initially hetero-resistant populations proceed to fully resistant ones through periodic exposure to sub-therapeutic companion drug levels. Thus, early detection of small drug-resistant populations may allow interventions to avert development of full drug resistance. Existing drug-susceptibility tests have limited resolution (Xpert MTB/RIF, ≥65% [43]; pyrosequencing, ≥10% [44]; line probe assay, ≥5% [50]); and mycobacteria growth indicator tube, ≥1% of a mixed population) for hetero-resistance, and none accurately quantify the proportion of resistant subpopulations.

Next-generation sequencing provides rapid, accurate, efficient (through highly streamlined target enrichment prior to sequencing) [51], and quantitative (i.e., high resolution for hetero-resistance) detection of resistance-conferring mutations [52, 53]. TDS approaches, such as single molecule-overlapping reads (SMOR) [54], are able to rapidly and inexpensively identify resistant microbes representing ≥0.1% of a microbial community. As benchtop (and even handheld) [55] sequencers, along with cloud-based tools, become more available, this method has promise for rapid comprehensive detection and quantification of drug resistance in clinical samples—in particular, for patients at elevated risk for adverse treatment outcome.

3.0   STUDY DESIGN

This is a randomized, open-label, three-arm trial evaluating the safety and drug-drug interactions of co-administered BDQ and DLM. It is anticipated that study participants will be hospitalized per standard of care for initiation of MDR-TB or RR-TB treatment for at least the first 2 **weeks** after randomization. Participants may also be hospitalized for longer than 2 **weeks** if they are too ill for discharge.

To evaluate QT prolongations and examine the observed precision of estimates around the primary outcome (QT prolongation), an interim analysis will be conducted when week 24 QT data is available for at least 12 participants on the BDQ+DLM arm.

An optional LP will be performed at weeks 8 or 24 in up to 16 participants who agree to this procedure for measuring concentrations of delamanid and/or bedaquiline in CSF.

Multidrug Background Treatment (MBT)
In addition to study TB drugs, all participants will receive a multidrug background treatment (MBT) for MDR-TB or RR-TB that includes at least three drugs to which the organism is thought or known to be susceptible (See section 5.4). In many participants, this will be a standardized, locally available regimen, but individualization of regimens based on available cultural and susceptibility data, or treatment history may be needed. Participants will need to take or have been taking MBT for at least 7 days and no more than 60 days prior to entry.

Study TB Drugs
Participants will be randomized to one of three arms. Arm 1 participants will receive BDQ at a dose of 400 mg once daily for 2 weeks followed by 200 mg thrice weekly (TIW) for 22 weeks. Arm 2 participants will receive DLM at a dose of 100 mg BID for 24 weeks. Arm 3 participants will receive both BDQ and DLM (same doses and duration as in Arms 1 and 2).

Treatment Schema:	STUDY TREATMENT		FOLLOW-UP TREATMENT
Arm	Weeks 1-2	Weeks 3-24	Weeks 25+
1	BDQ_{400QD}+ MBT	BDQ_{200TIW}+MBT	MBT*
2	DLM_{100BID}+ MBT	DLM_{100BID}+MBT	MBT*
3	BDQ_{400QD}+ DLM_{100BID} + MBT	BDQ_{200TIW} + DLM_{100BID} + MBT	MBT*

*Note: After week 24, participants will continue to receive multidrug treatment provided by local TB programs.

Bedaquiline (BDQ_{400QD}): 400 mg once daily (7/7)
Bedaquiline (BDQ_{200TIW}): 200 mg thrice weekly
Delamanid (DLM_{100BID}): 100 mg twice daily (7/7)

Study ART
Patients with HIV infection can participate provided they are taking an acceptable ART regimen (See section 5.4.4). For those participants without contraindications, study DTG at a dose of 50 mg once daily will be offered, to be used in combination with two NRTIs until study completion.

Pharmacokinetic sampling
Assays will be performed for DLM and its DM-6705 metabolite, and for BDQ and its M2 metabolite. Intensive and sparse PK sampling will be performed per section 6.1.

Hair sampling
Hair collection will be performed for measurement of DLM, BDQ, and MBT drugs (levofloxacin, kanamycin, etc.) over the course of the study to assess long-term drug exposures.

ECG monitoring
ECGs will be performed at baseline and then every 2 weeks during administration of TB study drugs and then post-study TB drug discontinuation at week 28.

Follow-up
Participants will be followed for a total of 128 weeks (24 weeks on study TB drugs, then 104 weeks after study TB drug completion for most participants), including quarterly visits beginning at the 36-week visit until the 96-week visit.

Infection Control
Strict infection control practices will be followed, including the wearing of N95 masks where appropriate and in facilities that adhere to WHO infection control principles (≥ 12 air exchanges per hour, air cleaning with UV light, and administrative controls).

4.0   SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1   Inclusion Criteria

   4.1.1   Men and women age ≥18 years of age.

   4.1.2   Documented pulmonary infection due to strains of MTB with (a) resistance to INH and RIF (MDR-TB) or (b) resistance to RIF but not INH (RR-TB) from a sputum sample collected within 60 days prior to entry. Must be lab confirmed by either genotypic (e.g., Hain GenoType MTBDRplus) or phenotypic (susceptibility testing on liquid or solid culture) methods.

   NOTE: MDR- or RR-TB diagnosis for purposes of meeting the inclusion criterion can be from a study testing laboratory or from an outside laboratory, as long as it is from a sputum sample collected within 60 days prior to entry.

   4.1.3   Laboratory confirmation of infection with an MTB strain that is susceptible to fluoroquinolones and aminoglycosides by either genotypic testing (such as Hain GenoType MTBDRsl) or phenotypic testing (susceptibility testing on liquid or solid culture) within 60 days prior to entry.

   NOTE: Fluoroquinolone and aminoglycoside susceptibility testing for purposes of meeting the inclusion criterion can be from a study testing laboratory or from an outside laboratory, as long as it is from a sputum sample collected within 60 days prior to entry.

   4.1.4   HIV-1 infection status must be documented as either absent or present, as defined below:

   Absence of HIV-1 infection, as documented by any licensed rapid HIV test or HIV-1 enzyme or chemiluminescence immunoassay (E/CIA) test kit, within 60 days prior to entry.

   OR

   HIV-1 infection, documented by any licensed rapid HIV test or HIV-1 E/CIA test kit at any time prior to entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load.

   NOTE: The term "licensed" refers to a US FDA-approved kit, which is recommended. For sites that are unable to obtain an FDA-approved kit, a kit that has been certified or licensed by an oversight body within the country and validated internally is acceptable.

   WHO and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different

from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.5   For HIV-positive participants only: CD4+ count greater than or equal to 100 cells/mm^3 within 60 days prior to entry. CD4+ count must be obtained from a laboratory certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program.

4.1.6   For HIV-positive participants only: for those who have been on ART for ≥6 months and have an HIV-1 viral load >500 copies/mL within 60 days prior to entry, an HIV-1 genotype within 60 days prior to entry must show that at least one fully active NRTI is available to the participant within the country program.

4.1.7   For females of reproductive potential, negative serum pregnancy test within 48 hours prior to entry.

4.1.8   Female and male participants of reproductive potential who are participating in sexual activity that could lead to pregnancy must agree to use one of the following forms of birth control while receiving TB study medications and for 6 months after stopping TB study medications:

- **M**ale or female condoms
- **D**iaphragm or cervical cap with spermicide, if available
- **I**ntrauterine device (IUD)
- **O**ral contraceptives or Depo-Provera

NOTE A: Female participants who are not of reproductive potential are eligible without requiring the use of contraceptives. Participant-reported history is acceptable documentation of menopause (i.e., at least 1 year amenorrheic), hysterectomy, or bilateral oophorectomy or bilateral tubal ligation; these participants are all considered not of reproductive potential.

NOTE B: Male participants who are not of reproductive potential (i.e., documented azoospermia) or whose female partner/s are not of reproductive potential (as defined above) are eligible without requiring the use of contraceptives.

NOTE C: For HIV-positive female participants of reproductive potential, the use of contraceptives is required for the full duration of time the participant is taking dolutegravir (ie, through study completion at week 128). Contraceptive options for women of reproductive potential while taking dolutegravir include the following:

- **Contraceptive subdermal implant**
- **Intrauterine device or intrauterine system**

- **Combined estrogen and progestogen oral contraceptive**
- **Injectable progestogen**
- **Contraceptive vaginal ring**
- **Percutaneous contraceptive patches**

4.1.9 Chest x-ray performed within 60 days prior to entry to classify participant as having cavitary or non-cavitary disease.

4.1.10 Documentation of Karnofsky performance score ≥50 within 14 days prior to study entry.

4.1.11 Ability and willingness of participant or legally authorized representative to provide informed consent.

4.1.12 Willingness to be hospitalized for the required inpatient component of the study.

4.1.13 Taking MBT for a minimum of 7 days within the 10 days prior to entry.

4.2 Exclusion Criteria

4.2.1 History of clinically relevant, currently active or underlying gastrointestinal, hepatic, cardiovascular, nervous system, psychiatric, metabolic (e.g., untreated hypothyroidism), renal, respiratory (other than due to TB), inflammatory, neoplastic, skin, immunological or infectious disease, which is not stable and controlled, that in the opinion of the investigator would preclude safe participation in the trial.

4.2.2 Current clinically relevant extrapulmonary TB, in the opinion of the site investigator, including but not limited to CNS TB or TB osteoarthritis.

4.2.3 Previous treatment for MDR- or RR-TB, other than for the qualifying episode, at any time in the past.

4.2.4 Receipt of BDQ or DLM at any time in the past.

4.2.5 Breast-feeding.

4.2.6 QTcF interval >450 ms within 72 hours prior to entry.

4.2.7 Clinically significant ECG abnormality in the opinion of the site investigator within 60 days prior to entry, including but not limited to second or third degree atrioventricular (AV) block, prolongation of the QRS complex over 120 ms (in both male and female participants), or clinically important arrhythmia.

4.2.8 Current clinically relevant cardiovascular disorder in the opinion of the site investigator, including but not limited to heart failure, coronary heart disease, arrhythmia, or tachyarrhythmia.

4.2.9 Known family history of Long QT Syndrome in a first-degree relative (i.e., parent, offspring, or sibling).

4.2.10 Requirement or expected requirement for protease inhibitors (PIs), EFV, or any other medication that is a moderate to strong inhibitor or inducer of CYP3A and CYP3A4 over the 24 weeks of study treatment. Drug information may be found on the ACTG Drug Interactions Database, located at:
http://tprc.pharm.buffalo.edu/home/di_search/

NOTE: Participants taking a PI or EFV can be switched to a treatment that is allowed in the study, but the PI must be stopped at least 2 days prior to starting study MDR- or RR-TB drugs and EFV must be stopped at least 7 days prior to starting study MDR- or RR-TB drugs.

4.2.11 Requirement or expected requirement for a medication that significantly prolongs QTc, including but not limited to moxifloxacin (levofloxacin is acceptable), from 72 hours prior to study entry through 4 weeks after discontinuation of study treatment (week 28).

4.2.12 Requirement or expected requirement of clofazimine, a drug that might cause QT prolongation at current treatment doses on its own and can potentiate QT prolongation when given together with BDQ for prolonged periods, from 7 days prior to study entry through week 24 (discontinuation of study treatment).

4.2.13 For individuals receiving the WHO short course regimen that contains clofazimine, receipt of more than 21 cumulative days of clofazimine at any time prior to, or at the time of, study entry.

4.2.14 Known allergy/sensitivity or any hypersensitivity to components of study TB drugs or their formulation or to the nitroimidazole class of antibiotics.

4.2.15 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.16 Any of the following laboratory abnormalities within 14 days prior to entry at any network-approved non-US laboratory that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

   a. Serum creatinine >1.4 x ULN
   b. Lipase >1.6 x ULN
   c. ALT >2.5 x ULN
   d. Total bilirubin >1.6 x ULN
   e. Potassium <3.4 or >5.6 mmol/L; magnesium <0.59 mmol/L; calcium <1.75 mmol/L

4.2.17   Known current hepatitis B or C infection, current treatment for hepatitis B or hepatitis C infection, or positive for hepatitis B surface antigen or hepatitis C antibodies within 60 days prior to entry.

4.2.18   Among participants with HIV infection, in whom use of DTG is anticipated, any of the following:

a.   Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, esophageal varices, or persistent jaundice), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
b.   History or presence of allergy to DTG or its components
c.   Severe hepatic impairment (Class C) as determined by Child-Pugh classification
d.   Previous use of raltegravir

4.2.19   Documentation of any new and/or unstable AIDS-defining illness (other than TB) as defined by the CDC within 60 days prior to entry.

4.2.20   Acute or serious illness (other than TB) requiring systemic treatment and/or hospitalization within 60 days prior to entry.

4.3   Study Enrollment Procedures

4.3.1   Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

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

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) 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 final amendment Registration Notification issued by the DAIDS PRO 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.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the parent or legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.

For participants from whom a signed informed consent has been obtained, an ACTG Screening Checklist must be entered through the Data Management Center (DMC) Participant Enrollment System.

4.3.2 Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the protocol, an ACTG Screening Failure Results form must be completed and keyed into the database.

4.4 Co-enrollment Guidelines

- Co-enrollment in other trials of investigational agents is not allowed.
- Sites are encouraged to co-enroll participants in A5243, "Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses." Co-enrollment in A5243 does not require permission from the A5343 protocol chairs.
- For specific questions and approval for co-enrollment in other studies, sites must contact the protocol chairs via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Participants currently receiving MBT for MDR- or RR-TB will be randomized with equal probability to one of three arms:

Arm 1: Bedaquiline 400 mg orally (PO) once daily (QD) for 2 weeks followed by Bedaquiline 200 mg PO three times weekly (TIW) for 22 weeks

Arm 2: Delamanid 100 mg PO twice daily (BID) for 24 weeks

Arm 3: Bedaquiline 400 mg PO QD + Delamanid 100 mg PO BID for 2 weeks followed by

Bedaquiline 200 mg PO TIW +
Delamanid 100 mg PO BID for 22 weeks

*Note: HIV-1 positive participants will be offered dolutegravir through study completion (128 weeks), which should be given with two NRTIs.

*Note: After week 24, participants will continue to take MBT provided by local TB programs.

5.1.2 Administration

5.1.2.1 Bedaquiline Administration

Bedaquiline will be administered as four 100 mg tablets (400 mg) by mouth QD for 2 weeks, followed by two 100 mg tablets (200 mg) by mouth TIW for 22 weeks, for all study arms involving the use of this drug.

Bedaquiline should be given one hour after a meal or food intake.

5.1.2.2 Delamanid Administration

Delamanid will be administered with food as two 50 mg tablets (100 mg) by mouth BID for 24 weeks, for all study arms involving the use of this drug. Delamanid dosing should be separated in time from other drugs by at least one hour.

5.1.2.3 Dolutegravir Administration

Dolutegravir will be administered at a dose of one 50 mg tablet once daily, to be used in combination with two NRTIs until study completion.

*Note: NRTIs will not be provided by the study.

5.1.3 Treatment Duration

Participants in all study arms will remain on study TB treatment, with Bedaquiline, Delamanid or a combination of the two drugs, for a total of 24 weeks.

Participants will have 185 days from enrollment to complete 168 days (24 weeks) of TB study drug.

5.2 Study Product Formulation and Preparation

5.2.1 Bedaquiline: Bedaquiline will be supplied as tablets for oral administration. Store at 25°C (77°F); excursions permitted at 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Dispense in original container.

5.2.2   Delamanid: Delamanid will be supplied as film-coated tablets, in blister packs, for oral administration. Delamanid is stable for 6 months at 25°C/60% relative humidity (RH), for 6 months at 40°C/75%. Store at 25°C (77°F); excursions permitted at 15-30°C (59-86°F). The Clinical Research Products Management Center (CRPMC) should be contacted if excursions occur outside of the permitted range of 15-30°C (59-86°F). Dispense in original container.

5.2.3   Dolutegravir: Dolutegravir will be supplied as tablets for oral administration. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

5.3   Pharmacy: Product Supply, Distribution, and Accountability

5.3.1   Study Product Acquisition/Distribution

Delamanid will be provided by Otsuka Pharmaceutical Company, Ltd.

Bedaquiline will be provided by Janssen Scientific Affairs, LLC.

Dolutegravir will be provided by ViiV Healthcare, Ltd.

Study products will be available through the NIAID CRPMC. The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or –sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at: https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

5.3.2   Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section Study Product Management Responsibilities. At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.4   Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed,

investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the updated ACTG Drug Interactions Database located at: http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1   Required Medications

Multidrug background treatment (MBT):
In general, participants will receive a standardized MBT regimen for MDR- or RR-TB except in cases where the participant has known resistance to one of the components of local standard treatment. MBT will be provided by the local program. In South Africa, for example, the current initial standard-duration MBT regimen is high dose INH (15 mg/kg), ethambutol, ethionamide, pyrazinamide, moxifloxacin, terizidone and kanamycin, which is modified according to susceptibility testing with the Hain MTB*dr* line probe and/or phenotypical INH susceptibility testing as this becomes available (e.g., for RR-TB, a lower dose of INH may be used). Levofloxacin will be used instead of moxifloxacin in the MBT in this study (through week 28) as it has much less potential to prolong the QT interval. Levofloxacin will be obtained locally.

In some countries, the WHO shorter-duration MDR-TB regimen is now available. The components of the regimen are high-dose INH, prothionamide or ethionamide, kanamycin or amikacin, moxifloxacin, ethambutol, pyrazinamide, and clofazimine (given for 4-6 months, the 'intensive phase') followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol (given for 5-7 months, the 'continuation phase'). In this trial, levofloxacin will be used instead of moxifloxacin during the period of co-administration with bedaquiline or delamanid and for 4 weeks after (through week 28). In addition, bedaquiline or delamanid or both will be substituted for clofazimine during the period of study TB drug treatment (after which time clofazimine will be added back to the regimen). This substitution is reasonable given that bedaquiline or delamanid are each potent sterilizing agents and the evidence for their individual contributions to microbiologic activity of multidrug regimens is similar to that of clofazimine [10, 56-6**4**].

5.4.2   Prohibited Medications

A list of prohibited medications is posted on the A5343 PSWP. It should be noted specifically that moxifloxacin is not allowed from 72 hours before study entry through 4 weeks after discontinuation of study treatment (week 28). Clofazimine is not allowed from 7 days before study entry through discontinuation of study treatment (week 24). (Note that moxifloxacin's effects on QT are immediate whereas clofazimine's effects take some time to develop or resolve given this drug's large volume of distribution and long half-life.) In addition, dofetilide (or pilsicainide) is prohibited as DTG may inhibit its renal tubular secretion resulting

in increased dofetilide concentrations and potential for toxicity.

5.4.3 Precautionary Medications

A list of precautionary medications is posted on the A5343 PSWP.

5.4.4 Medications for Treatment of HIV Co-Infection

Only the following ART regimens are allowed during study TB treatment: (1) study-provided DTG plus two NRTIs or (2) nevirapine plus two NRTIs. NRTIs will be provided by the local program. Protease inhibitors (PI) and EFV are absolutely contraindicated because they significantly inhibit or induce CYP3A4, respectively. Participants taking a PI or EFV can be switched to a treatment that is allowed in the study, but the PI must be stopped at least 2 days prior to starting study MDR- or RR-TB drugs and EFV must be stopped at least 7 days prior to starting study MDR or RR-TB drugs.

For those participants who are HIV treatment-naïve, it is recommended that DTG (study ART) plus two NRTI be started approximately 2 weeks following initiation of study TB drugs. For those participants already on ART with EFV or a boosted PI at the time of screening or who require a switch from their previous ART for another reason, it is recommended that DTG-based ART be started the day following discontinuation of their previous regimen. DTG must be given together with two NRTIs.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1a Schedule of **Evaluations (SOE)**: Screening through Treatment

Evaluation	Screening (-60 days)	Entry (days -7 to 0)	Start of TB Study Drugs (day 0)	Treatment (weeks 1-8 ±3 days and weeks 10-24 ±7 days)															
				1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24
Documentation of HIV status	X																		
Medical History	X	X																	
Medication History	X	X																	
Signs/Symptoms, Diagnoses, Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination[1]	X	X																	
Targeted Physical Examination[1]			X		X		X				X		X		X		X		X
Hematology		X			X		X				X		X		X		X		X
Liver Function Tests	X[2]	X			X		X				X		X		X		X		X
Chemistry	X[2]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B Surface Antigen	X																		
Hepatitis C Antibodies	X																		
Thyroid Stimulating Hormone		X											X						
Pregnancy Testing[3]	X		As clinically indicated																
Urinalysis		X																	
HIV Viral Load (if HIV+)	X[4]	X																	X[5]
HIV-1 Genotype (if HIV+)	X[6]																		
CD4+ (if HIV+)	X																		X
Sputum AFB Smear and Culture In Liquid Media[7]	X	X		X	X	X	X	X	X	X	X	X	X		X		X		X
Drug Susceptibility Testing (DST)	X										X[8]		X[8]						X[9]
Chest X-Ray	X																		
ECG	X	X[10]			X		X		X		X	X	X	X	X	X	X	X	X
PK Sampling (intensive)[11]					X						X								X
PK Sampling (sparse)[11]							X		X			X	X	X	X	X	X	X	
Pre-assessments for Optional LP [12]								X										X	
Optional LP for Protocol-related Research[13]									X										**X**
Hair Sampling		X									X				X				X

Evaluation	Screening (-60 days)	Entry (days - 7 to 0)	Start of TB Study Drugs (day 0)	Treatment (weeks 1-8 ±3 days and weeks 10-24 ±7 days)															
				1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24
Stored Whole Blood		X																	
Adherence Assessment				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] A visual acuity test will be done at entry and weeks 4, 8, 12, 16, 20, and 24 for those participants on ethambutol.

[2] Screening liver function tests and chemistry must be performed within 14 days prior to entry.

[3] Women of reproductive potential who are taking dolutegravir will be required to have pregnancy testing every two weeks during the first 24 weeks (i.e., weeks 2-24).

[4] Required only for HIV-positive participants who have been on ART for ≥ 6 months.

[5] For HIV-1 RNA quantification in participants who initiated DTG while on study: If the 24 ±6-week window around DTG initiation does not fall within 24 weeks ± 3 days of study entry (initiation of BDQ and/or DLM), an additional visit may be scheduled for collection of plasma for the HIV-1 RNA quantification.

[6] Required only for HIV-positive participants on ART for ≥ 6 months who have a screening HIV-1 viral load >500 copies/mL.

[7] Two sputum samples should be collected at the screening visit, at entry, and weeks 2 and 4; three sputum samples should be collected at the week 8 and week 24 visits.

[8] Sputum specimens will be stored for possible DST should subsequent treatment failure or culture reversion occur.

[9] Isolates of MTB from positive cultures will be stored for TDS and DST should subsequent treatment failure or culture reversion occur.

[10] This ECG may be done at day -1 or day 0. These ECG results must be obtained prior to initiation of study TB drug(s). For participants who discontinued moxifloxacin and/or clofazimine prior to study entry, these ECG results must be obtained at least 72 hours after the last dose of moxifloxacin and 7 days after the last dose of clofazimine, and prior to initiation of study TB drug(s).

[11] See section 10.0 for instructions. Note that extra plasma will be stored for possible measurement of companion drugs in the future. Samples will not be collected for the intensive and sparse PK testing for participants who prematurely discontinue study treatment.

[12] Participants undergoing a LP must have safety bloods (CBC/INR [international normalized ratio]) performed and medical history reviewed at least the prior visit to their LP. See section 6.3.10 and Appendix I for instructions.

[13] Not all participants will undergo the optional LP procedure. The LP will be performed at either week 8 or week 24, not both. Participants must have safety bloods performed and medical history reviewed at least one week prior to their LP. See section 6.3.11 and Appendix I for instructions.

6.1b SOE: Follow-up and Premature Discontinuation

Evaluation	Follow-up (weeks 28-128 ±2 weeks)								Premature Study Discontinuation Evaluations
	28	36	48	60	72	84	96	128	
Signs and Symptoms, Diagnoses, Medications	X	X	X	X	X	X	X	X	X
Complete Physical Examination									X
Targeted Physical Examination	X	X	X	X	X	X	X	X	
HIV Viral Load (if HIV+)			X[1]						
CD4+(if HIV+)			X						
Liver Function Tests	X								
Chemistry	X								
Pregnancy Testing[2]	As clinically indicated								
Sputum AFB Smear and Culture in Liquid Media	X	X	X			X	X	X	X
Drug Susceptibility Testing (DST)[3]		X	X				X	X	X
ECG	X								X[4]
PK Sampling (sparse)[5]	X								
Hair Sampling			X		X		X	X	
Adherence Assessment	X[6]								X

[1] For HIV-1 RNA quantification in participants who initiated DTG while on study: If the 48 ±6-week window around DTG initiation does not fall within 48 ± 2 weeks of study entry, an additional visit may be scheduled for collection of plasma for the HIV-1 RNA quantification.

[2] **Women of reproductive potential who continue taking dolutegravir after week 24 will be required to have pregnancy testing at all subsequent study visits (i.e., weeks 28-128).**

[3] DST may be performed if sputum smear or culture is positive. Two sputum samples should be collected at the week 48 and week 128 (or premature discontinuation) visits; TDS will be performed at these visits.

[4] ECG is not required at this visit if the participant discontinued after week 28.

[5] Samples will not be collected for sparse PK testing for participants who prematurely discontinue study treatment.

[6] For participants who do not complete TB study drugs by week 24.

6.2   Timing of Evaluations

6.2.1   Screening Evaluations

Screening evaluations must occur prior to the participant starting any study medications, treatments, or interventions.

Screening
Screening evaluations to determine eligibility must be completed within 60 days prior to study entry, unless otherwise specified. In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database. Of note, participants who present for screening who have not started MBT can start MBT via the local TB program and must have received at least 7 days of MBT prior to entry.

6.2.2   Entry Evaluations

Participants must begin study TB treatment as soon as possible within 7 days after randomization (entry). For participants with HIV infection switching from EFV to study DTG at the time of enrollment, DTG should be started on the day of entry following blood collection for HIV viral load. For participants who discontinued moxifloxacin and/or clofazimine prior to study entry, the entry (day -1 or 0) ECG must be performed at least 72 hours after the last dose of moxifloxacin and 7 days after the last dose of clofazimine and prior to initiation of study TB drug(s). (Sites may find it more convenient to switch participants from moxifloxacin to levofloxacin during screening.)

6.2.3   Post-Entry Evaluations

Start of TB Study Drug
Start of TB study drug may occur at entry or within 7 days after entry (i.e., randomization). Start of TB study drug is considered day 0. The timing of on-study evaluations is based on the start of TB study drug.

On-Treatment Evaluations
During weeks 1-8, visits should be conducted within ±3 days. During weeks 10-24, visits should be conducted within ±7 days. All participants are expected to be hospitalized for 2 **weeks** starting at entry. Participants may also be hospitalized for longer than 2 **weeks** if they are too ill for discharge. In certain circumstances (e.g., family or personal urgent issues), it may be allowable for participants to be discharged from the hospital early. Those participants who are discharged early will be allowed to remain on study and continue to receive the study drug.

Post-Treatment Evaluations
During weeks 28-128, visits should be conducted within ±2 weeks.

6.2.4   Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
All case report forms (CRFs) must be completed and keyed for the period up to and including week 0.

Premature Treatment Discontinuation Evaluations
Participants who prematurely permanently discontinue study TB treatment will be referred to the National Tuberculosis Program (NTP) for treatment of his or her MDR or RR-TB according to local standard of care. The participant will continue to be followed on study, off study drugs for the duration of the study and undergo all evaluations (except intensive and sparse PK sampling) according to the schedule in sections 6.1a and 6.1b. The participant will be followed until the end of the study, through the last study visit at week 128.

Premature Study Discontinuation Evaluations
Participants who prematurely permanently discontinue the study will have discontinuation evaluations performed as noted in the **SOE**.

6.3   Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS Web site for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf**.

All stated evaluations are to be recorded on the CRF and keyed into the database unless otherwise specified. This includes events that meet the International Council for Harmonisation (ICH) definitions for a serious adverse event (SAE):
• Results in death
• Life-threatening
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability/incapacity
• Congenital anomaly/birth defect
• Other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

NOTE: Adverse events that require expedited reporting via the DAIDS Adverse Experience Reporting System (DAERS) are listed in section 11.4.2.

To grade diagnoses, signs and symptoms, and laboratory results, sites must refer to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, which can be found on the DAIDS RSC Web site: http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables. Please also see section 7.1 for study-specific grading criteria.

6.3.1   Documentation of HIV-1 Status

HIV-1 infection must be documented as indicated in section 4.1.4. HIV status will not be reported on a CRF.

6.3.2   Medical/Medication History

Medical History
The medical history must include all diagnoses that occurred within the past 30 days and meet the ACTG criteria for clinical events and other diagnoses.

In addition to reporting the diagnoses that meet the above criteria, the following diagnoses should be reported regardless of when the diagnosis was made:
- AIDS-defining conditions
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Cardiac history including history of arrhythmias, coronary artery disease, and heart failure
- Hypothyroidism

Smoking history (ever/never/current) must be recorded

Any allergies to any medications and their formulations must also be documented.

Medication History
A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history (HIV-related items are for HIV-1 positive participants only).

Medication Category	Complete History or Timeframe
TB treatment	Complete
Antiretroviral therapy	Complete
Prescription drugs for treatment of opportunistic infections	Within past 60 days
Prescription drugs for prophylaxis of opportunistic infections	Within past 60 days
Prescription and non-prescription drugs (other)	Within past 60 days

Medication Category	Complete History or Timeframe
Alternative or complementary medications (Record as yes/no on CRF; if yes, record details in source document.)	Within past 60 days

6.3.3   Clinical Assessments

Complete Physical Exam
A complete physical examination is to include an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema; and Karnofsky performance test. The complete physical exam will also include signs and symptoms, diagnoses, and vital signs (temperature, pulse, respiration rate, and blood pressure). Height and weight to be measured and recorded. A visual acuity test will be done at entry for those participants on ethambutol. The results of this test will be reported in the source documents only.

Targeted Physical Exam
A targeted physical examination is to include vital signs (temperature, pulse, respiration rate, and blood pressure) and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit. Weight to be measured and recorded. A visual acuity test will be done at weeks 4, 8, 12, 16, 20, and 24 for those participants on ethambutol. The results of this test will be reported in the source documents only.

Signs and Symptoms
At entry, all grades that occurred within 14 days prior to entry must be recorded; post-entry, all signs and symptoms Grade ≥3 must be recorded. For QTcF prolongation, the grade is to be determined using the Quintiles ECG reads (not the site's reads) and the supplemental toxicity table in section 7.1.1. Record all signs and symptoms that led to a change in BDQ, DLM, and/or DTG, regardless of grade. Further evaluation will be required for those events that meet Expedited Adverse Event (EAE) or ICH reporting requirements.

Diagnoses
Record specific diagnoses identified by the ACTG criteria for clinical events and other diseases. During the course of the trial, audiometry testing will be performed as per routine National TB Program guidelines.

Post entry, see section 7.3 for collection requirements for pregnancy.

Refer to section 7.1 for AE collection requirements.

TB Medications

- *Study TB Treatment (BDQ and/or DLM) Modifications:* Record all study TB drug modifications, including start/stop dates, initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 2 days for drugs given daily and 5 days for drugs given thrice weekly, at each visit. Record any permanent discontinuation of treatment. Report the initiation of study TB drug within 2 days of the first dose.
- *MBT Drugs:* MBT drugs started or stopped since the last study visit must be recorded on the CRF, including actual or estimated start dates and stop dates, initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 2 days for drugs given daily and 5 days for drugs given thrice weekly, at each visit. Record any permanent discontinuation of any TB drugs.

ART Medications

- Study ART (DTG) Modifications: Record all DTG modifications, including start/stop dates, initial doses, participant-initiated and/or protocol-mandated modifications, inadvertent and deliberate interruptions of more than 2 days, at each visit. Record any permanent discontinuation of treatment.
- Other ART Drugs: All modifications to ART including start/stop dates, initial doses, participant-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation of ART will be recorded at each visit. Participant-initiated interruptions include both inadvertent and deliberate interruptions of any ART. Treatment interruption is failure for any cause to take ART for more than 72 hours.

Concomitant Medications

Medications started or stopped since the last study visit must be recorded on the CRF, including actual or estimated start dates and stop dates. Alternative and complementary medications will be recorded as yes/no on the CRF.

6.3.4   Laboratory Evaluations

At screening and entry, all laboratory values that occurred within 60 day of entry, unless otherwise specified, must be recorded. Laboratories must be a network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs. For post-entry assessments, report all Grade ≥3 laboratory values, unless otherwise specified. All laboratory toxicities that led to a change in BDQ, DLM, and/or DTG, regardless of grade, must be recorded. Further evaluation will be required for those events that meet EAE or ICH reporting requirements. **Record abnormal laboratory findings as per section 7.1**.

Hematology

Complete blood count **(CBC)**, to include hemoglobin, platelets, white count, and neutrophil count will be performed. If INR is tested, record Grade ≥2.

Liver Function Tests
AST, ALT, albumin, total bilirubin, and ALP.

Blood Chemistry
The following will be tested in the chemistry evaluation: lipase, creatinine kinase, glucose, electrolytes (potassium, magnesium, calcium), and creatinine.

Hepatitis B Surface Antigen
This test will be performed at screening.

Hepatitis C Antibodies
This test will be performed at screening.

Thyroid stimulating hormone (TSH)
This test will be performed at entry and week 12.

Pregnancy Test
For women with reproductive potential: Screening test must be serum. For later time points, serum or urine β-HCG may be used; urine test must have a sensitivity of 15-25 mIU/mL. **For HIV-infected women of reproductive potential receiving dolutegravir, pregnancy testing will be performed at screening and every two weeks during the first 24 weeks (weeks 2-24). At the end of study TB drug treatment (bedaquiline and/or delamanid, week 24), women of reproductive potential may elect to remain on dolutegravir, provided they agree to adhere to protocol contraception requirements as described in Note C of section 4.1.8. In this case, pregnancy testing will be performed at all subsequent study visits. Participants may also choose to switch to efavirenz-based antiretroviral therapy, in which case pregnancy testing frequency will be unchanged, i.e., performed as clinically indicated.** For pregnancy on study, refer to section 7.3. **Note that women who become pregnant will be discontinued from study medications and will be followed through the end of the study period. Pregnancy outcome will be recorded per section 7.3, and pregnancies will be reported to the Antiretroviral Pregnancy Registry. Referral to obstetrical care will be made by the study team for any on-study pregnancies that occur.**

Urinalysis
A dipstick urinalysis will be performed to assess proteinuria and hematuria.

6.3.5   Virologic Studies

HIV-1 Viral Load (HIV-positive participants)
This test is required only at screening for participants who have been on ART for ≥6 months. For these participants, if the screening test is done within 14 days prior to entry, it does not need to be repeated at entry. For all other participants

and/or time points, refer to the **SOE**. Quantitations must be performed at a DAIDS-approved laboratory in real time using a licensed assay.

HIV-1 Genotype (HIV-positive participants)
Genotypic-resistance testing will be performed at screening for participants who have been on ART for ≥6 months and have a screening HIV-1 viral load >500 copies/mL. The test must be performed at an ACTG regional genotyping laboratory.

6.3.6   Immunologic Studies

CD4+ (HIV-positive participants)
Obtain absolute CD4+ count within 60 days prior to entry and as per section 6.1a. CD4s should be performed by a laboratory certified for protocol testing by the DAIDS Immunology Quality Assurance (IQA) Program. Screening CD4+ count does not need to be reported on a CRF.

6.3.7   TB Diagnostics and Microbiology

Sputum Acid-Fast Bacilli (AFB) Smear and Culture
At screening, entry, and weeks 2 and 4 during the intervention phase, and at week 48 and week 128 (or premature discontinuation), two sputum samples will be collected for sputum AFB smear and culture in liquid medium. At weeks 8 and 24, three sputum samples will be collected for sputum AFB smear and culture; at all other visits indicated in the **SOE**, one sputum sample will be collected for AFB smear and culture. For all cultures demonstrating growth of AFB, species will be identified to at least the level of MTB complex versus non-tuberculous mycobacteria. One sputum sample will be collected and stored for TDS (see below) at each of the following eight visits: screening; entry; weeks 2, 4, 8, 24, 48, and 128 (or premature discontinuation). Isolates of MTB from positive cultures will be stored. Refer to the A5343 Manual of Procedures (MOPS) for sputum collection and laboratory procedure details.

Drug Susceptibility Testing (DST)
For each participant, the first study isolate of *M. tuberculosis* will have culture-based phenotypic DST performed at the study site-designated laboratory for INH, RIF, fluoroquinolone, and aminoglycoside resistance. In addition, phenotypic DST should be performed for any MTB isolates obtained at or after the week 16 study visit. For each participant, all isolates cultured from sputum should be stored frozen; in the event of participant relapse, DST will be performed for the last isolate collected prior to culture conversion. Refer to the A5343 MOPS for laboratory procedure details.

Note that MDR or RR-TB diagnosis for purposes of meeting inclusion criterion at time of screening can be from a study testing laboratory or from an outside laboratory, as long as it is from a sputum sample collected within 60 days prior to entry (see sections 4.1.2 and 4.1.3).

Chest X-Ray
The chest x-ray will be posterior-anterior. Extent of disease and cavitation status will be documented.

TDS
We will use SMOR analysis, a novel TDS approach, to identify microbes resistant to DLM, BDQ, and all background regimen drugs representing ≥0.1% of a microbial community in longitudinal fashion [54].

Given storage and batched analysis (i.e., quarterly), and the unknown nature and significance of small microbial-resistant subpopulations, SMOR results will not be used for clinical management in real time. TDS will be accompanied (preceded) by culture techniques enriched with resuscitation promoting factors at sites able to perform these cultures within 2 days of collection. One sputum sample at each of these eight visits (i.e., screening, entry, weeks 2, 4, 8, 24, 48, and 128 [or premature discontinuation] will be collected and stored for TDS). TDS will be done on the sputum specimen itself without a culture step; if a culture isolate is available (i.e., from the prior specimens sent for culture), deep sequencing will be done on the culture isolate as well for comparison.

The final sputum specimen at each time point will be collected for TDS. For example, if there are three sputum collections, one sample will be stored for deep sequencing and the other two samples will be stored for culture. If a participant cannot produce more than one or two samples at later time points in the study, a sputum specimen will not be collected for TDS so as to not interfere with the secondary endpoints (involving culture conversion) of the trial.

6.3.8   ECG

Resting ECGs will be conducted at the site. Because of the diurnal variation of QT interval, ECGs for each participant should be done at approximately the same time of day throughout the study, before lunch approximately 4-6 hours post-dose (approximate time of maximal concentration, or T_{max}, of study TB drugs).

A screening ECG must be performed within 72 hours prior to entry. At all visits beginning at entry (performed at day -1 or day 0), ECG will be performed in triplicate (collection of three ECGs 5-10 minutes apart). Specific instructions related to ECG procedures are outlined in the MOPs available on the protocol-specific website. On days where ECG testing and PK testing are scheduled, the participant should have ECGs performed followed immediately by PK sampling.

(To minimize the variability in QT intervals, ECG trace data are also automatically transmitted to the central or core ECG laboratory for determination of QT interval. Statistical analyses to address study objectives will use ECG data as determined at the core ECG laboratory.)

For participants who discontinue moxifloxacin and/or clofazimine prior to study entry, the entry (performed at day -1 or day 0) ECG results must be obtained at least 72 hours after the last dose of moxifloxacin and 7 days after the last dose of clofazimine, and prior to initiation of study TB drug(s).

6.3.9   Pharmacokinetic Studies

See section 10.0, Pharmacology Plan. Details for intensive PK and sparse PK sampling are in section 10.2.2. For participants on Arms 1 and 3, intensive and sparse PK visits should be scheduled for a day when a BDQ dose is due to be taken. Blood samples for study TB drug concentrations may be collected from an indwelling catheter; if a catheter cannot be placed or maintained successfully or if a single sample is being collected for sparse PK, direct venipuncture will be used.

On the days there is intensive PK sampling, a standardized meal will be provided (see MOPs for details.)

Plasma PK samples from PK sampling days will also be stored for measurement of companion drugs should this be of future scientific interest.

6.3.10 **Pre-assessments for Optional LP**

Participants who agree to an LP will first undergo assessments to ensure that the procedure will be appropriate for them. The assessment visit should be done at the week 7 visit (for the week 8 LP), and/or at the week 22 visit (for the week 24 LP). The assessments will include the following:
- **Medical history (including for history of bleeding diathesis, known presence of cerebral lesion)**
- **CBC/INR**

Evaluation of the Assessments
Participants with any of the following will not be considered for the LP:
- **Platelet count <100/mm^3**
- **INR >1.4 times the ULN**
- **History of any allergies to anesthetics**
- **Suspected raised intracranial pressure**
- **Current diagnosis of multiple sclerosis**
- **Current diagnosis of active CNS infection such as fungal meningitis or progressive multifocal leukoencephalopathy (PML), which could alter CNS/CSF inflammatory measures**
- **Known presence of intracerebral mass lesion that is judged by the site investigator to affect the safety of a LP**
- **History of bleeding diathesis**
- **Current use of anticoagulant medications (e.g., anticoagulation dose warfarin, enoxaparin [Lovenox], heparin, dabigatran [Pradaxa],**

apixaban [Eliquis], rivaroxaban [Xarelto], and edoxaban. Use of aspirin or clopidogrel [Plavix] is acceptable. Low-dose lovenox or heparin for deep venous thrombosis prophylaxis is also acceptable.)

- **Any other known contraindication to LP that, in the opinion of the investigator, would preclude safe participation in this nested study.**

NOTE: If the participant is unable to participate given the results of the pre-LP assessments conducted at week 7, then the above assessments will need to be repeated at the week 22 visit, and the LP must be done at week 24 if the participant qualifies.

6.3.11 Optional LP for Protocol-related Research

An LP will be performed at weeks 8 or 24 in up to 16 participants who agree to this procedure for measuring concentrations of delamanid and/or bedaquiline in CSF as outlined in Appendix I.

The A5343 Laboratory Processing Chart (LPC), located on the A5343 PSWP, describes the specific procedures for the collection and storage of these specimens.

NOTE A: Participants currently enrolled under Version 3.0 who have not yet completed week 22, and new participants enrolling into Version 4.0 can opt to have the LP done. Participants currently enrolled under Version 3.0 will need to re-consent to Version 4.0 in order to be approached regarding the LP. Reconsent for participants currently enrolled under Version 3.0, as well as the additional consent for the optional LP, may be performed at any visit prior to and including week 22. Participants currently enrolled under Version 3.0 who have completed week 22 will not be approached to participant in the nested study and will not undergo reconsent for version 4.0 of the protocol.

NOTE B: If a participant consents to undergo the optional LP but does not meet requirements of the pre-LP assessments, or withdraws consent prior to the LP, the participant will not be included in this nested study and will be replaced within this nested study.

6.3.12 Hair Sampling

Hair collection will be performed for measurement of DLM, BDQ, and/or MBT drugs (levofloxacin, kanamycin, etc.) over the course of the study to assess long-term drug exposures (see section 10.2.3).

6.3.1**3** Stored Whole Blood

A whole blood sample will be collected and stored for future pharmacogenomics analyses.

6.3.1**4** Adherence Assessment/ Directly Observed Therapy (DOT)

Study staff or others approved by the study staff will provide DOT for the morning study drug doses as follows:

Arm 1: BDQ 7 days per week for 2 weeks, followed by 3 days per week for 22 weeks.

Arms 2 and 3: DLM 7 days per week for 2 weeks, followed by 5 days per week for 22 weeks

Note that only the doses listed above must be given via DOT during the first 24 weeks of the study. All other doses do not require DOT.

During weeks 25–96, study DOT supporters or others approved by the study staff will provide twice-weekly support to participants to ensure they continue with background MDR-TB, RR-TB and, where appropriate, HIV treatment and remain engaged with the study. In addition, participants will receive extensive counseling, pill boxes, and adherence cards for study TB drugs. Pill count for study TB drugs (BDQ and DLM only) will be recorded on a CRF.

7.0   CLINICAL MANAGEMENT ISSUES

Except for QTcF interval, A5343 will use the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, as a guideline for grading toxicities.

This section provides guidelines for management of specific toxicities related to study TB drugs (BDQ and DLM) as well as TB drugs that are likely to be part of MBT, such as ethionamide (or prothionamide), levofloxacin, terizidone, high-dose INH, pyrazinamide, and/or kanamycin (or amikacin or capreomycin). It also provides guidelines for management of potential toxicities related to DTG. It also provides guidelines for the management of pregnancy. For any other AEs not discussed in section 7.1, follow toxicity management instructions in section 7.2.

Every attempt should be made to continue to follow participants who discontinue study drugs because of a Grade 3 or 4 AE until resolution of AE can be documented and through week 128 of the study.

The A5343 Clinical Management Committee (CMC) is available to discuss toxicity management of study drugs with investigators. The A5343 CMC consists of the A5343 protocol chairs, statisticians, DAIDS medical officers, DAIDS pharmacist, data managers, clinical trials specialist, and other protocol team members selected by the A5343 protocol chairs.

7.1   Specific Management of Toxicities Related to Study-Provided Drugs or MBT

7.1.1   QTcF Prolongation

Participants in this trial will be receiving at least one agent (BDQ, DLM, or both) that has the potential to prolong the QTcF interval. Grading will be based on the average of triplicate ECGs at each visit. Grading will be as follows:

Grade 1	Grade 2	Grade 3	Grade 4
(1) Absolute QTcF >480 and ≤500 ms and QTcF change from baseline >0 ms and ≤30 ms; or	(1) Absolute QTcF >480 ms and ≤500 ms and QTcF change from baseline >30 ms and ≤ 60 ms; or	1) Absolute QTcF >500 ms; or	Life-threatening consequence, e.g., torsades de pointes or other associated serious ventricular dysrhythmia.
(2) absolute QTcF ≤480 ms and QTcF change from baseline >30 and ≤60 ms	(2) absolute QTcF ≤480 and QTcF change from baseline >60 ms.	(2) absolute QTcF >480 and QTcF change from baseline >60 ms.	

If Grade 2 QTc prolongation develops during the course of study treatment, the participant will be monitored more closely, with once weekly ECG testing, and correction of electrolytes where necessary. If Grade 3 QTc prolongation occurs, study TB drugs and levofloxacin will be discontinued and the participant will be hospitalized for monitoring until the abnormality returns to Grade 2 or lower. Electrolytes will be checked and repleted where necessary. Repeat ECG following repletion of electrolytes should be performed, and if QTcF reading is a Grade ≤2, study TB drugs may be restarted, at the discretion of the investigator. If Grade 3 finding remains, study TB drugs will be permanently discontinued.

For a Grade 4 event, the participant will be hospitalized and discontinued permanently from study TB medications. The participant will be referred to the NTP for treatment of his or her MDR or RR-TB according to local standards of care. The participant will continue to be followed on study, off study drugs.

The immediate clinical management of participants should be based on the site's interpretation of the ECG, unless a report from Quintiles is available. Sites should report the following events to the study team and to DAIDS immediately: (1) Grade 4 QT prolongations, (2) deaths, and (3) results of repeated ECGs after holding study TB drug for a Grade 3.

7.1.2 ALT or Bilirubin Elevation

Many anti-TB drugs including the study TB drugs and components of MBT can cause alterations in liver function tests. Participants entering this trial will have active TB. Elevation in liver function tests is not unexpected. Concomitant illnesses, including HIV infection, and other medications, such as ART, including DTG, may also alter these laboratory parameters. Therefore, changes in liver function enzymes or ALT should be evaluated within the clinical context of the abnormalities. LFTs will be checked regularly for all study participants, as per the **SOE**. All participants who have new Grade ≥3 elevation of ALT should be evaluated for hepatitis B and C virus infection and have an INR checked.

For participants with normal or Grade 1 LFTs at entry who develop asymptomatic or symptomatic Grade 3 elevations during study treatment, study TB drugs and MBT (and DTG, where applicable) should be discontinued for up to a week and held until levels and symptoms are Grade ≤2, at which time therapy may be reintroduced. For participants entering the study with a Grade 2 elevation, they will be allowed to continue on study drugs unless they are symptomatic or the investigators feel it is unsafe for the participant to continue the medication. If Grade 3 toxicity develops after re-introduction of the study medications or if the Grade 3 toxicity does not resolve within 14 days, then the participant will be discontinued from study medications and referred to the National TB Program (NTP) for treatment of their MDR or RR-TB according to local standards of care and, where applicable, to the local HIV clinic. The participant will continue to be followed on study, off study drugs. All medications may be restarted if the laboratory abnormalities were thought secondary to a concomitant illness. Study TB drugs (but not DTG) can be restarted if there has been documented acute viral hepatitis and the ALT or bilirubin take longer than 14 days to reach Grade ≤2 toxicity.

Study TB drugs and study ART will be permanently discontinued if any of the following liver chemistry criteria are met: (1) ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin; bilirubin fractionation required) (2) ALT ≥3 × ULN with symptoms of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR (3) Grade 4 elevation of ALT or direct bilirubin.

Participants permanently discontinued from study TB drugs will be referred to the NTP for treatment of his or her MDR or RR-TB according to local standards of care. The participant will continue to be followed on study, off study drugs for the duration of the study treatment (24 weeks). Similarly, participants permanently discontinued from DTG will be referred to the HIV clinic for HIV treatment according to local standards of care.

In consultation with the core team, careful assessments should be done to rule out the use of alcohol, non-study medication-related toxicity, or viral hepatitis (including viral hepatitis complicated by immune reconstitution inflammatory

syndrome) as the cause for any liver toxicity that warrants permanent study drug discontinuation based on the liver stopping criteria specified above. Evaluations to be considered (but are not required) include:

- Viral hepatitis serology including: Hepatitis A IgM antibody; Hepatitis B Surface Antigen (HBsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test);
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH);
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging to evaluate liver disease.

7.1.3   Allergic reaction

Participants may continue study drugs for Grade 1 or 2 allergic reactions at the discretion of the study investigator. The participant should be advised to contact the study team immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to a study drug should permanently discontinue that study drug. Participants should be treated as clinically appropriate and followed until resolution of the AE. These participants will remain on-study until the completion of study follow-up.

7.1.4   Hearing loss

Hearing tests are to be done according to local National Program guidelines to assess for harmful effects of injectable anti-TB medications.

Ototoxicity hearing loss occurs if there is:
- 20dB decrease at any one frequency
- 10dB decrease at any two adjacent frequencies
- Loss of response at three consecutive test frequencies where responses were previously obtained

If there is any hearing loss prior to treatment and worsening of the grade of hearing by one grade, the injectable (kanamycin, capreomycin, or amikacin) should be stopped. If hearing was normal at the time of treatment initiation and Grade ≥2 hearing loss develops on-study, the injectable should be stopped.

7.1.5   Neutropenia

Participants entering this trial will have active TB and some will have HIV infection. Neutropenia is common. Zidovudine has also been associated with bone marrow suppression and may cause neutropenia.

If a participant develops Grade 3 or Grade 4 neutropenia and is on zidovudine, he or she will have his or her zidovudine discontinued and another effective NRTI will be added to the ART regimen, in collaboration with the participant's HIV care provider. If the Grade 3 or 4 abnormality continues after 2 weeks off of zidovudine, the study treatment plus MBT should be discontinued and held for up to 14 days until levels and symptoms are Grade ≤ 2, at which time therapy may be reintroduced. If Grade 3 toxicity develops after re-introduction of the study medication or if the Grade 3 toxicity does not resolve within 14 days, then the participant will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB according to local standards of care.

If a participant enters the study with Grade 2 neutropenia, he or she will be allowed to continue on the study regimen if he or she develops a Grade 3 neutropenia, unless he or she is symptomatic or the investigators feel it is unsafe for the participant to continue the medication.

If a participant not taking zidovudine develops Grade 4 neutropenia, he or she will be permanently discontinued from the study medications and referred to the National Tuberculosis Program (NTP) for treatment of his or her MDR or RR-TB according to local standards of care. The participant will continue to be followed on study, off study drugs.

All participants experiencing any grade of neutropenia will have their CBC with differential counts checked weekly.

7.1.6   Thrombocytopenia

Participants entering this trial will potentially have active TB and some will have HIV infection. Thrombocytopenia is expected. Zidovudine and linezolid have also been associated with bone marrow suppression and may cause thrombocytopenia; a minority of participants in this trial may be receiving one of these medications.

If a participant who is not taking zidovudine or linezolid develops Grade 3 or Grade 4 thrombocytopenia and is on zidovudine or linezolid, he or she will have his or her zidovudine or linezolid discontinued. Another effective NRTI will be added to the ART regimen to replace zidovudine. If the Grade 3 or 4 elevation continues after 2 weeks off of zidovudine or linezolid, the study regimen should be held for up to 14 days until levels and symptoms are Grade ≤ 2, at which time therapy may be reintroduced. If Grade 3 toxicity develops after re-introduction of

the study medication or if the Grade 3 toxicity does not resolve within 14 days, then the participant will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB according to local standards of care. For **participants** entering the study with a Grade 2 thrombocytopenia, they will be allowed to continue on study drug if they develop a Grade 3 abnormality unless they are symptomatic or the investigators feel it is unsafe for the patient to continue the medication.

If a participant enters the study with Grade 2 thrombocytopenia, he or she will be allowed to continue on the study regimen if he or she develops a Grade 3 thrombocytopenia, as long as the local investigators deem it is safe for the participant to continue.

If a participant develops Grade 4 thrombocytopenia, he or she will be discontinued from the study medications and referred to the NTP for treatment of his or her MDR or RR-TB according to local standards of care. The participant will continue to be followed on study, off study drugs.

All participants experiencing any grade of thrombocytopenia will have their CBC checked weekly.

7.1.7   Anemia

If any participants develop Grade 3 or Grade 4 low hemoglobin value and is on zidovudine or linezolid, they will have their zidovudine or linezolid discontinued and another effective NRTI will be added to the ART regimen. If the Grade 3 or 4 elevation continues after 2 weeks off of zidovudine or linezolid, the study regimen should be held for up to 14 days until levels and symptoms are Grade ≤2, at which time therapy may be reintroduced. If Grade 3 toxicity develops after re-introduction of the study medication or if the Grade 3 toxicity does not resolve within 14 days, then the participants will continue to be followed on study, but will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB according to local standards of care.

For participants entering the study with a Grade 2 low hemoglobin, they will be allowed to continue on study drug if they develop a Grade 3 abnormality unless they are symptomatic or the investigators feel it is unsafe for the participant to continue the medication.

7.1.8   Severe Rash/Cutaneous Reaction

Moderate to severe rash potentially related to drug hypersensitivity may occur with any of the study provided TB drugs as well as other drugs the participants may be taking. In addition, mild to moderate rash is an expected adverse reaction for DTG; rash episodes related to DTG generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy, and tend to resolve within two to three weeks. The index case of hypersensitivity

with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported for DTG in clinical trials. It may not be possible to determine which, if any, of the study drugs is the cause.

Participants with a Grade 1 rash may continue study drugs at the study investigator's discretion. Participants should be advised to contact the study team immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Participants may continue study drugs for an isolated Grade 2 rash. However, study drugs (and all other concurrent medications suspected in the investigator's causality assessment) should be permanently discontinued for any Grade ≥3 rash or for any Grade ≥2 rash that is associated with any of the following: increase in ALT, Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity: fever, generalized malaise or fatigue, muscle or joint aches, blisters, oral lesions, eye inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver abnormalities (e.g., jaundice, dark or tea colored urine, pale colored stools/bowel movements, nausea, vomiting, loss of appetite, or right upper quadrant abdominal pain). If the etiology of the rash can be definitely diagnosed as being unrelated to study drugs and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

Participants taken off study drug for rash will be referred to the NTP and the local HIV clinic for MDR or RR-TB and HIV treatment, according to local standards of care. The participant will continue to be followed on study, off study drugs.

7.1.9   Nausea and/or Vomiting

Although common, nausea and/or vomiting following initiation of therapy with the study medications and/or ARV medications usually subsides or resolves during the first few weeks of treatment. For some patients, nausea can persist for a long period of time, largely owing to ethionamide or prothionamide.

Steps in the management of nausea include taking the medication with food and administration of antiemetic or splitting the ethionamide dose. Antiemetics can only be used if they do not have drug-drug interactions with the study drugs and if they do not have overlapping toxicities with study drugs. Participants with vomiting should have their hydration status assessed daily and given volume resuscitation if clinically indicated depending on site-specific standard practices.

Participants with Grade 3 or 4 nausea and/or vomiting can have their study medications held for up to 14 days until they are at Grade ≤2. If they do not reach

Grade ≤2 within 14 days or if Grade 3 or 4 nausea and/or vomiting occur after reintroduction, then the participant will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB and the local HIV clinic for treatment of their HIV infection according to local standards of care. The participant will continue to be followed on study, off study drugs.

7.1.10 Diarrhea

Diarrhea is a common side effect of infection and medication toxicity. If no infectious cause of diarrhea is found and onset is temporally related to new medication, symptomatic management with antidiarrheal agents is appropriate. Antidiarrheals (e.g., loperamide) can only be used if they do not have clinically significant drug-drug interactions with the study drugs and if they do not have overlapping toxicities with study drugs. Participants with diarrhea should have their hydration status assessed daily and given volume resuscitation if clinically indicated depending on site-specific standard practices.

Participants with Grade 3 or 4 diarrhea can have their study medications held for up to 14 days until they are at Grade ≤2. If they do not reach Grade ≤2 within 14 days or if Grade 3 or 4 diarrhea occur after reintroduction, then the participant will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB and to the local HIV clinic for HIV treatment according to local standards of care. He or she will be followed on study but off study drugs.

7.1.11 Peripheral Neuropathy

INH and ethionamide have both been associated with the development of peripheral neuropathy. If any participants develop new or worsening Grade 1 or 2 neuropathy during the course of the study, they will continue on INH/ethionamide, undergo investigation for treatable causes of the impairment (e.g., glucose, vitamin B12 levels), be treated symptomatically according to local standards, and given pyridoxine 100 mg daily. If the participants develop new or worsening Grade 3 or 4 peripheral neuropathy, INH/ethionamide will be temporarily discontinued, while receiving symptomatic treatment and pyridoxine 100 mg daily. If they do not have stabilization or improvement of symptoms after 14 days, then INH/ethionamide will not be restarted.

7.1.12 Arthritis/Arthralgia

Arthritis and arthralgias are common symptoms experienced by patients on pyrazinamide. Since continuation on pyrazinamide is not an essential part of the study regimen, this is the one instance where it may be acceptable to temporarily or permanently discontinue pyrazinamide, if this agent is felt to be the likely cause of the symptoms. If the symptoms resolve within 14 days when pyrazinamide is discontinued or continued at a lower dose, then the other drugs

in the regimen may be continued and the participant will not be classified as having been intolerant of the regimen.

If any participants develop Grade 1, 2 or 3 arthritis or arthralgia during the course of the study, they will continue on study drugs and treated symptomatically according to local standards. If they develop Grade 4 arthritis or arthralgia, they will be discontinued from pyrazinamide for up to 14 days until they are at Grade ≤2. If they do not reach Grade <2 within 14 days, then these participants will be discontinued from study medications and referred to the NTP for treatment of their MDR or RR-TB according to local standards of care and followed on study but off study drugs. If they reach Grade <2 within 14 days but Grade 4 arthritis or arthralgia occur after reintroduction of pyrazinamide, then pyrazinamide will be permanently stopped but the participants may remain on study drugs.

7.1.13 Neuropsychiatric Symptoms

Terizidone or cycloserine have been commonly associated with development of neuropsychiatric side effects. Fluoroquinolones and high-dose INH are less commonly associated with neuropsychiatric side effects.

If any participants develop Grade ≥2 neuropsychiatric side effects during the course of the study, consideration may be given to holding or stopping terizidone or cycloserine for 2 weeks. Should symptoms worsen or fail to resolve, consideration could be given to discontinuation or substitution of fluoroquinolones or INH. If Grade 4 symptoms fail to resolve after discontinuation for fluoroquinolones, then study drugs should be discontinued until symptoms resolve.

7.1.14 Serum creatinine

All participants experiencing Grade ≥1 serum creatinine elevation will have their creatinine checked weekly. These participants will have their injectable medication interrupted until creatinine normalizes.

7.1.15 Suicidal Ideation

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is

recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

If the participant expresses suicidal ideations or intents, the data will be captured as AEs. Any suicide thought or attempt that qualifies as an EAE will be reported using the standard EAE mechanism.

7.1.16 Ophthalmologic toxicity

Ophthalmologic toxicity can occur with ethambutol treatment. Participants who develop new visual symptoms or decreased visual acuity will have ethambutol stopped and be referred for ophthalmological examination.

7.2   Toxicity Management – Other

This section describes the toxicity management plan for toxicities not described in 7.1, using DAIDS grading.

Grade 1 or 2
Participants who develop a Grade 1 or 2 AE or toxicity may continue study drugs without dose adjustment. Participants experiencing Grade 1 or 2 toxicities will be managed at the discretion of the site investigator. Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia) should be corrected and rechecked.

Grade 3
If there is compelling evidence that the AE has NOT been caused by the study drugs, dosing may continue at the discretion of the site investigator/clinician. Except as stated in the above sections, participants who develop a Grade 3 AE or toxicity thought to be secondary to study drugs or of unknown etiology will have study drugs withheld. MBT drugs may also need to be held. Investigators will discuss toxicity management with the A5343 CMC and study drugs and/or MBT may be restarted, depending on the clinical situation; such decisions will be made on a case-by-case basis after consultation with the CMC. The participant should be reevaluated weekly if at all possible until the AE returns to Grade $\leq$2 or until stabilized and no longer in need of such frequent monitoring. Participants developing Grade 3 toxicity felt to be due to study drugs that does not resolve within 14 days will be discontinued from the study medications and referred to the NTP for treatment of MDR or RR-TB according to local standards of care. They will continue to be followed on-study, off study drugs.

Grade 4
Participants who develop a Grade 4 AE or toxicity, not specifically addressed above, will have all medications withheld and should be reevaluated weekly if at all possible until the AE returns to Grade $\leq$2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator. If the AE resolves and the site investigator has compelling evidence that the toxicity is NOT related to the study medications, they may be restarted.

If study drugs are permanently discontinued due to a toxicity, then the participant should continue to be followed on study and referred to the NTP for management of their MDR or RR-TB according to local standards of care.

7.3   Pregnancy

If a participant becomes pregnant during the study, she will be discontinued from study medications and referred to the NTP for treatment of her MDR or RR-TB according to local standards of care and to a prenatal care program for management of her pregnancy according to local standards of care. HIV-positive women be referred to their local HIV clinic for appropriate care. She will be followed through the end of the study period. At the end of the pregnancy, the outcome and AEs for the participant and the infant will be recorded on an outcome CRF.

If a female participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on a CRF at the end of the pregnancy.

Pregnancies that occur on study among women taking ART should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Fax: 44-1628-789-666 or 910-246-0637; Phone: 910-679-1598.

7.4   Expected Toxicities of MBT Drugs

Drug AEs can range from minor side effects, toxic reactions, hypersensitivity reactions or idiosyncratic reactions. Since patients with MDR or RR-TB receive combination chemotherapy, it is often difficult to determine which drug is the source of the undesired effect. Some AEs present soon after treatment is initiated while others tend to manifest later. Some of the AEs to second-line anti-TB drugs are described below.

Table: Common **A**dverse **E**ffects of **S**econd-line **D**rugs

Drug	Adverse effects
Ethionamide or prothionamide	Gastrointestinal disturbance, hepatitis. Hypothyroidism: tends to be a late effect and symptoms can be subtle Rarely causes peripheral neuropathy
Terizidone or cycloserine	Neurological and psychiatric disturbances: headache, irritability, depression, psychosis, seizures, suicidal ideation Peripheral neuropathy: presents as paraesthesia such as tingling and numbness, starting at the feet and spreads proximally. May be accompanied by myalgia, weakness and ataxia.
Kanamycin, amikacin, capreomycin	Pain at injection site

Drug	Adverse effects
	Electrolyte wasting is often asymptomatic, patients may complain of cramps or palpitations; hypokalaemia and hypomagnesaemia, may occur early or late in treatment Nephrotoxicity - this adverse effect is common, occult in onset and can be fatal Ototoxicity: impaired hearing or impaired balance is almost always due to the injectable agents. May be dose-dependent. Peripheral neuropathy
Levofloxacin	Generally well tolerated, occasional gastrointestinal disturbance, joint pain. Prolongation of the QT interval, minimal if any. Infrequently causes seizures and psychosis.
High-dose isoniazid	Gastrointestinal intolerance Moderate rises in serum transaminase concentrations are common. Severe hepatotoxicity is rare. Peripheral neuropathy
Clofazimine	Skin discoloration Ichthyosis
Ethambutol	Ophthalmologic toxicity
Pyrazinamide	Arthralgia Gastrointestinal intolerance. Hypersensitivity reactions are rare, but some patients complain of pruritus and slight flushing of the skin. Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare. As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usually occurs, but this is often asymptomatic.
All drugs	Skin rashes - ranging from pruritus to Steven Johnson Syndrome

Source: Adapted from World Health Organisation, 2008 Guidelines.

8.0   CRITERIA FOR DISCONTINUATION

8.1   Permanent and Premature Treatment Discontinuation

- Failure by the participant to attend three consecutive study visits.
- Protocol-defined drug-related toxicity (see section 7.0 Toxicity).
- Requirement for prohibited concomitant medications (see section 5.4.2).
- Pregnancy or breast-feeding.

- Request by participant to terminate treatment.
- Clinical reasons believed life threatening by the physician, even if not addressed in the toxicity section of the protocol.

8.2   Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the IRB/Ethics Committee, Food and Drug Administration (FDA), NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

9.0   STATISTICAL CONSIDERATIONS

9.1   General Design Issues

ACTG A5343 is a randomized, open-label, three-arm trial of the safety of and drug-drug interactions between co-administered bedaquiline (BDQ) and delamanid (DLM), when added to multidrug background treatment (MBT) for infection with drug-resistant TB (DR-TB). The study is 128 weeks in duration (24 weeks of treatment with BDQ and/or DLM, then 104 weeks of follow-up). **Protocol versions 1.0-3.0 required that participants be hospitalized for at least the first 2 months of DR-TB treatment. Following an interim review conducted in October 2017, the SMC determined that 2 weeks of hospitalization was sufficient.**

Participants will be randomized to one of three arms. Arm 1 participants will receive BDQ 400 mg QD for two weeks followed by 200 mg thrice weekly for 22 weeks. Arm 2 participants will receive DLM 100 mg BID for 24 weeks. Arm 3 participants will receive both BDQ and DLM (same dose amounts and duration as in Arms 1 and 2). Participants with HIV-1 infection may enter the study provided their CD4 count is ≥100 cells/mm^3. Randomization will be stratified by HIV status, with balancing by institution. The total accrual target is 84, or 28 participants per arm, which is anticipated to yield 25 participants per arm who are evaluable for the primary endpoints. **An interim analysis will be conducted when week 24 QT data is available for at least 12 participants on the BDQ+DLM arm, to assess QT prolongations and to evaluate the observed precision on primary outcome estimates.**

Among anti-TB drugs, BDQ and DLM exhibit novel and distinct mechanisms of action; thus their combined use holds promise for the treatment of DR-TB. There is hope that, in the treatment of DR-TB, they may displace older drugs associated with significant toxicities. However, independently BDQ and DLM have each been associated with prolongations in Fridericia-adjusted QT intervals (QTcF) of 12-15 ms. The study team seeks: (a) to estimate the combined effects of these two drugs (with MBT) on QT prolongation (QTcF increases from baseline; Arm 3 participants), and (b) to compare the combined effects of these two drugs (with MBT) on QT prolongation in Arm 3

participants to QT prolongations seen with BDQ or DLM alone (also with MBT; Arms 1 and 2, respectively).

The rationale for the choice of QT prolongation (change from baseline in QTcF duration) as the outcome measure (in contrast to a categorical or binary outcome, e.g., absolute QTc >500 ms) is two-fold: (1) the ICH guidance document identifies analyses of central tendency in QTc duration changes from baseline as the primary analysis to be used in assessing the proarrhythmic potential for non-antiarrhythmic drugs (with occurrence of absolute QTc intervals above specific thresholds to be used as a secondary measure, and to be used in drug discontinuation criteria for the safety of participants in the study) [62], and (2) the continuous measure is more sensitive and provides greater power than a categorical/binary outcome. The power consideration is especially important given the relatively small sample size (which reflects the urgency of identifying treatment options for patients infected with MDR or RR-TB).

QTc prolongation will be measured by changes from baseline in QT intervals (durations) adjusted for heart rate using Fridericia's correction, QTcF. The rationale for using the Fridericia correction is as follows. The duration of the (uncorrected) QT interval typically exhibits an inverse relationship to heart rate (i.e., the duration of the QT interval is proportional to the duration of inter-beat interval). For this reason, when assessing prolongation relative to baseline, the measured QT interval is generally corrected for heart rate. In adults, Bazett's correction ($QTcB = QT/RR^{0.5}$, where RR represents the interbeat interval) tends to overcorrect at elevated heart rates and undercorrect at heart rates below 60 beats per minute. Fridericia's correction ($QTcF = QT/RR^{0.33}$) is thought to be more accurate than Bazett's correction in participants with such altered heart rates.

Primary objectives 1 and 2 will be addressed via estimation of arm-specific QTcF values at baseline (week 0) and on-treatment (weeks 8-24) and estimation of changes from baseline; a mixed-effects analysis of variance (ANOVA) model will be used for this estimation.

Secondary objectives include: (a) estimation of arm-specific proportions of participants who exhibit QTcF above 500 ms at any time during administration of study TB drug(s) when not present at baseline, (b) estimation of arm-specific proportions of participants with a QTcF increase from baseline of more than 60 ms at any time during administration of study TB drug(s), (c) description of visit- (week-) specific QTcF changes by study arm, (d) assessment of drug-drug interactions, and (e) description of arm-specific safety and tolerability.

Exploratory objectives include PK/PD modeling that incorporates concurrent: (a) concentrations of BDQ, DLM and their metabolites and (b) QTcF. Models may include external data. PK/PD modeling can provide additional sensitivity to address these objectives, and can provide results with greater clinical applicability (e.g., by providing thresholds for PK parameters above which clinically significant QT prolongations are likely). Another exploratory objective is to estimate arm-specific proportions of participants exhibiting TB culture conversion at 8 and 24 weeks, and to estimate time-to-conversion over the first 24 weeks of study treatment, although given the sample sizes in

each arm, treatment efficacy estimates will be imprecise and used for description purposes. Systemic exposure to BDQ, DLM and other TB drugs, as measured via PK assay of hair samples, will be described. Among participants with concurrent HIV infection who initiate DTG as part of their ART regimen within ±4 weeks of study entry, the following proportions will be estimated: (1) with suppressed HIV-1 viral load below 50 c/mL at weeks 24 (±6) and 48 (±6) (after study entry), (2) discontinuing DTG prior to week 24, and (3) exhibiting grade 3 or higher signs/symptoms, diagnoses or laboratory values. The proportion of participants with favorable TB outcome at week 128 will be reported, by arm. Relationships between drug concentrations (parent drug and metabolites of BDQ and DLM in plasma and hair) and emergence of drug-resistant subpopulations (at several time points, as characterized by TDS) will be examined.

9.2   Outcome Measures

9.2.1   Primary Outcome Measures

9.2.1.1   Mean baseline QTcF, on-treatment QTcF, and change from baseline in QTcF among participants on each arm, as estimated from a mixed-effects ANOVA model, where participant-specific QTcF measurements from the week 0 visit contribute to estimation of baseline QTcF, and participant-specific QTcF measurements from weeks 8 through 24 contribute to estimation of the on-treatment QTcF.

The rationale for mean QTcF (averaged over visits) as the primary outcome measure is that, given the small sample size, such averaging will improve statistical power. The rationale for choosing weeks 8-24 to contribute to the primary outcome measure is that a long half-life is observed for both study TB drugs. For DLM, both the maximum concentration of DM-6705 (DLM active metabolite) in plasma and the maximum QT effect were observed at week 8. With loading doses, plasma concentrations of BDQ are highest at 2 weeks (2 weeks after the loading dose). Concentrations then drop through about week 4, then exhibit a gradual increase and level off around week 16. For BDQ, the largest mean increase in QT duration was observed at 18 weeks, and differences from baseline of about this magnitude persisted to week 24 (likely due to the long terminal half-lives of BDQ and its active M2 metabolite). It is expected that any additive or larger than additive effect on QT duration of the two drugs combined would be seen after week 8.

If a participant discontinues study TB drug permanently prior to week 24 due to Grade 3 or higher prolongation in QT interval (as defined in Section 7.1), the QTcF value from the participant's last visit will be carried forward to subsequent weeks, under the assumption that if the participant had continued study TB drug(s), the QT prolongation would likely have persisted (if not increased).

If a participant discontinues study drug permanently prior to week 24 for a reason other than Grade 3 or higher prolongation in QT interval, available QTcF values obtained while taking study TB drug will be included but will not be carried forward. (The participant will be considered unevaluable as of the date after the last dose of (either) study TB drug(s).)

For temporary discontinuations of study TB drug: (a) If the discontinuation lasts for 7 or fewer days, the ECG at the next scheduled visit will be performed and the QTcF value from that visit will be used in the analysis. (b) If the discontinuation lasts for 8-14 days, the ECG at the next scheduled visit will be performed and the QTcF value from that visit will be treated as missing.

Visit-specific QTcF values are the average of QTcF values calculated from three separate complexes 5-10 minutes apart, as measured during the study visit. If fewer than three are available, the one or two available QTcF values are used. The rationale for multiple ECGs at a given visit is as follows. Compared to a single QTcF measurement, clinically relevant decreases in ECG variability are seen when the outcome measure is an average of more than one ECG. The most common numbers of QTcF values used in clinical trials are one (no replicates), 3, and 6, and thus reviewers have experience interpreting such. The rationale for measuring QTcF at a single time of day (rather than multiple times of day and averaging hour-specific differences between on-treatment and baseline visits) is as follows: unlike with some drugs that prolong QT, after multiple BDQ and DLM doses, QT readings do not vary appreciably over the dosing interval. For a given participant, we will attempt to measure around the same time of day to control for diurnal variability; however, there is no need to exclude or reschedule ECGs when they are collected at different time of day from a previous visit.

9.2.1.2   Arm-specific mean change from baseline in QTcF among participants on all arms, as estimated from a mixed-effects ANOVA model, where participant-specific QTcF measurements from the week 0 visit contribute to estimation of baseline QTcF, and participant-specific QTcF measurements from the week 8 through week 24 visits contribute to estimation of the on-treatment QTcF, and details of data handling are as given above in 9.2.1.1.

9.2.2   Secondary Outcome Measures

9.2.2.1   Occurrence of absolute QTcF above 500 ms at any time during study treatment when not present at baseline.

9.2.2.2   Occurrence of QTcF change from baseline of more than 60 ms at any time during study treatment.

9.2.2.3 Visit-specific QTcF changes from baseline during study treatment, and at week 28 (4 weeks after discontinuation of study TB drug, in participants who complete 24 weeks of study treatment).

9.2.2.4 Occurrence of each of the following, at any time during study treatment: (a) absolute QTcF >480 and ≤500 ms and (b) QTcF increase from baseline of >30 and ≤60 ms.

9.2.2.5 In Arms 1 and 3, participant-specific PK parameters for BDQ and its metabolite, estimated using noncompartmental methods applied to concentrations from intensive PK sampling visits (weeks 2, 8, and 24). Week 2, 8, and 24 PK parameters will be summarized separately.

9.2.2.6 In Arms 2 and 3, participant-specific PK parameters for DLM and its metabolite, estimated using noncompartmental methods applied to concentrations from intensive PK sampling visits (weeks 2, 8, and 24). Week 2, 8, and 24 PK parameters will be summarized separately.

9.2.2.7 Among participants who take at least one dose of study TB treatment: occurrence of Grade 3 or higher adverse events of any type at any time while on study TB drug (safety); and discontinuation of study TB drug(s) for any reason (tolerability).

9.2.2.8 Among participants who take at least one dose of study TB treatment: occurrence of death at any time while on study TB drug (safety).

9.2.3 Exploratory Outcome Measures

9.2.3.1 Participant-specific on-treatment (medians of visit-specific QTcF measurements from visits at weeks 8-24) and post-treatment (week 28) QTcF changes from baseline and concurrent concentrations of BDQ, its M2 metabolite, DLM and its DM-6705 metabolite.

9.2.3.2 Single early-morning sputum samples collected weekly (after initiation of study treatment) through week 8, every other week through week 12 and every 4 weeks through week 24. (Two samples will be collected at weeks 8 and 24.) These samples will be cultured on liquid medium. Culture conversion at weeks 8 and 24 is declared if both samples for the week have a time-to positivity of ≥ 42 days. (If one of the two specimens is contaminated, the single sample will be used to determine culture conversion.) Time-to-positivity results at all weeks will be used in nonlinear mixed effects modeling as described in 9.6.3.2.

9.2.3.3 Participant-specific hair concentrations for BDQ, DLM and their metabolites, as well as other components of the MBT regimen.

9.2.3.4 Among participants with MDR or RR-TB and HIV co-infection who initiated DTG within ±4 weeks of study entry (as part of their ART regimen), <u>proportion</u> of participants with HIV-1 RNA ≤50 copies/mL at 24 (±6) weeks and 48 (±6) weeks after start of co-treatment.

9.2.3.5 Among participants who receive concurrent dolutegravir-based ART and at least one dose of study treatment, occurrence of Grade 3 or higher AEs of any type at any time while taking dolutegravir-based ART and MDR or RR-TB treatment. Discontinuation of dolutegravir for any reason.

9.2.3.6 Favorable TB outcome at week 128 [6**5**]. A participant is classified as having a favorable outcome if she or he (1) has negative sputum culture via liquid medium from samples collected on at least two of weeks 84, 96, and 128, provided none of these are positive, and (2) has not been classified as having an unfavorable outcome on/before week 128. A participant is classified as having an unfavorable outcome if any of the following occurs: (1) death (from any cause, from the time of first dose of study drug through week 128), (2) treatment failure (the presence of a positive mycobacterial culture from at least one specimen of weeks 84, 96, or 128), (3) treatment discontinuation (discontinuation of study TB drug, for any reason, during weeks 0–24), or (4) recurrence (diagnosis of MDR-, RR-, or XDR-TB on or before week 128 after exhibiting negative cultures via liquid medium on two or more prior occasions, weeks 0–72).

9.2.3.7 Participant- and visit-specific plasma AUCs and hair concentrations of DLM, its DM-6705 metabolite, BDQ, its M2 metabolite, and participant- and visit-specific emergence of drug-resistant subpopulations characterized by TDS.

9.3 Randomization and Stratification

Participants will be randomized, using permuted blocks, with equal probability to Arms 1, 2 and 3. Randomization will be stratified by HIV-1 status, with balancing by institution.

9.4 Sample Size and Accrual

Sample size
Co-primary objectives are to estimate QT prolongation (i.e., changes from baseline in QTcF) for participants taking both BDQ and DLM (Arm 3), and to compare such changes seen for participants in Arm 3 to changes seen on Arms 1 and 2 (BDQ alone and DLM alone, respectively [with MBR]). These objectives will be addressed by fitting a single mixed-effects ANOVA model to baseline and on-treatment QTcF measurements collected from participants on all 3 arms, as described in 9.6.1.1 and 9.6.1.2. Changes

from baseline and differences between arms therein will be represented by estimated contrasts and associated 95% CIs.

The sample size calculations below, however, are based on non-model-based calculations of means and t-based inference. It is recognized that within-participant correlation may increase the variability around estimates of primary outcome measures. Power for the mixed-model contrasts were calculated for several scenarios (not shown). For all scenarios studied, assuming 20 evaluable participants per arm, the resulting power was good (above 95%) to detect a 10 ms difference between QTcF changes on Arm 3 compared (separately) to Arms 1 and 2.

The standard deviations (SDs) of differences (s_{diff}) in QTcF, post-baseline (BL, where baseline refers to measurements taken at entry prior to administration of study TB drug(s); (single week, mean of 3 ECGs measured 5-10 minutes apart) minus BL (single week, mean of 3 ECGs measured 5-10 minutes apart), are 7-10 ms when measured by the core ECG laboratory ERT (personal communication. Dr. Joel Morganroth). (a) Using the formula for the variance of differences, $s_{diff}^2 = s_{BL}^2 + s_{PBL}^2 - 2*\rho*s_{3BL}*s_{3PBL}$ (where s_{3BL} and s_{3PBL} represent the standard deviations of the BL and post-BL QTcF measurements, respectively, when the analysis [outcome] measure is the average of 3 separately reported intervals measured 5-10 minutes apart during a single ECG procedure), and (b) assuming that $s_{3BL} = s_{3PBL}$, and (c) for a range of s_{diff} values and within-subject correlations ("historical rho"), Table 9.1 gives corresponding SDs of QTcF values from a single visit when each QTcF value is based on 3 (s_{3BL}), 2 (s_{2BL}) and 1 (s_{1BL}) QTcF intervals (hereafter, "reads") reported by a central reader. (s_{1BL} is calculated as sqrt(3)*s_{3BL}, and s_{2BL} is calculated as s_{1BL}/sqrt(2), where sqrt denotes square root.)

For example, if the SD of within-subject changes from baseline in QTcF (based on **three** reads at each visit) is 7 ms, and the true within-subject correlation is 0.4, the SD of QTcF at a single visit is 6.4 ms when the QTcF is based on **three** reads, and 11.1 ms when the QTcF is based on a single read. If the SD of within-subject changes from baseline in QTcF (based on 3 reads at each visit) is 10 ms, and the true within-subject correlation is 0.7, then back-calculation to estimate the SD of QTcF at a single visit is 12.9 ms when the QTcF is based on 3 reads, and 22.4 ms when the QTcF is based on a single read. In subsequent tables, to be conservative, values for s_{1BL} of 10 and 20 ms are examined. Values for s_{diff} in the literature are typically in the 9-11 ms range, while a value of 7 ms is likely only for carefully controlled studies. For this reason, in subsequent tables, a value of 20 ms is assumed for s_{1BL} (slightly smaller than 22.4 ms in the last row of Table 9.1).

Table 9.1: Standard **D**eviations (s_{1BL}) in **M**illiseconds (ms) of a **S**ingle QTcF **M**easurement, as a **F**unction of **A**ssumed SD of **D**ifferences (s_{diff}) and **W**ithin-**S**ubject **C**orrelations.

s_{diff}, ms	Historical rho	SD (in ms) of QTcF measured at a single visit, when number of separately reported intervals (separate "reads,") (measured 5-10 minutes apart during a single ECG procedure) is…	
		…3 (s_{3BL})	…1 (s_{1BL})
7	0.4	6.4	11.1

	0.5	7.0	12.1
	0.6	7.8	13.6
	0.7	9.0	15.7
10	0.4	9.1	15.8
	0.5	10.0	17.3
	0.6	11.2	19.4
	0.7	12.9	22.4

For several sample sizes, Table 9.2 gives the anticipated precision, i.e., the half-widths of 95% CIs around estimates of: (a) QT change from baseline on Arm 3, (b) the difference in QT change from baseline between Arm 3 and each of Arms 1 and 2, and (c) the percent of participants exhibiting QTcF increase from baseline of >60 ms (at any time while taking study TB drug(s). Precisions given in the table are calculated based on the following assumptions: (a) The SD of QTcF from single on-treatment read is 20 ms. (b) Within-participant correlation between baseline and on-treatment means is 0.4. (c) For each visit, 3 ECGs will be read/reported, and will be averaged to determine the visit-specific QTcF. (d) For the primary outcome, the participant-specific on-study-TB-drug mean QT duration is the average of 9 visit-specific averages (weeks 8, 10, 12, 14, 16, 18, 20, 22 and 24), with a standard deviation of 3.8 ms (ignoring correlation within-participant of on-treatment QTcF values; note that other assumptions are very conservative). (For the last column, an event rate of 30% is assumed (high and therefore conservative), and the larger 'half' of the asymmetric CI is reported as the half-width.)

The total sample size (accrual target) is 84 participants. Table 9.2 indicates that accruing 28 participants per arm, anticipated to yield 25 evaluable participants per arm with complete ECG data (participant has 3 ECGs conducted at each of the 9 on-study-TB-drug visits and a single baseline visit (with 3 ECGs read/reported), CIs around Arm 3 QT prolongation are expected to be about ±4.5 ms, for good precision. For the estimates of differences in QT prolongation between Arm 3 and each of Arms 1 and 2, CIs are expected to give a precision of about ±6.0 ms. It is anticipated that no more than 10% of participants will discontinue study TB drug(s) before week 24, and that the majority of participants will have 3 QTcF values reported from each visit. (Anticipating loss to follow-up of about 10%, setting accrual targets of 28 per arm should provide 25 evaluable participants per arm. The anticipated precision in Table 9.2 assumes that all 25 evaluable participants will have QT values from each of the 3 ECGs conducted at each of the 9 visits contributing to the primary endpoint. Precision will be somewhat smaller if more than the anticipated 3 participants provide incomplete ECG data.) In the event that only 20 participants per arm are evaluable, CIs around estimates of Arm 3 QT prolongation would have a precision of about ±5.1 ms, and CIs around estimates of differences in QT prolongation between Arm 3 and each of Arms 1 and 2 would have a precision of about ±6.8 ms, which would still provide meaningful data.

Table 9.2:   Anticipated Precision (half-width of 95% CIs) for Estimating: (a) QT prolongations on Arm 3, (b) the difference in QT-prolongation between Arm 3 and each of Arms 1 and 2, and (c) the percent of participants exhibiting QTcF increase from baseline of >60 ms (at any time while taking study TB

drug(s)).

Number of evaluable participants per arm	PRECISION (CI half-width) in ms for estimating…		
	Within-participant QTcF changes from baseline on Arm 3	Between arm differences in within-participant QTcF changes from baseline (Arm 3 vs. Arm 1, and Arm 3 vs. Arm 2)	Percent of participants exhibiting QTcF increase from BL of >60 ms
20	5.1	6.8	31%
25	4.5	6.0	25%
30	4.0	5.5	20%

Accrual

The total accrual target is 84 participants. Across at least 2 ACTG sites enrolling to this study, we expect to enroll about 8-10 participants per month (all sites combined), in which case the accrual target would be met in less than 12 months after all sites have begun enrolling.

9.5   Monitoring

During the study, the safety and tolerability of the study medication will be monitored by means of adverse event reports (AER) and toxicity reports, reviewed by the study team, that present laboratory and clinical data, including QTcF prolongation events. All Grade 3 or higher adverse events and all adverse events leading to discontinuation of BDQ and/or DLM will be included in these reports. It is the responsibility of the study team to interpret the toxicity data and make any decisions needed to protect participants from undue risk. Concerns will be presented to the DAIDS Clinical Representative.

In these once monthly toxicity reports, the statisticians will also calculate and provide arm-specific proportions of participants exhibiting Grade 3 or higher QT prolongations (targeted AE), along with 95% CIs around the proportions, and will report these to the core team. (For the first 3 months after the first participant is randomized, and if the accrual rate is **eight** or more per month in the past month, this report will be generated and reviewed twice monthly.) Provided 10 or more Arm 3 participants have evaluable AE data through week 12 (available ECG data from 3 of the 9 visits at which ECGs contributing to the primary objective), if the upper bound of a 95% confidence interval (CI) around the proportion of Arm 3 participants exhibiting Grade 3 or higher QT prolongations exceed a threshold of 70%, the team will evaluate the events carefully in conjunction with the DAIDS Representative and the Study Monitoring Committee (SMC, appointed by the chair of the ACTG Tuberculosis Transformative Science Group [TB TSG]) to consider whether there should be study modifications. Table 9.3 gives the probabilities of this level of concern, for several true rates of Grade 3 or higher QT prolongations, for several observed numbers of participants, and for several threshold values.

Ideal characteristics of the trigger for DAIDS Representative and TB TSG SMC evaluation are that the trigger is: (1) unlikely to occur for low probabilities of the targeted

AE (under 10-20%, say) and (2) likely to occur for high probabilities of the AE (30% and above). Table 9.3 shows the probabilities of the trigger occurring for various true probabilities of the targeted AE, for numbers of participants observed and for particular choices for threshold. For example, if the true probability of the targeted AE is 5%, applying the trigger rule with data available from only **seven** participants, there is a 30% probability of triggering evaluation for a threshold of 50%. If the true AE probability is 30%, there is a high probability (>50%) of triggering evaluation with available data from 7, 10, 15 or 20 participants, when the threshold is set to 50%. The threshold of 50% is applied once there is ECG data from at least 10 participants on Arm 3. This trigger gives a high probability of evaluation (≥85%) if the true AE rate is ≥30%, and a low probability of evaluation (≤26%) if the true AE rate is ≤10%.

Balanced against the need for effective treatment against multidrug-resistant TB, an incidence of 50% for Grade 3 or higher QT intervals may be acceptable in practice. The higher threshold of 70% is chosen as a trigger for SMC review so that the SMC will only review in the case of a strong signal.

Sites should report the following events to the study team and to DAIDS immediately: (1) Grade 4 QT prolongations, (2) deaths and (3) results of repeated ECGs after holding study TB drug for a Grade 3.

Approximately 6 months after the first participant enrolls, an interim review for safety will occur. A Study Monitoring Committee (appointed by the chair of the ACTG Tuberculosis Scientific Committee) will review adverse event summaries, as well as accrual, off-treatment and off-study rates by study arm. Adverse event summaries will include the arm-specific proportions of Grade 3 or higher QT prolongations (with 95% CIs), rates of all Grade 3 or higher and all Grade 4 or higher signs/symptoms and laboratory values, and plots of arm- and visit-specific QT interval changes from baseline.

The study team will also monitor accrual, to ensure accrual targets are met, and will review data availability reports prepared by study statisticians and/or the lab data manager regularly to ensure that samples for primary and secondary endpoints are collected as expected.

Table 9.3. For **S**elected **N**umbers of **O**bserved **P**articipants and **T**rue **R**ates of **A**dverse **E**vent (AE, Grade 3 or higher QT prolongation), this table gives probabilities that the upper bound of an 95% exact, Clopper-Pearson CI (around the estimated probability AE) is above several thresholds (data are deemed consistent with an AE rate this high).

Number of Participants Observed	True Probability of AE	Threshold…			
		0.50	0.70	0.80	0.90
7	0.05	0.30	0.04	0.00	0.00
	0.10	0.52	0.15	0.03	0.00
	0.20	0.79	0.42	0.15	0.03
	0.30	0.92	0.67	0.35	0.13

	0.50	0.99	0.94	0.77	0.50
10	0.05	0.09	0.00	0.00	0.00
	0.10	0.26	0.01	0.00	0.00
	0.20	0.62	0.12	0.03	0.00
	0.30	0.85	0.35	0.15	0.01
	0.50	0.99	0.83	0.62	0.17
15	0.05	0.01	0.00	0.00	0.00
	0.10	0.06	0.00	0.00	0.00
	0.20	0.35	0.02	0.00	0.00
	0.30	0.70	0.13	0.02	0.00
	0.50	0.98	0.70	0.30	0.06
20	0.05	0.00	0.00	0.00	0.00
	0.10	0.01	0.00	0.00	0.00
	0.20	0.20	0.00	0.00	0.00
	0.30	0.58	0.05	0.01	0.00
	0.50	0.98	0.59	0.25	0.02

9.5.1   Interim review to assess the need for an initial hospitalization of 2 months

Based on comments from the March 2017 SMC review, to increase the rate of accrual and to reduce the burden of study participation on participants, the team **wanted** to shorten the duration of the initial hospitalization that **was** required when the participant begins taking TB study drug(s), provided it is safe to do so. An interim analysis **was to be** conducted when QTcF data through week 8 are available for at least 12 participants on the BDQ+DLM regimen. For participants on the BDQ+DLM arm, the mean of participant-specific mean QTcF changes from baseline at week 8 **was to be** calculated, along with the corresponding 95% CI. This summary **was to be** provided to the SMC.

The interim review **occurred in October 2017 and** supports the hypothesis that the observed QTcF intervals are consistent with a true QT prolongation of no higher than 40 ms. **Therefore,** the SMC recommend**ed** that the duration of hospitalization for participants initiating TB study drug(s) be reduced from 2 months to 2 weeks. (Note that those participants who would require inpatient stay based on local practice or severity of illness would stay for longer than 2 weeks, as necessary.)

Table 9.4 below shows that with an interim review sample size of 12, if the true population QT prolongation is 30 ms, there is only a 1 in 3 chance of retaining the original 2-month hospitalization, and if the true population QT prolongation is 40 ms, the original 2-month duration is retained with high probability (≥98%).

Table 9.4. For several hypothesized true QT prolongations and several interim review sample sizes, this table shows the probability (expressed as percent) that the 95% CI around within-participant change from baseline in QTcF fails to

exclude a value as high as 40 ms (95% CI upper bound is above 40 ms).

True QT prolongation	Number of participants with Week 8 QT data available						
	6	7	8	9	10	11	12
10	1%	<1%	<1%	<1%	<1%	<1%	<1%
20	20%	10%	6%	3%	1%	1%	<1%
30	69%	64%	57%	48%	46%	37%	34%
40	98%	98%	97%	98%	98%	97%	98%
50	>99%	>99%	>99%	>99%	>99%	>99%	>99%
60	>99%	>99%	>99%	>99%	>99%	>99%	>99%
70	>99%	>99%	>99%	>99%	>99%	>99%	>99%

9.5.2 Interim analysis to assess QT prolongations and the observed precision to date of estimates of QT prolongations

Because this trial has been slow to accrue, and given the urgent need for information on the safety of co-administration of bedaquiline and delamanid for patients with highly resistant forms of TB, an interim analysis will be performed when week 24 QT data is available for at least 12 participants on the BDQ+DLM arm. Results will be shared with the SMC.

The interim analysis will present:
(1) Arm-specific averages of week 24 QTcF changes from baseline,
(2) Arm-specific averages of week 8 QTcF changes from baseline,
(3) The estimated difference between (a) the average week 24 QTcF change from baseline on the BDQ+DLM arm and (b) the sum of the week 24 averages seen on the BDQ-alone and the DLM-alone arms,
(4) The difference between the average week 24 QTcF change from baseline on the BDQ+DLM arm and (b) (separately) on the BDQ-alone and the DLM-alone arms,
(5) Corresponding confidence intervals (CIs) around each of these point estimates, and
(6) The precision (half-widths of CIs) for each estimate.

Point estimates. Arm-specific week 24 QTcF changes from baseline are defined as the average of participant-specific changes, where participant-specific change is calculated as the average of changes from baseline at weeks 8 through 24; all participants with week 24 data are included. Arm-specific week 8 QTcF changes from baseline are defined as the averages of change from baseline at week 8 only.

Confidence intervals for measures (1), (2) and (3). Based on the method of Repeated Confidence Intervals, 99.9% CIs will be constructed. To maintain at least 95% simultaneous coverage for both the interim and final analysis CIs, a 95.1% confidence level will be used for CIs in the final analysis.

Precision for measure (4). To allow comparison of *observed* precision to the precision *anticipated* under the original protocol assumptions, 95% CIs around

point estimates for measure (4) will be calculated. The CIs themselves will not be reported, but the precision will be. Table 9.5 below is an extension of Table 9.2 above: a row for 12 evaluable participants per arm has been added.

Table 9.5-1: Anticipated precision (half-width of 95% CIs) for estimating: (a) arm-specific QT prolongations at week 24, and (b) the difference in QT-prolongation between Arm 3 and each of Arms 1 and 2. Precision estimates are based on the original protocol assumptions.

| Number of evaluable participants per arm | PRECISION (CI half-width) in ms for estimating… | |
	Arm-specific average of week 24 within-participant QTcF changes from baseline	Between arm differences in week 24 QTcF changes from baseline (Arm 3 vs. Arm 1, and Arm 3 vs. Arm 2)
12	7.0	9.0
20	5.1	6.8
25	4.5	6.0
30	4.0	5.5

9.6   Analyses

9.6.1   Primary analyses

9.6.1.1   A mixed-effects ANOVA model (with fixed effects for treatment arm and "period" (baseline vs. on-treatment), and random effects for participant) will be fit to data from participants on all arms. The QTc prolongation on Arm 3 will be represented as the estimated contrast (difference between QTc duration during weeks 8-24 and QTc duration at week 0) along with the corresponding model-based 95% CI. (See 9.2.1.1 for definitions of handling of data from participants who discontinue study treatment before week 24 and of missing data.) QTc prolongations on Arms 1 and 2 will be similarly estimated.

9.6.1.2   A mixed-effects ANOVA model (with fixed effects for treatment arm and "period" (baseline vs. on-treatment), and random effects for participant) will be fit to data from participants on all arms. The difference between QTc prolongations on Arms 3 and 1 will be estimated as the corresponding contrast (Arm 3 change from baseline minus Arm 1 change from baseline) along with the corresponding model-based 95% CI. No adjustments will be made for multiple comparisons. Arms 2 and 3 will be similarly compared. (See 9.2.1.1 for definitions of handling of data from participants who discontinue study treatment before week 24 and of missing data.)

9.6.2   Secondary analyses

9.6.2.1   Arm-specific proportions of participants exhibiting new QTcF >500 ms will be reported, along with the associated 95% exact, Clopper-Pearson binomial CI. (Because the study TB drugs have a long half-life, participants will be included in the proportion whether or not they took study TB drug(s) through Week 24.) Between-arm comparisons will not be conducted.

9.6.2.2   Arm-specific proportions of participants exhibiting QTcF change from baseline >60 ms at any visit after the first dose of study TB drug through week 24 will be reported, along with the associated 95% exact, Clopper-Pearson binomial CI. (Because the study TB drugs have a long half-life, participants will be included in the proportion whether or not they took study TB drug(s) through week 24.) Between-arm comparisons will not be conducted.

9.6.2.3   Arm- and visit-specific medians, ranges and interquartile ranges of within-participant QTcF changes from baseline will be reported, beginning with the first on-treatment ECG in the **SOE**, and continuing through the last ECG measured after scheduled discontinuation of study TB drug(s) at week 28. For participants who discontinue study TB drug(s) prematurely, QTcF changes will be excluded from analysis; however, in a sensitivity analysis, QTcF changes from such participants will be carried forward as described in 9.2.1.1. (Statistical summaries of QTcF changes from baseline measured after scheduled discontinuation of study TB drug(s) allow characterization of the resolution of QT changes.)

On a single graph but with separate lines (colors, symbols) for each arm, week-specific mean changes and associated 95% CIs will be plotted against week, to allow a visual comparison of arms with respect to time effects. The arm- and week-specific summaries will also be tabulated. Between-arm comparisons will not be conducted.

9.6.2.4   Arm-specific proportions of participants exhibiting each of the following (at any time during study treatment) will be reported, along with the associated 95% exact, Clopper-Pearson binomial CI: (a) QTcF >480 and ≤500 ms and (b) QTcF change from baseline >30 and ≤60 ms. Between-arm comparisons will not be conducted.

9.6.2.5   Participant-specific PK parameters for BDQ and its M2 metabolite will be summarized by week (weeks 2, 8, and 24). Effects of DLM co-administration on BDQ PK parameters will be estimated by (week-specific) geometric mean ratios (GMRs; BDQ/metabolite PK parameter with DLM divided by BDQ/metabolite PK parameter without DLM), and the associated 90% CI around the GMR.

9.6.2.6   Participant-specific PK parameters for DLM and its DM-6705 metabolite will be summarized by week (Weeks 2, 8, and 24). Effects of BDQ co-administration on DLM PK parameters will be estimated by (week-specific) geometric mean ratios (GMRs; DLM/metabolite PK parameter with BDQ divided by DLM metabolite PK parameter without BDQ), and the associated 90% CI around the GMR.

9.6.2.7   Arm-specific proportions of participants exhibiting each of the following will be reported, along with the associated 95% exact, Clopper-Pearson binomial CI: (a) Grade 3 or higher clinical or laboratory adverse event of any type, and (b) early discontinuation of study TB drug for any reason.

9.6.3   Exploratory analyses

9.6.3.1   PK/PD modeling will be used to characterize relationships between (a) QTcF changes from baseline and (b) concurrently-collected plasma concentrations of BDQ, DLM and their metabolites.

9.6.3.2   Arm-specific proportions of participants exhibiting culture conversion will be estimated for weeks 8 and 24 using a modified intention-to-treat (MITT) analysis wherein participants without confirmed MDR or RR-TB or *Mycobacterium tuberculosis* growth at baseline and participants who did not take at least one dose of study TB drugs are excluded from analysis. So that the 24-week culture conversion rates will not be overestimated, participants who experience dose limiting adverse events or die (from any cause) will be included in the analysis by retaining them in the risk group through Week 24. Description of change in time-to-detection over time on MGIT (liquid) culture (decline over time in viable mycobacteria in the sputum) will also be explored, using a nonlinear mixed-effects, repeated time-to-event model [6**6**].

9.6.3.3   Drug concentrations in hair will be reported using descriptive statistics.

9.6.3.4   Among participants with MDR or RR-TB and HIV co-infection who initiated DTG within ± 4 weeks of study entry (as part of their ART regimen), proportions of participants exhibiting each of the following will be reported, along with the associated 95% exact, Clopper-Pearson binomial CI: (a) HIV-1 RNA ≤50 copies/mL 24 (±6) and 48 (±6) weeks after initiating DTG, (b) Grade ≥3 clinical or laboratory adverse event of any type at any time while taking DTG and (c) early discontinuation of DTG for any reason. Overall proportions will be presented as well as proportions in the following subgroups: ART-naïve at study entry (or having initiated ART within 4 weeks of study entry), on ARV with HIV-1 RNA >50 copies/mL at time of study entry and on ARV with HIV-1 RNA ≤50 at study entry.

9.6.3.5   Arm-specific proportions of participants exhibiting favorable outcomes at week 128 will be estimated using a modified intention-to-treat (MITT) analysis, wherein participants without confirmed MDR or RR-TB or MTB growth at baseline and participants who did not take at least one dose of study TB drugs are excluded from analysis. Kaplan-Meier survival analysis will be used to estimate the proportion of participants exhibiting favorable week 128 outcomes.

9.6.3.6   Exploratory plots will be examined, the details of which will be given in the Statistical Analysis Plan. For example, for each DLM, its DM-6705 metabolite, BDQ and its M2 metabolite, and for the plasma-based drug-exposure metric AUC and the hair-based metric (time-averaged) concentration, the distribution of drug-resistance phenotypes will be tabulated for two to four drug-exposure "bins" created by splitting the continuous exposure metric into halves, thirds, or fourths.

9.6.3.7   Concentrations of BDQ and DLM in CSF, and CSF to plasma ratios of BDQ and DLM, will be summarized by week and hour, and by hour (both weeks combined). Pharmacologists will conduct nonlinear mixed-effects modeling to estimate partition coefficient and half-life of the distribution between plasma to CSF.

10.0   PHARMACOLOGY PLAN

10.1   Pharmacology Objectives

See Sections 1.3.5, 1.3.6, and 1.4.1.

10.2   Pharmacology Study Design

10.2.1   Overview

The overall aims of the PK investigation are: 1) To evaluate the relationship between BDQ and DLM PK and QT interval changes in participants on MBT with DLM, BDQ or the 2 drugs in combination; 2) To identify any important PK drug-drug interactions between the two study TB drugs.

An initial noncompartmental analysis (9.2.2.5 and 9.2.2.6) will be used to evaluate differences in measures of exposure of the respective drugs and metabolites at 2 weeks, 8 weeks, and 24 weeks between the treatment arms, using the intensive PK data.

An integrated population PK model for each drug with or without its major metabolite (M2 and DM6705, respectively), which will characterize the PK during the 24-week treatment and during the post-study drug period will be developed. The model will be supported by:

1) intensive PK sampling over a 24-hour dosing interval (for 24 hours immediately after the morning doses of BDQ and/or DLM) at week 2 (corresponding to the end of the loading dose phase for BDQ), during week 8 (at which time the maintenance doses of both drugs are established) and during week 24 (corresponding to the end of treatment when maximal accumulation may be seen); 2) sparse sampling corresponding to ECG times; and 3) post-study drug samples at 28 weeks.

Population PK modelling will be used to identify important covariate effects and to evaluate the effect of concomitant BDQ on DLM PK and the effect of concomitant DLM on BDQ PK, as well as estimation of drug exposures at the time of ECG assessments.

A PK-PD model will be developed to examine the relationship between QTcF measurements and BDQ, DLM and their respective metabolites.

10.2.2 Methods and Timing for Assessing, Recording, and Analyzing PK Outcome Measures

Intensive PK sampling: Blood samples will be taken over a 24-hour period at weeks 2, 8, and 24 (see section 6.1 and table below). Every effort should be made to ensure that the week 2 intensive PK sampling for BDQ is collected on day 12, 13, or 14 to allow for PK assessment following an observed dose of 400 mg of BDQ. On PK sampling days, a standardized meal will be provided, as described in the MOPS. The date and time of the meal should be recorded on the CRF. DLM will be dosed immediately after the standardized meal, while BDQ and the other TB medicines will be dosed one hour after the meal. PK sampling will be performed immediately after the meal but prior to drug dosing (predose), and at 4 (±0.5) h, 6 (±0.5) h, 8 (±0.5) h, 11 (±1) h and 23 (±1) h, as outlined in the table below, where time is set to 0 hour at the time of the DLM dose or 1 hour before the BDQ dose:

EVENT	ARM 1 (BDQ)	ARM 2 (DLM)	ARM 3 (BDQ+DLM)
Standard meal	- 0.5 h	- 0.5 h	- 0.5 h
Pre-dose PK sample	- 0.25 to 0 h	- 0.25 to 0 h	- 0.25 to 0 h
DLM dose	-	0 h	0 h
BDQ dose	1 h	-	1 h
Other TB drug doses	1 h	1 h	1 h
ECG	(±3.5 to 4 h)	(±3.5 to 4 h)	(±3.5 to 4 h)
PK sample*	-	4 (±0.5) h	4 (±0.5) h
PK sample**	6 (±0.5) h	-	6 (±0.5) h
PK sample	8 (±05) h	8 (±05) h	8 (±05) h
PK sample	11 (±1) h	11 (±1) h	11 (±1) h
PK sample	23 (±1) h	23 (±1) h	23 (±1) h

* For analysis of DLM and its metabolite only.
** For analysis of BDQ and its metabolite only.
All other PK samples to be analyzed for both drugs and their respective metabolites.

Sparse PK sampling: Sparse sampling will be conducted at weeks 4, 6, 10, 12, 14, 16, 18, 20, 22, and 28. PK sampling days are scheduled for days when ECGs are also collected. ECGs are performed in triplicate, and ECG evaluation should be followed immediately by PK sampling. The exact time of the dose preceding the PK sampling and the exact time of the PK sample collection should be noted.

The actual (24-hour clock) times of BDQ, DLM, and MBT doses and samples will be recorded in the CRF, as well as the time of the 2 prior doses for BDQ and DLM. If the required specimen is not obtained or sent to the lab, information about why should be included on the CRF. On days when PK samples are collected for intensive PK analysis, ECG should precede the PK collection.

10.2.3   PK: Blood and Hair Collection and Processing
Detailed blood and hair collection, processing, handling, and storage procedures can be found in the A5343 LPC and MOPS. Plasma PK samples from PK sampling days will also be stored for measurement of MBT drugs should this be of future scientific interest.

10.2.4   Pharmacogenomics: Host Genetic Analysis

A whole blood sample will be collected and stored to evaluate for pharmacogenomics should relationships between genetics and PK variability be discovered in the future as these could potentially serve as explanatory variables in PK analyses.

10.2.5   Laboratory Performing the Assays

Plasma BDQ, M2, DLM, and DL6705 concentrations, **and CSF BDQ and DLM concentrations,** will be determined by a validated procedure performed according to written standard operating procedures. The intraday accuracy and intraday precision will be obtained with quality control samples, which will be analyzed concurrently with each set of volunteer samples. Quality control procedures will be in place to ensure stability of sample materials. Hair assays for MBT, BDQ, M2, DLM and DL6705 are being developed in the analytical laboratory at University of California at San Francisco (UCSF) and hair concentrations will be determined by a validated procedure performed according to written analytic validation reports and standard operating procedures.

10.3   Primary and Secondary Data, Modeling, and Data Analysis

See Sections 9.6.2.5 and 9.6.2.6 for descriptions of noncompartmental analyses to be performed using intensive PK sampling data.

In addition, the drug concentration-time data from all PK visits (intensive and sparse) will

be analyzed using nonlinear mixed-effects (NLME) modeling using the software NONMEM. A stepwise procedure will identify the structural model best describing the data for each drug and its metabolite. Various structural models will be evaluated varying the number of compartments and testing different absorption models. Allometric scaling will be tested in the model to account for the effect of body size on the PK parameters, using total body weight or fat-free mass. Other covariate effects (such as those of race, sex, HIV co-infection status, time on treatment, albumin) will be evaluated and retained if they result in statistically important improvement in model fit. The effect of drug-drug interactions will be investigated on clearance, bioavailability, and other primary parameters of importance. Graphical and statistical diagnostic tools will be used during model development for model selection and data tracking.

PK/PD models will be developed to explore the relationship between drug and metabolite concentrations and QTcF. Details are provided in the Statistical Analysis Plan.

10.4   Anticipated Outcomes

See Hypothesis 1.1.2.2.

QTcF will correlate with DM6705 concentrations but not with DLM, BDQ, or M2 concentrations.

11.0   DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

11.1   Records to Be Kept

Case report forms (CRF) will be provided for each participant. Participants must not be identified by name on any CRFs. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

11.2   Role of Data Management

11.2.1 Instructions concerning the recording of study data on CRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

11.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

11.3   Clinical Site Monitoring and Record Availability

11.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts), to ensure protection

of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect sites' regulatory files to ensure that regulatory requirements are being followed and sites' pharmacies to review product storage and management.

11.3.2   The site investigator will make study documents (e.g., consent forms, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, the NIAID, the OHRP, the industry supporter(s) or designee, **other local, US, and international regulatory entities** for confirmation of the study data.

11.4   Expedited Adverse Event **(EAE)** Reporting to DAIDS

11.4.1   Adverse Event Reporting to DAIDS
Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

The DAERS, an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES (now part of the NIAID Clinical Research Management System) at CRMSsupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

11.4.2   Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study through the week 48 visit. Thereafter, the SUSAR Reporting category will be used.
- The study agents for which expedited reporting are required are: bedaquiline and delamanid and dolutegravir.
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are as follows:

  - Any liver toxicity that warrants permanent study drug discontinuation based on liver stopping criteria in 7.1.2.
  - If any participant experiences a possible suicidality-related adverse event (PSRAE) ≥Grade 3 while participating in this study that is considered by the investigator to meet ICH-E2A definitions for seriousness, the investigator will collect information using a PSRAE CRF in addition to reporting the event on a SAE CRF. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a

preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related.
- Episodes of ventricular tachycardia or fibrillation, syncope, and seizure.
- Grade 3 QTcF prolongation, as defined in section 7.1.1.
- Grade 3 pancreatitis.
- Grade 3 myalgias or creatine kinase.
- Grade 3 rash.
- Any Grade 4 event, including laboratory values.

Any AE leading to permanent study drug discontinuation will be reported as an EAE at the time it is decided that the study drug will be permanently discontinued.

11.4.3   Grading Severity of Events

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, must be used and is available on the DAIDS RSC Web site at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables. One exception is QT grading (see Section 7.1 above).

11.4.4   Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

12.0   HUMAN PARTICIPANTS

12.1   Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document (Appendix II) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, or legal guardian, and this fact will be documented in the participant's record.

12.2   Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, **other local, US, and international regulatory entities** as part of their duties, or the industry supporters or designee.

12.3   Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, or the industry supporters, or other government agencies as part of their duties to ensure that research participants are protected.

13.0   PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporters prior to submission.

14.0   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 Centers for Disease Control and Prevention and the National Institutes of Health. As TB is a respiratory infection, appropriate infection control procedures will be employed, as described in section 3.0.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

15.0   REFERENCES

1. World Health Organization. 2013. Global Tuberculosis Report 2013. HO/HTM/TB/2013.11. Geneva, Switzerland.

2. World Health Organization. 2013. Multidrug-resistant Tuberculosis (MDR-TB), 2013 Update. http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf.

3. WHO MDR-TB Treatment Guidelines, 2016 [found at: http://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/resources/en/]

4. Klopper M, Warren R M, Hayes C, et al. Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa. Emerg Infect Dis 2013;19:449-55. doi: 10.3201//EID1903.120246; 10.3201//EID1903.120246.

5. Loewenberg S. India reports cases of totally drug-resistant tuberculosis. Lancet 2012; 379:205.

6. Slomski A. South Africa warns of emergence of "totally" drug-resistant tuberculosis. JAMA 2013;309:1097-8. doi: 10.1001/jama.2013.1802; 10.1001/jama.2013.1802.

7. Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. Clin Infect Dis 2012;54:579-81. doi: 10.1093/cid/cir889; 10.1093/cid/cir889.

8. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis - 2011 Update. WHO/HTM/TB/2011.6. URL: http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/en/index.html Accessed July 29, 2013. Published by World Health Organization, Geneva, Switzerland.

9. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9:e1001300. doi: 10.1371/journal.pmed.1001300 [doi].

10. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010;182:684-92. doi: 10.1164/rccm.201001-0077OC. Epub 2010 May 4.

11. Aung KJ, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014;18:1180-7. doi: 10.5588/ijtld.14.0100.

12. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. Int J Tuberc Lung Dis 2014;18:1188-94. doi: 10.5588/ijtld.13.0075.

13. Kuaban C, Noeske J, Rieder HL, et al. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. Int J Tuberc Lung Dis 2015;19:517-24. doi: 10.5588/ijtld.14.0535.

14. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. Science 2005;307:223-7. doi: 10.1126/science.1106753.

15. Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006;3:e466. doi: 10.1371/journal.pmed.0030466.

16. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360:2397-405. doi: 10.1056/NEJMoa0808427.

17. Diacon AH, Donald PR, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC 207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob. Agents Chemother 2012;56:3271-6. doi: 10.1128/AAC.06126-11.

18. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. N Engl J Med 2012;366:2151-60. doi: 10.1056/NEJMoa1112433.

19. Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. Eur Respir J 2013;41:1393-400. doi: 10.1183/09031936.00125812. Epub 2012 Sep 27.

20. Centers for Disease Control and Prevention. 2013. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep. 62:1-12. doi: rr6209a1 [pii].

21. **Arnold F, Parasuranman S, Arokiasamy P, Kothari M. Nutrition in India. National Family Health Survey (NFHS-3), India, 2005-06. Mumbai: International Institute for Population Sciences; Calverton, Maryland, USA; 2009.**

22. **Berenguer J, Moreno S, Laguna F, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. N Engl J Med 1992;326:668-72. doi: 10.1056/NEJM199203053261004.**

23. **Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004;8:286-98.**

24. **Thwaites G, Chau TT, Mai NT, Drobniewski F, McAdam K, Farrar J. Tuberculous meningitis. J Neurol Neurosurg Psychiatry 2000;68:289-99.**

25. **Thwaites GE, Lan NT, Dung NH, et al. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192:79-88. doi: 10.1086/430616.**

26. **Tho DQ, Torok ME, Yen NT, et al. Influence of antituberculosis drug resistance and Mycobacterium tuberculosis lineage on outcome in HIV-associated tuberculous meningitis. Antimicrob Agents Chemother 2012;56:3074-9. doi: 10.1128/AAC.00319-12 [doi].**

27. **Daikos GL, Cleary T, Rodriguez A, Fischl MA. Multidrug-resistant tuberculous meningitis in patients with AIDS. Int J Tuberc Lung Dis 2003;7:394-8.**

28. **Luque S, Grau S, Alvarez-Lerma F, et al. Plasma and cerebrospinal fluid concentrations of linezolid in neurosurgical critically ill patients with proven or**

suspected central nervous system infections. Int J Antimicrob Agents 2014;44:409-15. doi: 10.1016/j.ijantimicag.2014.07.001 [doi].

29. **Sun F, Ruan Q, Wang J, et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother 2014;58:6297-301. doi: 10.1128/AAC.02784-14 [doi].**

30. Svensson EM, Murray S, Karlsson MO, Dooley KE. Rifampicin and rifapentine significantly reduce concentrations of bedaquiline, a new anti-TB drug. J Antimicrob Chemother 2015;70:1106-14.

31. Svensson E.M, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. http://www.ncbi.nlm.nih.gov/pubmed/25114140. Antimicrob Agents Chemother. 2014;58:6406-12.

32. Song I, Borland J, Chen S, et al. Effect of food on the pharmacokinetics of the integrase inhibitor dolutegravir. Antimicrob Agents Chemother 2012;56:1627-9.

33. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013;381:735-43. doi: 10.1016/S0140-6736(12)61853-4. Epub 2013 Jan 8.

34. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol 2013;75:990-6.

35. Van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naïve adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012;12:111-18.

36. Walmsley S, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013;369:1807-18.

37. CPTR 2014 Rapid DST Workshop Report. Koné Kaniga, Janssen. Accessed on March 6, 2015 at: http://www.cptrinitiative.org/2014/11/25/cptr-rapid-dst-workshop-day-2/.

38. Andries K, Villellas C, Coeck N, et al. Acquired resistance of Mycobacterium tuberculosis to bedaquiline. PLoS One 2014;9(7):e102135.

39. Assessment report Deltyba, Procedure No.: EMEA/H/C/002552. European Medicines Agency, Committee for Medicinal Products for Human Use; 2013.

40. Research Excellence to Stop TB Resistance (RESIST-TB). DR-TB Clinical Trial Progress Report. Accessed on January 8, 2015 at: http://www.resisttb.org/?page_id=1602.

41. Lanoix JP, Betoudji F, Nuermberger E. Novel regimens identified in mice for treatment of latent tuberculosis infection in contacts of patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2014;58:2316-21.

42. Selkon JB, Devadatta S, Kulkarni KG, et al. The emergence of isoniazid-resistant cultures in patients with pulmonary tuberculosis during treatment with isoniazid alone or isoniazid plus PAS. Bull World Health Organ 1964;31:273-94.

43. Yeager RL, Munroe WG, Dessau FI. Pyrazinamide (aldinamide) in the treatment of pulmonary tuberculosis. Am Rev Tuberc 1952;65:523-46.

44. Vall-Spinosa A, Lester W, Moulding T, Davidson PT, McClatchy JK. Rifampin in the treatment of drug-resistant Mycobacterium tuberculosis infections. N Engl J Med 1970;283:616-21.

45. Pasipanodya JG, McIlleron H, Burger A, Wash PA, Smith P, Gumbo T. Serum drug concentrations predictive of pulmonary tuberculosis outcomes. J Infect Dis 2013;208:1464-73.

46. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. Am J Respir Crit Care Med 2006;173:350-6.

47. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet 1999;353:1843-7.

48. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet 2002;360:528-34.

49. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Clin Infect Dis 2005;40:1481-91.

50. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. Lancet 2014;383:1230-9.

51. Cegielski JP, Dalton T, Yagui M, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2014;59:1049-63.

52. Blakemore R, Story E, Helb D, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. J Clin Microbiol 2010;48:2495-501.

53. Lin SY, Rodwell TC, Victor TC, et al. Pyrosequencing for rapid detection of extensively drug-resistant Mycobacterium tuberculosis in clinical isolates and clinical specimens. J Clin Microbiol 2014;52:475-82.

54. Folkvardsen DB, Svensson E, Thomsen VO, et al. Can molecular methods detect 1% isoniazid resistance in Mycobacterium tuberculosis? J Clin Microbiol 2013;51:1596-9.

55. Mardis ER. Next-generation DNA sequencing methods. Annu Rev Genomics Hum Genet 2008;9:387-402.

56. Daum LT, Fourie PB, Bhattacharyya S, et al. Next-generation sequencing for identifying pyrazinamide resistance in Mycobacterium tuberculosis. Clin Infect Dis 2014;58:903-4.

57. Eilertson B, Maruri F, Blackman A, Herrera M, Samuels DC, Sterling TR. High proportion of heteroresistance in gyrA and gyrB in fluoroquinolone-resistant Mycobacterium tuberculosis clinical isolates. Antimicrob Agents Chemother 2014;58:3270-5.

58. Colman RE, Schupp JM, Hicks ND, et al. Detection of low-level mixed-population drug resistance in Mycobacterium tuberculosis using high fidelity amplicon sequencing. PLoS One 2015;10:e0126626.

59. Oxford Nanopore Technologies. The MinION™ device: a miniaturised sensing system. Accessed on February 21, 2015, at: https://nanoporetech.com/technology/the-minion-device-a-miniaturised-sensing-system/the-minion-device-a-miniaturised-sensing-system.

60. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [E14. International Conference on Harmonisation. October 2005.]

61. Fox GJ, Benedetti A, Cox H, et al. Group 5 drugs for multidrug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J 2017; 49. pii: 1600993. doi: 10.1183/13993003.00993-2016.

62. Tang S, Yao L, Hao X, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. Clin Infect Dis 2015;60:1361-7. doi: 10.1093/cid/civ027.

63. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371:723-32. doi: 10.1056/NEJMoa1313865.

64. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. Int J Tuberc Lung Dis 2015;19:979-85. doi: 10.5588/ijtld.14.0944.

65. Furin J, Alirol E, Allen E et al. Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults. Int J Tuberc Lung Dis 2016;20:290-4.

66. Chigutsa E, Patel K, Denti P, et al. A time-to-event pharmacodynamic model describing treatment response in patients with pulmonary tuberculosis using days to positivity in automated liquid mycobacterial culture. Antimicrob Agents Chemother 2013;57;789-95.

67. **Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2014;14:947-57. doi: 10.1016/S1473-3099(14)70852-7 [doi].**

68. **Seddon JA, Visser DH, Bartens M, et al.. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. Pediatr Infect Dis J 2012;31:711-16. doi: 10.1097/INF.0b013e318253acf8 [doi].**

69. **Akkerman OW, Odish OF, Bolhuis MS, et al. . Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. Clin Infect Dis 2016;62:523-4. doi: 10.1093/cid/civ921 [doi].**

70. **Wager TT, Hou X, Verhoest PR, Villalobos A. Moving beyond rules: the development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties. ACS Chem Neurosci 2010;1:435-49. doi: 10.1021/cn100008c [doi].**

71. **Blennow K, Fredman P, Wallin A, et al. Protein analysis in cerebrospinal fluid. II. Reference values derived from healthy individuals 18-88 years of age. Eur Neurol. 1993;33:129-33.**

APPENDIX I: ASSESSMENT OF CEREBROSPINAL FLUID (CSF) CONCENTRATIONS OF DELAMANID AND BEDAQUILINE AMONG PARTICIPANTS WITH MDR-TB

1.0 <u>**OBJECTIVE**</u>

1.1 To measure plasma and lumbar (cerebrospinal fluid) CSF concentrations of delamanid (DLM) and/or bedaquiline (BDQ) (total and unbound) in up to 16 participants (within the A5343 study) who are receiving one or both drugs for treatment of MDR-TB or RR-TB.

2.0 <u>**BACKGROUND**</u>

Tuberculous Meningitis (TBM)
TBM is a devastating illness, killing and disabling more patients than any other form of TB; particularly young children under 5 years of age [1-4]. In endemic regions, TBM is often the leading cause of bacterial meningitis [5]. TBM is characterized by a progressive granulomatous inflammation of the basal meninges resulting in hydrocephalus, brain infarction, and death if left untreated [6]. Among treated patients, outcomes are uniformly poor with mortality of 30-50% in adults and 20% in children; among those who survive, serious neurologic sequelae are common [7].

Multidrug resistant (MDR) TBM
Drug-resistant TBM, specifically multidrug-resistant (MDR) TBM, caused by M. tuberculosis that is resistant to at least rifampicin and isoniazid, has especially poor outcomes. MDR-TBM confers a 12-fold higher risk of death in children [8]. In adults, infection with isoniazid monoresistant TBM results in slower clearance of mycobacteria from CSF but no difference in clinical response or outcomes; however, infection with an MDR-TB isolate results in a 12-fold higher risk of death [9]. In patients co-infected with MDR-TB and HIV, outcomes are especially frightful, with nearly 100% mortality [10, 11].

Penetration of drugs with activity against MDR-TB into central nervous system (CNS) and CSF
To construct an MDR-TBM treatment regimen, a drug combination must be selected that has the following properties: (1) adequate penetration into CNS and CSF both early and late in the disease at doses that are clinically safe; (2) activity against most DR strains; (3) sterilizing activity (e.g., inclusion of a drug that can kill metabolically less-active bacilli that must be eradicated to effect cure); and (4) low risk of clinically relevant acquired resistance (that is, the drugs must protect each other from emergence of resistance). Drugs must be present at adequate concentrations in the CSF and CNS both early in treatment, when there is typically significant inflammation and the blood-CSN and blood-CSF barriers are leaky, and later when inflammation is reduced by treatment with steroids and antimicrobial therapy.

Current treatment for MDR TB and its CNS/CSF penetration
Standard World Health Organization (WHO) recommended treatment of MDR-TB typically includes a fluoroquinolone, an aminoglycoside, cycloserine (or terizidone), and ethionamide or isoniazid plus one or both of the following: pyrazinamide, ethambutol. BDQ, DLM, clofazimine and/or linezolid are commonly used for MDR-TB with additional resistance or drug intolerance requiring a substitution. Fluoroquinolones, ethionamide, and cycloserine (or terizidone) have good-to-excellent CSF penetration. Aminoglycosides enter the CSF well but only when there is inflammation, thereafter penetration is poor. Linezolid achieves a CSF:plasma area under the concentration-time curve (AUC) ratio of 0.77 [12]. Patients with TBM receiving linezolid at a dose of 600 mg twice daily had quicker Glasgow coma scale recovery in a small clinical study of 33 patients with severe TBM [13]. However, linezolid dose and duration are limited by toxicities and high inter-patient variability. Clofazimine in CSF has not been measured.

Bedaquiline and/or delamanid for CNS-TB?
When looking at predictors of good CNS and CSF penetration, bedaquiline has features suggesting poor uptake including a hydrogen bond donor, large molecular weight, high protein binding, and a high distribution co-efficient. Animal studies found low CNS tissue uptake of the drug (Janssen IB). BDQ CSF concentrations have only been measured in one patient with MDR-TBM. Drug concentrations collected via a lumbar drainage system after 5 weeks of dosing were undetectable at all time points following an observed dose [12].

DLM has never been measured in human CNS or CSF, but there are characteristics of its structure that would suggest it has a reasonably high likelihood of achieving satisfactory concentrations in these matrices. DLM is a large polar molecule, it has no hydrogen bond donors, and it has some molecular characteristics in common with antipsychotics, which suggest good penetration [13]. Negative features for CSF and CNS penetration include high protein binding (97-99% in man) and a distribution coefficient of 4.4 at pH of 7.4 (<2 is most desirable). Animal studies showed penetration into the brain following administration of 14C-delamanid. In in vitro experiments, DLM was not a substrate of P-glycoprotein (P-gp; also known as MDR1), but its metabolite (which does not contribute meaningfully to activity but has a modest association with QT prolongation) is a P-gp substrate (Otsuka IB); DLM is, thus, not likely to be actively pumped out of CSF via P-gp.

Therefore, DLM has characteristics that make us think it is quite likely to cross the blood-CNS and blood-CSF barriers and be active in those compartments. If so, DLM could be an anchor drug for MDR-TBM and potentially a companion drug for drug-sensitive TBM, given rifampicin's poor CNS and CSF penetration and DLM's sterilizing activity. BDQ may not penetrate meaningfully into CSF, but this requires confirmation.

3.0   RATIONALE

A5343 participants will not have meningitis with inflamed and thus more penetrable blood-CNS and blood-CSF barriers. Therefore, CSF concentrations will most meaningfully reflect those achieved later in MDR-TBM treatment when antibiotics and steroid treatment have largely restored the integrity of these barriers. This is a time in treatment when TB drugs must continue to penetrate the CSF/CNS in adequate concentrations to kill *M. tuberculosis* and cure the patient. Therefore, these values will be clinically relevant. Further, in the future, this data can be paired with early CSF data from patients with MDR-TBM (or from relevant alternative models) in other studies. MDR-TBM is relatively rare (so challenging to recruit), therefore clinicians are unlikely to prescribe BDQ or DLM to patients with MDR-TBM without some evidence that it penetrates into CSF/CNS, thus late PK assessments in MDR-TBM may not occur because of the tragically high early mortality in this population. This nested study will maximize the contribution of the PK-data accumulated in A5343 to advance what is known about BDQ and DLM in MDR-TB.

4.0   HYPOTHESES AND ANALYSES

4.1   Exploratory Hypotheses

4.1.1   Administration of BDQ and/or DLM for a minimum of 8 weeks in patients with RR or MDR pulmonary TB, without TB meningitis, will result in measurable drug concentrations (total and unbound) in the CSF.

4.1.2   BDQ and/or DLM CSF levels will follow a similar concentration curve to that found in plasma.

4.2   Primary Analyses

4.2.1   Total concentration of BDQ and/or DLM will be measured in plasma and CSF by mass spectrometry. If total concentration in CSF is measurable, unbound concentration in plasma will be measured where possible to evaluate differences in measures of exposure of the respective drugs.

4.3   Secondary Analyses

4.3.1   Nonlinear mixed-effects modeling will be used to describe the partition coefficient and half-life of the distribution between plasma to CSF. Thereafter CSF area under the curve (AUC) will be estimated for each individual and this information may be used for further

analysis in comparison with plasma parameters.

5.0   EVALUATIONS

This optional procedure is open to participants currently enrolled under Version 3.0 who have not yet completed week 22 and new participants enrolling into Version 4.0. Participants currently enrolled under Version 3.0 will need to be re-consented to Version 4.0 in order to be approached regarding the optional LP.

The intent is to have between 8-16 participants consent into Version 4.0 and participate in the optional LP procedure. Participant selection of the optional LP evaluation will be captured on a tracking CRF. Because the form is not available in real time, such accounting is approximate. The sites and the Protocol Data Manager will be in close contact to determine when 16 participants have had the LP evaluation. Once determined, additional participants will no longer be approached to consent for the LP. The intent is to have a total of eight participants contribute CSF PK data for BDQ (Arms 1 and 3) and eight participants contribute PK data for DLM (Arms 2 and 3), where Arm 1 = BDQ plus multidrug background therapy (MBT), Arm 2 = DLM plus MBT, and Arm 3 = BDQ and DLM plus MBT. At either the week 8 or week 24 visit, when the participants have an already-scheduled intensive plasma PK, a LP will be performed so that BDQ and/or DLM (total and unbound) concentrations can be measured in CSF. LP timing post-dose will be different for each participant. LP timing will occur in close proximity to a plasma PK sampling time so that CSF:plasma ratios can be determined at different time points over the dosing interval.

If a participant consents to undergo the optional LP but does not meet the requirements of the pre-LP assessments, or withdraws consent prior to LP, the participant will not be included in this nested study and will be replaced within this nested study.

For BDQ, CSF samples will be collected at either 6, 8, or 11-hour plasma PK. The BDQ concentration is expected to be low and therefore the 23-hour plasma PK sample will not have a corresponding CSF sample. For DLM, CSF samples will be collected at either 4, 8, or 11 hours post-dose. The 11-hour plasma concentration for DLM is expected to be the same as the 23-hour plasma concentration as DLM is dosed 12 hourly and therefore the 23-hour plasma sample will not have a corresponding CSF sample. Participants will be spread evenly across sampling times until an estimated two to three participants per drug per time point to a total of eight samples per drug has been achieved.

Participants will be evaluated for contraindications to LP. Safety bloods, including a complete blood count (CBC) and international normalized ratio (INR), will be performed through an ACTG-approved laboratory at the assessment visit prior to the LP either at week 7 or week 22. Participants who have a coagulopathy defined as platelets <100/mm^3 and/or INR >1.4 times the ULN, or other known contraindications to LP, in the opinion of the investigator, will not be considered

for the LP. The week 8 visit will be preferable for the LP. If the participant has already passed week 8 or is not able to undergo an LP at week 8, the participant will be reassessed for inclusion for the week 24 visit. If the participant is unable to participate given the pre-LP assessments (see section 6.3.10) conducted at week 7, then these assessments will need to be repeated at the week 22 visit. Otherwise, safety bloods will only be done at one time point.

PK modeling will be performed to describe drug penetration into CSF and drug exposures over time with oral dosing. Approximately 5-10 mL of CSF will be collected from each participant, the sample will be used for PK analysis, and the remaining CSF will be stored, in case measurement of companion drugs should be of scientific interest in the future. While no meningeal inflammation is expected in this population, CSF albumin will be quantified and the CSF/serum albumin ratio calculated as a marker of inflammation, which may affect the penetration of the drugs [14].

LABORATORY CONTACT INFORMATION FOR THE ABOVE TESTING

UCT SHIPPING ADDRESS FOR PK SAMPLES
Jennifer Norman/Shameema Witbooi
K50 Division of Clinical Pharmacology
Old Main Building, Groote Schuur Hospital
Observatory, 7925
Cape Town, South Africa
Phone (021) 404 7695
Fax (086) 669 1348
Email: Jennifer.Norman@uct.ac.za/Shameema.witbooi@uct.ac.za
LDMS lab code: 499

6.0   REFERENCES

1. Arnold F, Parasuranman S, Arokiasamy P, Kothari M. Nutrition in India. National Family Health Survey (NFHS-3), India, 2005-06. Mumbai: International Institute for Population Sciences; Calverton, Maryland, USA, 2009.
2. Berenguer J, Moreno S, Laguna F, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. N Engl J Med 1992;326:668-72. doi: 10.1056/NEJM199203053261004.
3. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis 2004;8:286-98.
4. Thwaites G, Chau TT, Mai NT, Drobniewski F, McAdam K, Farrar J. Tuberculous meningitis. J Neurol Neurosurg Psychiatry 2000;68:289-99.
5. Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2014;14:947-57. doi: 10.1016/S1473-3099(14)70852-7 [doi].
6. Seddon JA, Visser DH, Bartens M, et al.. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. Pediatr Infect Dis J 2012;31:711-

16. doi: 10.1097/INF.0b013e318253acf8 [doi].

7. Thwaites GE, Lan NT, Dung NH, et al. Effect of antituberculosis drug resistance on response to treatment and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192:79-88. doi: 10.1086/430616.

8. Tho DQ, Torok ME, Yen NT, et al. Influence of antituberculosis drug resistance and Mycobacterium tuberculosis lineage on outcome in HIV-associated tuberculous meningitis. Antimicrob Agents Chemother 2012;56:3074-9. doi: 10.1128/AAC.00319-12 [doi].

9. Daikos GL, Cleary T, Rodriguez A, Fischl MA. Multidrug-resistant tuberculous meningitis in patients with AIDS. Int J Tuberc Lung Dis 2003;7:394-8.

10. Luque S, Grau S, Alvarez-Lerma F, et al. Plasma and cerebrospinal fluid concentrations of linezolid in neurosurgical critically ill patients with proven or suspected central nervous system infections. Int J Antimicrob Agents 2014;44:409-15. doi: 10.1016/j.ijantimicag.2014.07.001 [doi].

11. Sun F, Ruan Q, Wang J, et al. Linezolid manifests a rapid and dramatic therapeutic effect for patients with life-threatening tuberculous meningitis. Antimicrob Agents Chemother 2014;58:6297-301. doi: 10.1128/AAC.02784-14 [doi].

12. Akkerman OW, Odish OF, Bolhuis MS, et al. . Pharmacokinetics of bedaquiline in cerebrospinal fluid and serum in multidrug-resistant tuberculous meningitis. Clin Infect Dis 2016;62:523-4. doi: 10.1093/cid/civ921 [doi].

13. Wager TT, Hou X, Verhoest PR, Villalobos A. Moving beyond rules: the development of a central nervous system multiparameter optimization (CNS MPO) approach to enable alignment of druglike properties. ACS Chem Neurosci 2010;1:435-49. doi: 10.1021/cn100008c [doi].

14. Blennow K, Fredman P, Wallin A, et al. Protein analysis in cerebrospinal fluid. II. Reference values derived from healthy individuals 18-88 years of age. Eur Neurol. 1993;33:129-33.

APPENDIX II: SAMPLE INFORMED CONSENT

Division of AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)
For protocol A5343

A Trial of the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, among Participants Taking Multidrug Treatment for Drug-Resistant Pulmonary Tuberculosis

SHORT TITLE FOR THE STUDY: Bedaquiline and Delamanid for Multidrug-Resistant Tuberculosis

INTRODUCTION

You are being asked to take part in this research study because you have tuberculosis that is resistant to some of the drugs generally used to treat it (which is known as multidrug resistant tuberculosis or MDR-TB) or you have tuberculosis that is resistant to an anti-tuberculosis drug call rifampin (which is known as rifampin monoresistant tuberculosis or RR-TB). This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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

WHY IS THIS STUDY BEING DONE?

Current drug treatments for MDR-TB and RR-TB are not well tolerated and patients on these drugs often have a lot of side effects. Bedaquiline and delamanid are newly approved anti-TB drugs and are both well tolerated. However, the combined effects of these two drugs have not been studied. The main purpose of this study is to determine if these two anti-TB drugs can be safely used together. This study will specifically look at the effect of the drugs on your heart, since both of these drugs have an effect on the electrical activity of the heart. The study will also look at the levels of these drugs in your blood and whether taking them together affects these levels.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you decide to join this study, you will be expected to be in the hospital for at least the first 2 **weeks** of the study, so that you may be monitored closely. You would be hospitalized longer than 2 **weeks** if you are too ill to leave the hospital.
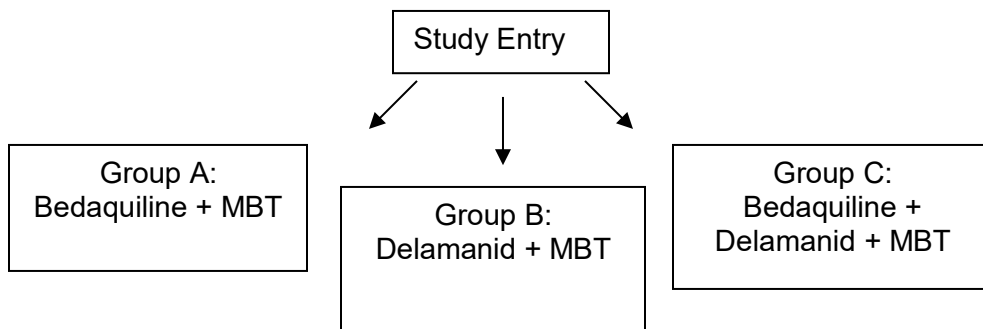
During the study, you will have screening and entry visits, weekly visits for 8 weeks after you enter the study, visits every other week until week 24, and **eight** additional visits between weeks 25 and 128. The schedule of visits and study procedures are explained in Appendix II-A.

If you do not join the study
If you decide not to take part in this study or if you do not meet the eligibility requirements, we will still use some of your information. As part of this screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4 cell count if you are HIV-positive) information is being collected from you so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

If you enter the study
At the study entry visit, you will be assigned to one of three treatment groups. Participants in groups A, B, and C will receive bedaquiline, delamanid, or both drugs in combination (group C), for 24 weeks together with your non-study medications prescribed to treat your TB (multidrug background treatment [MBT]):

```
                              ┌─────────────┐
                              │ Study Entry │
                              └─────────────┘
                            ↙        ↓        ↘
┌──────────────────┐  ┌──────────────────┐  ┌──────────────────┐
│    Group A:       │  │                  │  │    Group C:       │
│ Bedaquiline + MBT │  │    Group B:       │  │  Bedaquiline +    │
│                  │  │  Delamanid + MBT  │  │  Delamanid + MBT  │
└──────────────────┘  └──────────────────┘  └──────────────────┘
```

Because your assignment is random, like the flip of a coin, you will have an equal chance of being in one of the three groups. You will not be able to choose your group, but you and the study doctor, as well as the study staff, will know which group you are in.

The MBT will include at least 3 drugs to which your tuberculosis infection is thought or known to be sensitive. You will need to take or have been taking these drugs for at least 7 days within the 10 days before your study entry visit. There are two possible options for the MBT. In some countries, a longer course of treatment for MDR-TB or RR-TB is given that lasts for up to 24 months. In other countries, a shorter course lasting for 9-12 months may be given. In the shorter course, a medicine called clofazimine is used. This medicine can cause the same side effects as bedaquiline and delamanid. This side effect is an increase in the QT interval (a measure of the heart's electrical cycle). As we want to measure accurately the effect of bedaquiline and delamanid on your heart, you will not be given clofazimine until you have finished your bedaquiline and/or delamanid. While we cannot be sure, we think that bedaquiline and delamanid are as good as clofazimine in killing TB.

If you are infected with HIV (the virus that causes AIDS), your doctor will talk with you about the best options for treating your HIV if you join the study. If you are taking anti-HIV drugs that are

not recommended to be used with the TB drugs used in this study, the doctor may advise you to change your HIV drug treatment and may advise you to use an anti-HIV drug called dolutegravir. If so, this drug will be provided to you by the study.

In addition, you will be asked to have a small sample of hair (about 50-100 strands) cut from your head so that we can measure levels of the TB drugs in this small hair sample. Levels in hair may give us a better idea of long-term exposure to a drug. Of note, humans lose about 100 hairs from their head every day naturally, so this amount of hair removal should not be noticeable. Results of this testing will not be available to you.

At any visit prior to and including week 22, you may be asked to take part of a CSF (cerebrospinal fluid) sampling study (within A5343). CSF is the fluid that surrounds your brain and spinal cord. If you agree to take part of this CSF sampling study, you will have optional lumbar puncture done at weeks 8 or 24. You will be asked to sign a separate consent form for this optional procedure.

Other
If you agree, some of your blood that is left over after all required study testing is done may be stored (with usual protections of your identity) and used for future ACTG-approved research that is separate from this study. Genetic testing will not be done on these blood samples. Samples collected from you will be stored in the US. These samples may be stored for an indefinite period of time. Results of testing performed on these samples will not be given to you. You may withdraw your consent for research on stored specimens at any time and the specimens will be discarded. No matter what you decide, it will not affect your participation in the study.

_____ YES, I agree to have my leftover blood stored.

_____ NO, I do not agree.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 84 people will take part in this study

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 2 years.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early if:
• You request to be taken off the study.
• The study is stopped or cancelled.
• **Your primary care provider thinks the study is no longer good for you.**

The study doctor may also need to take you off the study drug(s) without your permission if:
- You fail to attend 3 consecutive study visits.
- Continuing the study drug(s) may be harmful to you.
- You need a treatment that you may not take while on the study.
- You are a woman who becomes pregnant or is breast-feeding.
- You are not able to take the study drug(s) as required by the study.

If you must stop taking the study drug(s) before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED BEDAQUILINE, DELAMANID AND/OR DOLUTEGRAVIR, OR ONCE I LEAVE THE STUDY, HOW WOULD THESE STUDY DRUGS BE PROVIDED?

During the study:
If you must permanently stop taking study-provided bedaquiline, delamanid, and/or dolutegravir before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:
After you have completed your study participation, the study will not be able to continue to provide you with bedaquiline, delamanid, and/or dolutegravir that you received on the study. If continuing to take these or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. Many of the side effects of the study TB drugs have similar side effects as other treatments you would receive for your TB infection. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study drugs. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Risks of Anti-TB Medications
Some medications used to treat TB may be associated with diarrhea/loose or watery bowels, including bloody diarrhea, which may be serious.

Bedaquiline
The most common side effects of bedaquiline are:
- headache
- dizziness with change in position
- diarrhea
- nausea
- joint pain
- increase of a chemical called uric acid in the blood, which may be associated with an increased risk of joint pain or gout, a type of arthritis.
- vomiting
- increase in the QT interval (a measure of the heart's electrical cycle). A prolonged QT interval may increase the risk of heart rhythm disturbances, which in rare cases, may be fatal. You should tell your doctor if you have had heart problems, including a slow heart rate, or had low thyroid hormone levels. You will have periodic ECGs (electrocardiograms) to monitor the electrical activity of your heart including QT interval.
- elevations in some liver tests called transaminases. You should not drink alcohol while you are taking study medication or other TB drugs as alcohol may also cause elevation of liver tests.
- inflammation of the nose and/or throat

An increased risk of death was seen in the bedaquiline treatment group (9 out of 79 participants, 11.4%) compared to the placebo treatment group (2 out of 81 participants, 2.5%) in one placebo-controlled study. The participants taking bedaquiline died from many different causes and it is unclear if the events were related to bedaquiline. No participant died because of a large increase in the QT interval.

In another later study, there was an increased risk of kidney damage because of vomiting and dehydration from bedaquiline.

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

Delamanid
The most common side effects of delamanid are:
- nausea or vomiting
- abdominal discomfort
- headache
- tiredness
- anxiety or depression
- rash
- joint pain
- decreased blood counts
- increase in the QT interval
- liver disease
- fever

- chest pain
- jaundice (yellowing of the skin or whites of the eyes)

These adverse events could have been due to delamanid, the disease TB itself, other medications, or the development of other illnesses.

As of December 2014, delamanid, when taken together with other TB drugs, has been approved to treat MDR-TB in Europe, Japan, and South Korea.

For your safety, you will have blood tests and an ECG performed before you are allowed to participate in the study and receive study treatment with bedaquiline or delamanid or both, and you will have regular ECGs during the trial to watch for any important changes. If important changes in QT interval are found in your ECG, study TB drugs will be stopped immediately. You may be hospitalized for monitoring. Although cases of lengthened QT interval have happened before, no patients experienced any harm from it.

Risks of Combination Antiretroviral Drugs Used to Treat HIV Infection

Immune Reconstitution Syndrome:
In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:
- increase in fat around the waist and stomach area
- increase in fat on the back of the neck
- thinning of the face, legs, and arms
- breast enlargement

Dolutegravir
Recently, some new information about DTG from another study being done in Botswana was reported. This study found that women taking DTG when they became pregnant appeared to be more likely to have babies with an abnormality called a neural tube defect than women who were taking other HIV medicines when they became pregnant. A neural tube defect is an abnormality of the spine or brain that can be severe. This abnormality can cause babies to die. Neural tube defects usually happen in about 1 out of every 1000 babies. In the Botswana study, neural tube defects were found in about 1 out of 100 babies born to women who were taking DTG when they became pregnant. A baby's neural tube is formed in the first 4 weeks after pregnancy. In the Botswana study, no neural tube defects were found in babies born to women who started taking DTG in pregnancy, after the neural tube had formed. The drug company and regulatory authorities and different researchers are looking into this issue to see if DTG really does cause neural tube defects. In the meantime, the US FDA and other groups have recommended that women who are going to start DTG have a pregnancy test first. They

also recommend that women use birth control to prevent pregnancy while taking DTG. HIV-infected women who are able to become pregnant are allowed to participate in this study, but they must use a method of birth control in order to not become pregnant while taking DTG from the following list:
  • **Contraceptive subdermal implant**
  • **Intrauterine device (IUD) or intrauterine system**
  • **Combined estrogen and progestogen oral contraceptive**
  • **Injectable progestogen (Depo-Provera)**
  • **Contraceptive vaginal ring**
  • **Percutaneous contraceptive patches**

If you do become pregnant while on study and taking DTG, you must call the study doctor right away.

<u>Side Effects</u>
The following serious side effects have been associated with the use of dolutegravir. These include allergic reactions and liver problems, which may be life-threatening.

Contact your health care provider right away if you develop a rash while taking dolutegravir, especially if it's associated with any of the following symptoms:

  • **Fever**
  • **General ill feeling**
  • **Extreme tiredness**
  • **Muscle or joint aches**
  • **Blisters or sores in your mouth**
  • **Blisters or peeling skin**
  • **Redness or swelling of your eyes**
  • **Swelling of your mouth, face, lips, or tongue**
  • **Trouble breathing**
  • **Common cold (nasopharyngitis)**
  • **Diarrhea**

Contact your health care provider right away if you have any of the following symptoms that could be signs of liver problems:

  • **Yellowing of your skin or whites of your eyes (jaundice)**
  • **Dark or tea-colored urine**
  • **Pale-colored bowel movements**
  • **Nausea or vomiting**
  • **Loss of appetite**
  • **Pain, aching, or tenderness on your right side below your ribs**

People with pre-existing history of depression or other mental health illness may be at greater risk for suicidal thoughts, or attempts, which may lead to death. If your mental health illness worsens, or if you develop suicidal thoughts, call your healthcare provider

right away.

Other side effects include:
- **Changes in liver test results, more common in people with hepatitis B or C**
- **Trouble sleeping**
- **Tiredness**
- **Headache**

Tell your study doctor about any side effect that bothers you or that does not go away.

Risks of Non-Study Medications
There is a risk of side effects when non-study medications are taken with bedaquiline, delamanid, and dolutegravir. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. In addition, you must tell the study doctor or nurse before enrolling in any other research studies while on this study.

Risks of Drawing Blood
Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, lightheadedness, and in rare cases, fainting or infection.

Risks of ECG
You may experience mild irritation, slight redness and itching on your skin where the electrodes from the electrocardiogram machine are placed.

Risks of Hair Collection
There is a small risk of cutting or nicking the scalp during the hair collection, although this is extremely rare.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV or TB status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV or TB status. Please talk with the study staff if you have any concerns in this regard.

Risks to Stored Samples
There is a risk that your stored samples and/or health information may be misused. There are laws against this kind of misuse, but they may not fully protect you. The chance that this will happen is considered small because of the security taken with your samples and information.

ARE THERE RISKS RELATED TO PREGNANCY?

Bedaquiline and delamanid may be unsafe for unborn babies. If you are having sex that could lead to pregnancy, you must agree not to become pregnant or to impregnate your partner while

you are taking bedaquiline and/or delamanid and for 6 months after stopping the study drug(s). You must use one of the following methods of birth control that you discuss with the study staff:

- male or female condoms
- diaphragm or cervical cap with a cream or gel that kills sperm
- intrauterine device (IUD)
- oral contraceptives or Depo-Provera

If you become pregnant while taking part in this study, you will continue to be followed on the study and your pregnancy outcome will be recorded. If you are taking antiretroviral therapy (ART) for treatment of Human Immunodeficiency Virus (HIV), your pregnancy will be reported to the Antiretroviral Pregnancy Registry.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have tuberculosis.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- treatment with prescription drugs available to you
- treatment with experimental drugs, if you qualify
- no treatment

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the ACTG, OHRP, FDA, (insert name of site) Institutional Review Board (IRB) or Ethics Committee (EC), National Institutes of Health (NIH), **other local, US, and international regulatory entities**, study staff, study monitors, and drug companies supporting this study. An IRB or EC is a committee that watches over the safety and rights of research participants.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

You may be reimbursed for your time and travel expenses as part of your participation in this study. (Insert site-specific information about payment.)

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- name of the investigator or other study staff
- telephone number of above

For questions about your rights as a research participant, contact:
- name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- telephone number of above

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____   _____
Participant's Name (print)   Participant's Signature and Date

_____   _____
Participant's Legal Representative (print)   Legal Representative's Signature and Date
(As appropriate)

_____   _____
Study Staff Conducting   Study Staff's Signature and Date
Consent Discussion (print)

_____   _____
Witness's Name (print)   Witness's Signature and Date
(As appropriate)

APPENDIX II-A: A5343 STUDY VISITS

The study staff can answer any questions you have about individual study visits, how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

I.   Study Schedule

Evaluation or Procedure	Screening[1]	Entry[2]	Start of TB Study Drug[3]	Visits in First 24 Weeks[4]	Follow-up Visits[5]	Early Treatment or Study Discontin-uation[6]
Consent & contact information collected	√					
HIV status checked	√					
Physical exam	√	√	√	√	√	√
Blood collected (see blood tests below)	√	√		√	√	
Pregnancy test[7]	√			If needed	If needed	**If needed**
Pre-lumbar puncture (LP) assessments and optional LP[8]				√		
Urinalysis		√				
Sputum collected	√	√		√	√	√
Hair collected		√		√	√	
Chest x-ray	√					
ECG	√	√		√	√	√
Adherence questions				√		√

[1]Screening Visit: After you have read and signed the consent form, you will have several tests done to make sure that you meet the requirements for joining the study.
[2]Entry Visit: If you are able to join the study, you will enter the study and receive your treatment assignment. At this visit, you will find out if you receive bedaquiline, delamanid, or both drugs in combination.
[3]Start of TB Study Drug: This visit may occur at entry or within 7 days after entry. You will start your TB study drug at this visit.
[4]Visits in First 24 Weeks: You will have a visit every week for 8 weeks after you start TB study drug and then every other week until 24 weeks after the entry visit. This is the treatment period, during which you will receive study drugs. You will be hospitalized for at least the first 2 **weeks** of the treatment period.
[5]Follow-up Visits: After the first 24 weeks, you will have visits at weeks 28 and 36, every 12 weeks until week 96, and at week 128.
[6]Early Treatment or Study Discontinuation: If you stop the study drug early, you will be asked to

come in for an early treatment discontinuation visit.

[7]Women of reproductive potential who are taking dolutegravir will be required to have pregnancy testing every two weeks during the first 24 weeks (i.e., weeks 2-24) and during follow-up study visits at weeks 28, 36, 48, 60, 72, 84, 96, and 128.

[8]Not all participants will have an LP to collect cerebrospinal fluid (CSF) done at week 8 or 24. Only participants who are asked and wish to participate in the LP for CSF collection, and complete a separate consent form (see Appendix III), will have an LP done. Pre-LP assessments are required prior to the optional LP for participants who consent to have the LP done.

II.   Explanation of Evaluations

Below are descriptions of the evaluations. You will be told the results of all tests performed with the exception of those tests to look at the levels of study drugs in your body and for future ACTG-approved testing.

Consent and contact information collected
After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue and join the study. You will also be asked how to be contacted in case you miss a visit or there are problems with your tests, and whether you give the study team permission to contact you.

HIV-1 infection status checked
If there is no record available, another HIV-1 test will be done. If an HIV-1 test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV-1 test as soon as it is available.

Physical examination
You will have a physical exam and will be asked questions about your health and about any medicines you have taken or are taking now. At entry and weeks 4, 8, 12, 16, 20, and 24, your vision will also be checked if you are taking the anti-TB drug ethambutol.

Blood collected
Between 5 and 60 mL (1 teaspoon to 4 tablespoons) of blood may be collected at any one visit. Blood will be collected from you for various tests during the study including:

Hematology, chemistry and liver function tests
These are routine blood tests for safety. You will have blood for some or all of these routine tests drawn at every visit through week 28.

Hepatitis B surface antigen
This test shows if you are infected with hepatitis B. You will have blood drawn for this test at screening.

Hepatitis C antibodies
This test shows if you have been infected with hepatitis C. You will have blood drawn for this test at screening.

Thyroid Stimulating Hormone
This test shows how well your thyroid gland is working. You will have blood for this

test at entry and week 12.

HIV-1 viral load
This is a test that shows how much HIV is in your blood. If you are infected with HIV-1, you will have blood drawn for this test at entry, week 24, and week 48. If you have been on anti-HIV drugs for 6 months or longer, you will also have this test at screening and possibly also at entry.

HIV-1 genotype
This test is used to determine if the HIV in your blood has genetic mutations that are known to cause resistance to certain anti-HIV drugs. You will have this test at screening if you have been on anti-HIV for 6 months or longer and have an HIV-1 viral load at screening that shows the level of HIV in your blood is high enough for the genotype to be done.

CD4+ count
This is a test that shows how many infection-fighting cells you have in your blood. If you are infected with HIV-1, you will have blood drawn for this test at screening and weeks 24 and 48.

Pharmacokinetic sampling
These tests look at the levels of the anti-TB drugs in your body. You will have blood drawn for these tests at weeks 4, 6, 10, 12, 14, 16, 18, 20, 22, and 28. In addition, you will have blood drawn for intensive pharmacokinetic (PK) testing at weeks 2, 8, and 24. During these visits, five
or six PK blood samples will be taken over a 24-hour period. These blood samples will be collected from an indwelling catheter in your arm, if one can be placed and maintained successfully.

Pharmacogenomic analyses
Some blood will be collected and stored to look at how a person's genes affect their response to drugs.

Pregnancy test
Women who are able to become pregnant, you will be asked to give a small urine or blood sample (about 5 mL or 1 teaspoon) for a pregnancy test at screening and at other times during the study, if you think you might be pregnant. **Women receiving dolutegravir for treatment of HIV infection will have more regular testing for pregnancy (at every scheduled study visit).**

Pre-Lumbar Puncture (LP) Assessments and Optional LP
You may be asked to participate in an optional LP to collect your CSF. If you agree, you will have safety bloods done approximately one week prior to the LP. The LP will be done as described in Appendix III.

Urinalysis
You will be asked to provide a sample of urine at entry.

Sputum collected

You will be asked to provide sputum samples at screening, weeks 0-12, 16, 20, 24, 28, 36, 48, 84, 96, and 128. To provide this sample, you will be asked to cough deeply and then spit into a cup. If you need help to cough deeply, the clinic staff may ask you to briefly breathe a mist of saltwater through a tube or a mask. At some visits, these samples will be used for TB drug susceptibility tests, to see if your tuberculosis infection responds to TB drugs. Some of your sputum may be stored.

Hair Collected
You will have a small sample of hair (about 50-100 strands) cut from your head to measure levels of the TB drugs in this small hair sample. You will have a hair sample taken at entry and weeks 8, 16, 24, 48, 72, 96, and 128.

Chest x-ray
You will have a chest x-ray at screening.

ECG
You will have electrocardiograms to look at the electrical activity of your heart. These tests will be done at screening, at entry one day prior to TB study treatment or on the day you start TB study treatment, every 2 weeks for 24 weeks during TB study treatment, at week 28, and if you discontinue study treatment or the study early. If you discontinue the study treatment after week 28, an ECG is not required at the early treatment or study discontinuation visit.

Adherence questions
While you are taking study drugs, you will be asked questions about how well you remember to take the study drugs every week between weeks 1-8, every 2 weeks between weeks 10 and 24, and if you stop the study drugs or the study early. You will also be given pill boxes for your study drugs. Study staff or others approved by the study staff will watch you take one of your study drugs for some of your doses. This is called directly observed therapy or DOT. If you are on bedaquiline, this DOT will be done once a day in the morning 7 days per week for 2 weeks and then 3 days per week for 22 weeks. If you are on delamanid or both bedaquiline and delamanid, DOT will be done once a day in the morning on your delamanid dose 7 days per week for 2 weeks and then 5 days a week for 22 weeks. After week 24, study DOT supporters or others approved by the study staff will watch you take one of your study drugs twice each week.

APPENDIX III: CONSENT FOR OPTIONAL LUMBAR PUNCTURE (LP) AT WEEK 8 OR 24

At any visit prior to and including week 22, you may be asked and consented to take part in an optional LP that will be done at week 8 or 24. This optional procedure (as described below) will advance the scientific goals of this study but will offer no direct benefit to participants. Up to 16 participants will take part in the optional LP. If you are one of the 16 participants who agrees to have this procedure, neither you nor your doctor will receive any results from the procedures because the tests are for research purposes only. If you are asked and choose not to participate in the optional procedures, it will not affect your ability to take part in this study (A5343).

NOTE: If you are pregnant, the LP will not be done.

A.   Explanation of LP

Participants undergoing a LP must have safety bloods (CBC/INR) performed, along with an assessment of medical history approximately one week prior to your LP. The LP will be done at your week 8 or 24 visit. A LP is a medical procedure that involves removing a small amount of cerebrospinal fluid (CSF) from your spine. You should drink plenty of fluids the day before the LP procedure. The procedure will be performed at *[insert site-specific details]*. You will be asked to lie down on your side or to sit "backwards" in a chair (so that you are facing the back of the chair). An area of skin on your lower back will be sterilized with fluid. You will get an injection to numb the skin in the sterilized area. You may feel a burning sensation from the fluid that is injected. When the area is numb, the doctor will insert a thin needle between two of the bones in your spine. Approximately 5-10mL of CSF will be collected through the needle. The entire LP procedure will take about 30 minutes.

After the CSF collection, you may be asked to lie flat for up to 30 minutes to reduce the chance that you will get a headache. You should limit your physical activity for the remainder of the day. The study or clinic staff will call you the day after the procedure to check on how you are feeling.

B.   Risks Associated with LP

The risks of LP include local soreness at the site of needle entry, and pain and possible allergic reaction associated with local anesthesia. There is a small risk of headache or decreased blood pressure from removing the small amount of fluid or leaking of CSF after the procedure. There is a small risk of infection and a very small risk of damage to nerves in the lumbar spinal roots after the procedure, which could cause pain, numbness, or loss of sensation to the legs. Before the procedure, the area where the needle will be inserted will be cleaned with an antiseptic (such as betadine or rubbing alcohol) in order to reduce the risk of infection. A bandage will be placed on the skin where the needle went in, and the participants will be asked to remove the bandage the next day and tell the study doctor right away if any redness or tenderness is present. Participants will be asked to remain lying flat for up to 30 minutes after the procedure, and will be given fluid to drink after the procedure. The site staff will ask the participants

about history of any allergies to anesthetics and will not perform a LP in any participant with such a history. The site staff will perform safety blood tests a few days before the LP, and will not perform the LP if the blood results indicate it is not safe to do so.

C. **Storage of CSF Specimens**
CSF specimens may be stored and used in future study-related and/or unspecified future research. Your CSF specimens will be shipped and/or stored outside of the country where they were collected.

Please indicate below if you agree to have the LP done. No matter what you decide, it will not affect your participation in the study (A5343).

_____ (initials) YES, I agree to have the LP done.

_____ (initials) NO, I do not agree to have the LP done.

If you agree to have the LP done, please indicate below if you agree to have some of your CSF specimens stored.

_____ (initials) YES, I agree to have CSF stored.

_____ (initials) NO, I do not agree to have CSF stored.

SIGNATURE PAGE: A5343 INFORMED CONSENT FOR OPTIONAL LUMBAR PUNCTURE PROCEDURE

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in the optional LP procedure that will be done at weeks 8 or 24, please sign your name below.

_____   _____
Participant's Name (print)   **Participant's Signature and Date**

_____   _____
Study Staff Conducting   **Study Staff's Signature and Date**
Consent Discussion (print)

_____   _____
Witness's Name (print)   **Witness's Signature and Date**
(As appropriate)