ACTG NETWORK COORDINATING CENTER
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3000

LETTER OF AMENDMENT

DATE: September 13, 2024

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5356 Protocol Team

SUBJECT: Letter of Amendment #1 for Protocol A5356

The following information affects the A5356 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by your IRB/EC before implementation.

The following information may also affect the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. An LOA registration notification from the DAIDS PRO is not required prior to implementing the LOA. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

This LOA is being implemented to update the temperature storage for clofazimine.

The following is a change (noted in bold or strikethrough) to A5356, Version 3.0, 07/16/24, titled, "A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis." This change will be included in the next version of the A5356 protocol if it is amended at a future date.

1. A Protocol Signature Page (PSP) is appended for submission to DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. Section 5.2.4 is being updated for clofazimine to read as follows:

   5.2.4 Clofazimine: Clofazimine will be supplied as 100 mg capsules. Do not store above **25**~~30~~ºC (**77**~~86~~ºF). Protect from light and moisture.

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

A5356

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug Resistant Pulmonary Tuberculosis

A Multicenter Trial of the
ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections)

Sponsored by:
National Institute of Allergy and Infectious Diseases

Industry Support Provided by:
Otsuka Pharmaceutical Company, Ltd.
Pfizer, Inc.

IND # 156066

The ACTG Tuberculosis Transformative Science Group:	**Kelly Dooley, MD, PhD, Chair**
Protocol Chair:	**Constance A. Benson, MD**
Protocol Co-Vice Chair:	**Rodney Dawson, MBChB, FCP**
DAIDS Clinical Representative:	**Irina Gelmanova, MD, MPH**
Clinical Trials Specialist:	**Jennifer Tiu, BS, MPH**

FINAL Version 3.0
July 16, 2024

A5356
FINAL Version 3.0
16Jul2024

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title

TABLE OF CONTENTS

Page

CONTENTS (Cont'd) Page

CONTENTS (Cont'd) Page

SITES PARTICIPATING IN THE STUDY

A5356 is a multicenter study open to non-US **Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections** (ACTG) clinical research sites (CRSs) in countries with reported cases of drug-resistant tuberculosis.

Refer to the Site tab on the protocol's webpage on the ACTG member website for the list of eligible sites.

PROTOCOL TEAM ROSTER

Chair
Constance A. Benson, MD
The University of California, San Diego
Collaborative CTU
UCSD Antiviral Research Center
MC 8208
200 West Arbor Drive
San Diego, CA 92103-8208
Phone: 619-543-8080
E-mail: cbenson@ucsd.edu

Vice Chair
Rodney Dawson, MBChB, FCP
Centre for TB Research Innovation
University of Cape Town Lung Institute
P.O. Box 34560
George Street, Mowbray
Cape Town 7700, Western Cape
SOUTH AFRICA
Phone: 27-21-4066864
E-mail: rodney.dawson@uct.ac.za

DAIDS Clinical Representative
Irina E. Gelmanova, MD, MPH
TB Research Branch
Therapeutic Research Program
5601 Fishers Lane, **MSC 9830**
Rockville, MD 20852-9831
Phone: 301-332-4057
E-mail: irina.gelmanova@nih.gov

Statisticians
Michelle A. Kendall, MS
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
651 Huntington Avenue
FXB Building, Room 545A
Boston, MA 02115
Phone: 617-432-3869
E-mail: kendall@sdac.harvard.edu

Statisticians (Cont'd)
Sindy Du, MS
Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health
FXB Building
651 Huntington Avenue
Boston, MA 02115
Phone: 617-432-0062
E-mail: xdu@sdac.harvard.edu

Data Managers
Brandon Downing, BS
Frontier Science & Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. **7290**
E-mail: **downing**@frontierscience.org

Elizabeth Siciliano, MPH
Frontier Science & Technology Research
Foundation, Inc.
4033 Maple Road
Amherst, NY 14226-1056
Phone: 716-834-0900 Ext. 7276
E-mail: siciliano@frontierscience.org

Clinical Trials Specialist
Jennifer Tiu, BS, MPH
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Ste 777
Bethesda, MD 20817
Phone: 301-628-337**1**
E-mail: **jennifer.tiu**@dlhcorp.com

DAIDS Pharmacist
Oladapo Alli, PharmD
Pharmaceutical Affairs Branch
DAIDS, NIAID, NIH
5601 Fishers Lane, **MSC 9831**
Rockville, MD 20852
Phone: 240-627-3593
E-mail: oladapo.alli@nih.gov

Pharmacologists
Kimberly K. Scarsi, PharmD, MS
College of Pharmacy
University of Nebraska Medical Center
Department of Pharmacy Practice
Room 3021
986145 Nebraska Medical Center
Omaha, NE 8198-6145
Phone: 402-559-9916
E-mail: kim.scarsi@unmc.edu

Courtney V. Fletcher, PharmD
College of Pharmacy
University of Nebraska Medical Center
986120 Nebraska Medical Center
Omaha, NE 68198-6120
Phone: 402-559-4333
E-mail: cfletcher@unmc.edu

Investigators
Caryn Upton, MBBCh
TASK Applied Science CRS
Brooklyn Chest Hospital
1 Stanberry Road
Ysterplaat, Cape Town 7425
S**outh** A**frica**
Phone: 27-215-102-209
E-mail: dr.caryn@task.org.za

Eric Nuermberger, MD
Division of Infectious Diseases
Johns Hopkins University
Center for TB Research
1550 Orleans Street, Room 107
Baltimore, MD 21231
Phone: 410-502-0580
E-mail: enuermb@jhmi.edu

Sandra Wagner Cardoso, MD, PhD
Instituto de Pesquisa Clinica Evandro Chagas CRS
Avenida Brasil 4365, Manguinhos
Rio de Janeiro 21045-900
Brazil
Phone: 55-21-38659623
E-mail: dra.wagner@gmail.com

Investigators (Cont'd)
Giovanni Schifitto, MD
University of Rochester Adult HIV Therapeutic Strategies Network CRS
601 Elmwood Avenue
Rochester NY 14620
Phone: 585-275-0558
E-mail:
giovanni_schifitto@urmc.rochester.edu

Laboratory Data Manager
Kevin Knowles, MA, PhD
Frontier Science & Technology Research Foundation, Inc.
4033 Maple Road
Amherst, NY 14226
Phone: 716-834-0900 Ext. 7238
E-mail: knowles@frontierscience.org

Laboratory Specialists
William Murtaugh, MPH
ACTG Lab Center
10090 Wilshire Boulevard, Suite #260
Los Angeles, CA 90024
Phone: 310-794-9894
E-mail: wmurtaugh@milabcentral.org

Leah Spalding, BS
ACTG Lab Center
10090 Wilshire Boulevard, Suite #260
Los Angeles, CA 90024
Phone: 424-440-3491
E-mail: lspalding@milabcentral.org

Field Representatives
Jamile Costenaro, MSc
Hospital Nossa Senhora da Conceicao CRS
Avenue Francisco Trein, 596
Porto Alegre, 91350-200
Rio Grande do Sul
B**razil**
Phone: +55 51-33572603
E-mail: jamilegcbiomed@gmail.com

Field Representatives (Cont'd)

Dimas Kliemann, MD
Hospital Nossa Senhora da Conceicao CRS
Av. Francisco Trein, 596
Porto Alegre, 91350-200
Rio Grande do Sul
Brazil
Phone: 55-51-33572126
E-mail: dimaskliemann@gmail.com

International Site Specialist
Allan-Michael Bills, BS
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 301-628-3273
E-mail: allan-michael.bills@dlhcorp.com

Source Document Specialist
Josie Marshall, BS
ACTG Network Coordinating Center
DLH
6720B Rockledge Drive, Suite 777
Bethesda, MD 20817
Phone: 303-724-0803
E-mail: josie.marshall@dlhcorp.com

Community Scientific Subcommittee (CSS) Representative
Stanford Chimutimunzeve
Milton Park CRS
76 Mvumba Street
Mufakose Harare
ZIMBABWE
Phone: 263-774-76739
E-mail: stanchimutimunzeve@gmail.com

Industry Representatives
Nataša Lazarević
Otsuka Novel Products GmbH
Erika-Mann-Str. 21
Munich 80636
Germany
Phone: +49 **172 2647712**
E-mail: **nlazarevic**@otsuka-onpg.com

Industry Representatives (Cont'd)

Xiaoyuan Fan
Pfizer, Inc.
235 East 42nd Steet
New York, NY 10017
E-mail: **xiaoyuan.fan@pfizer.com**

STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5356@fstrf.org via e-mail. **The appropriate team member will generally respond within 1 working day.**

When sending messages to individual team members by role (e.g., Protocol Data Manager, Clinical Trials Specialist), sites should check the current roster on the ACTG Member Website.

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to **or removed from** the actg.protA5356 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 Clinical Management Committee (CMC). Send an e-mail message to actg.cmcA5356@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.teamA5356@fstrf.org. **Include the study number and "laboratory question" in the e-mail subject line.**

Data Management
- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRF), the eCRF schedule of events, randomization/registration, delinquencies, and other data management issues, contact **Brandon Downing and Elizabeth Siciliano** directly. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the **Frontier Science & Technology Research Foundation** (FSTRF) website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer ACTG-119 SOP, and contact **Brandon Downing and Elizabeth Siciliano** directly.
- For other questions, send an e-mail message to actg.teamA5356@fstrf.org (Attention: **Brandon Downing and Elizabeth Siciliano**).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists, **contact the Randomization Desk at the Frontier Science Data Management Center (DMC)**. Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
For questions about the DMC portal or Medidata Rave, contact DMC User Support. Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 **x7302**.

Computer and Screen Problems
Contact the SDAC/DMC programmers. Send an e-mail message to actg.support@fstrf.org or call 716-834-0900, extension 7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist **(CTS)**. Send an e-mail message to actg.leadA5356@fstrf.org (Attention: **Jennifer Tiu**).

Copies of the Protocol
To request a hard copy of the protocol, send a message to ACTGNCC@dlhcorp.com via e-mail. Electronic copies can be downloaded from the **protocol-specific web page (PSWP) on the** ACTG **member** website.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or Investigator Brochures, contact the DAIDS Regulatory Support Center (RSC). **Send an e-mail message to** RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, **contact DAIDS Protocol Registration. S**end an e-mail message to protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation, contact the ACTG Site Coordination group at actgsitecoordination@dlhcorp.com **with a cc to the study's CTS**.

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call or e-mail Oladapo Alli, protocol pharmacist, at 240-627-3112; E-mail: oladapo.alli@nih.gov.

Study Drug Orders
Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741 **between 8 AM and 5 PM Eastern Time (ET). Outside of this timeframe, sites may use other contact information found in the CRPMC Online Site Management and Ordering System (COSMOS)**.

IND (Investigational New Drug) Number or Questions
The IND number will be available on the PSWP **approximately** 30 days **after** the submission **of the final protocol version** to the **Food and Drug Administration (**FDA**)**. 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
For any questions related to EAE reporting, contact DAIDS through the RSC Safety Office. **Send an e-mail message to** DAIDS RSCSafetyOffice@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 A5356 team members. Send an e-mail **message** to actg.teamA5356@fstrf.org.

Protocol-Specific Web Page
Additional information about management of the protocol can be found on the A5356 PSWP **on the ACTG member website**.

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

AFB	acid-fast bacillus
BDQ	bedaquiline
CFZ	clofazimine
DLM	delamanid
DOT	directly observed therapy
DR-TB	drug-resistant TB (defined as MDR-TB, RR-TB, pre-XDR-TB, or XDR-TB)
DST	drug-susceptibility testing
EBA	early bactericidal activity
EFV	efavirenz
FQ	fluoroquinolone
GCLP	Good Clinical Laboratory Practice
Group A Drugs	levofloxacin or moxifloxacin, bedaquiline and linezolid (these may change in the future)
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LFX	levofloxacin
LZD	linezolid
MDR-TB	multidrug-resistant tuberculosis (strains of *Mycobacterium tuberculosis* with confirmed resistance to at least rifampicin and isoniazid)
MIC	minimum inhibitory concentration
MTB	*Mycobacterium tuberculosis*
OBR	optimized background regimen
OBT	optimized background therapy
PK	pharmacokinetic
Pre-XDR-TB	Pre-extensively drug resistant tuberculosis (defined as MDR/RR-TB strains that are resistance to any fluoroquinolone)
PZA	pyrazinamide
QD	once daily
QTcF	QT interval measure using the Fridericia correction method
RIF	rifampicin or rifampin
RR-TB	rifampicin-resistant TB
SOC	standard of care
TB	tuberculosis

TIW	three times per week
XDR-TB	extensively drug-resistant tuberculosis (defined as MDR/RR-TB strains that are also resistant to any fluoroquinolones and at least one additional Group A anti-TB drug; see above)

SCHEMA

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

DESIGN

A5356 is a phase II, prospective, randomized, two-arm, open-label, multicenter clinical trial to evaluate the anti-tuberculosis (TB) activity, safety, and tolerability of an injectable-free short course regimen for treatment of multidrug-/rifampicin-resistant (MDR-/RR-), pre-extensively drug-resistant (pre-XDR-), and extensively drug-resistant (XDR-) TB comparing two dosing strategies of linezolid (LZD) combined with bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ).

DURATION

72 weeks total: at least 26 weeks (6 months) of anti-TB treatment, with up to 46 weeks of follow-up.

SAMPLE SIZE

132 participants (66 per treatment arm).

POPULATION

Participants aged 18 years and older, with or without HIV, with newly diagnosed pulmonary MDR/RR-TB, pre-XDR-TB, or XDR-TB (collectively noted as DR-TB in the protocol).

Participants may be enrolled with a positive rapid molecular diagnostic test for MDR/RR-TB such as Cepheid Xpert MTB/RIF, Cepheid Xpert MTB/RIF Ultra, Cepheid Xpert MTB/XDR, Hain GenoType MTBDR*plus*, Hain GenoType MTBDRsl, or other World Health Organization (WHO)-endorsed rapid diagnostic test or with screening culture-based phenotypic drug susceptibility testing (DST) from a sputum specimen collected within 60 days prior to entry.

Participants living with HIV are required to either be on ART or be willing to start ART within 30 days after entry.

REGIMENS

At entry, all participants will be randomized 1:1 to one of two treatment arms (Arm A or Arm B). The only difference in treatment between the two arms is the dosing schedule for LZD, as shown below.

Arm A
Weeks 1-26: LZD 600 mg once daily (QD)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Arm B
Weeks 1-4: LZD 1200 mg QD
Weeks 5-26: LZD 1200 mg three times per week (TIW)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Participants who do not achieve sputum culture conversion by 16 weeks of treatment will extend their treatment by an additional 12 weeks for a total treatment duration of 38 weeks.

A5356 Study Treatment Regimens

Arm	Drug and dose	Weeks				
		On-treatment				Follow-up
		1-2	3-4	5-8	9-26 Or 9-38[a]	27-72 Or 39-72[a]
Arm A	LZD 600 mg QD	X	X	X	X	Follow up with no further treatment
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	
Arm B	LZD 1200 mg QD	X	X			
	LZD 1200 mg TIW			X	X	
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	

[a] Participants who do not achieve sputum culture conversion by 16 weeks of treatment will extend their treatment by an additional 12 weeks for a total treatment duration of 38 weeks.

Twenty participants in each arm will have an intensive pharmacokinetic (PK) visit (lasting 24 hours) at week 4. Arm B participants must complete this visit before dose adjustment of LZD during week 5.

For all participants who do not participate in the intensive PK visit, they will have an abbreviated PK visit (lasting about 4-5 hours) at week 4.

All participants will also have a single PK sample collected prior to their morning dose of TB treatment (to generally represent trough levels) at every study visit while on study treatment, that is, at study weeks 2, 6, 8,

12, 16, 20, and 26, and at weeks 30, 38, and/or 42 for participants requiring an extension of study treatment.

1.0 HYPOTHESIS AND STUDY OBJECTIVES

1.1 Hypothesis

1.1.1 Linezolid (LZD) administered at an initial dose of 1200 mg daily for 4 weeks followed by 1200 mg three times per week (TIW), plus bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ) will be associated with more rapid sputum culture conversion and acceptable rates of treatment discontinuations due to adverse events (AEs), intolerance, and death compared to LZD administered at a dose of 600 mg daily in combination with BDQ, DLM, and CFZ.

1.2 Primary Objectives

1.2.1 To compare time to sputum culture conversion in liquid media between treatment arms.

1.2.2 To estimate the occurrence of permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death within each treatment arm.

1.3 Secondary Objectives

1.3.1 To compare proportion with sputum culture conversion in liquid media at 8, 16, 26, and 38 weeks between treatment arms.

1.3.2 To compare permanent discontinuation of LZD due to AEs, intolerance, or death, temporary discontinuation of LZD for any reason, and dose reductions for LZD between treatment arms.

1.3.3 To compare the occurrence of treatment-related AEs between treatment arms.

1.3.4 To compare the occurrence of unfavorable TB treatment outcome at weeks 26, 38 (for those who extend treatment by 12 weeks), and 72 between treatment arms.

1.3.5 To determine LZD pharmacokinetic (PK) parameters for each LZD dosing strategy.

1.3.6 To determine DLM PK parameters within each treatment arm.

1.3.7 To compare adherence to LZD, BDQ, DLM, and CFZ between treatment arms as determined by recording of the number of observed doses based on directly observed therapy (DOT).

1.4 Exploratory Objectives

1.4.1 To investigate efficacy and safety between A5356 and contemporaneous DR-TB clinical trials.

1.4.2 To determine baseline prognostic risk factors for unfavorable TB treatment outcome.

1.4.3 To investigate unfavorable TB treatment outcome and treatment-related AEs by baseline prognostic risk factors between treatment arms.

1.4.4 To compare resistance to at least one study drug by week 26 (by week 38 for those who extend treatment by 12 weeks) and by week 72 between treatment arms.

NOTE: Drug susceptibility testing (DST) for this exploratory objective may be done at the local TB program laboratory, at a national TB program laboratory, or at a central laboratory designated by the ACTG for this purpose using either genotypic or phenotypic assays available in the laboratory as outlined in section 4.1.2.

1.4.5 To characterize the occurrence and signs and symptoms of MTB immune reconstitution inflammatory syndrome (MTB IRIS) events.

1.4.6 To describe exposure-outcome relationships between LZD PK parameters achieved with each dosing strategy and antimicrobial efficacy and LZD-related AEs and explore whether incorporation of exposure of other TB treatment drugs in the treatment regimen provides an improved understanding of exposure-response.

1.4.7 To describe exposure-outcome relationships between DLM PK parameters achieved and antimicrobial efficacy and DLM-related AEs.

1.4.8 If LZD and DLM PK exposure-outcome relationships suggest additional data are required for BDQ and CFZ PK exposure-outcome relationships, these may be performed pending availability of funding and data from other contemporaneous trials. BDQ and CFZ PK parameters will be assessed from the same samples collected for LZD analysis.

1.4.9 To explore whether efficacy, safety, and/or PK of LZD are associated with polymorphisms in human genes that may affect metabolism, disposition and toxicity of study drugs as well as concomitant medications (e.g., *NAT2* and *CYP2B6*).

2.0 INTRODUCTION

2.1 Background

Multidrug-/rifampicin-resistant tuberculosis (MDR-/RR-TB) is a major threat to human health worldwide. An estimated 3.4% of all new TB cases (an estimated 484,000 incident cases) and 18% of retreatment cases of TB are due to MDR-/RR-strains of MTB [1]. The greatest burden of MDR-/RR-TB is in India, China and the Russian Federation, accounting for almost half of all cases of MDR/RR-TB [1]. An estimated 6.2% of MDR-/RR-TB globally are extensively drug-resistant TB (XDR-TB). In 2018, the proportion of MDR/RR-TB cases with resistance to any fluoroquinolone (FQ), including levofloxacin, moxifloxacin, and ofloxacin, was 20.8% [1]. Diagnostic and treatment delays, lack of access to effective drugs in some areas, poor infrastructure support for DOT, lack of access to appropriate diagnostic testing and monitoring tools, HIV co-infection with its attendant role in enhancing TB acquisition and transmission in many settings, and the complexity of drug therapy that impacts treatment completion all contribute to the development of MDR-/XDR-TB. The epidemic of MDR-/RR-TB is currently one of the most important obstacles to global control of TB.

MDR-/RR-TB has generally required longer treatment courses, ranging from 18 to 24 months, with second-line anti-TB drugs that are often more toxic and less active than first line therapies. In most cases, despite long courses of treatment with multiple drugs, outcomes have been substantially less favorable than for drug-susceptible TB. A systematic review and meta-analysis of MDR-/RR-TB studies from 31 treatment programs in 21 countries analyzed available treatment outcomes from 4,959 participants enrolled in 26 trials and reported only 62% (95% CI 57-67) had successful treatment completion/cure, 13% (95% CI 9-17) defaulted, and 11% (95% CI 9-13) died [2]. An additional nine trials analyzed data from a total of 1,583 participants who had a mean follow-up duration of 27 months after completion of treatment; the proportion with successful outcomes was only 64% (95% CI 56-72) and 14% died [2]. Factors associated with worse outcomes included male sex, alcohol abuse, low basal metabolic index, sputum smear positivity at diagnosis, fluoroquinolone resistance, and XDR-TB. Factors associated with successful outcomes were surgical intervention, no prior TB treatment, and incorporation of a fluoroquinolone in the regimen. Of note, there were no data on use of LZD or newer anti-TB drugs in this review. Falzon et al. reported outcomes from nearly 7,000 participants with MDR-/RR-TB from 26 TB treatment centers indicating that treatment success rates for those with MDR /RR-TB isolates without additional resistance was 64%; the rate declined to 56% for those with MDR-/RR-TB and resistance to any additional second-line anti-TB drugs; to 48% for those with MDR-/RR-TB with resistance to fluoroquinolones; and to 40% for those with XDR-TB [3]. Similar outcomes were reported in a recent review of persons with XDR-TB, in which 43% of those who had XDR-TB isolates with no additional resistance had a favorable treatment outcome. This declined to 34% among those with additional resistance to second-line injectable anti-TB agents [4]. In most of these studies, the use of at least three or four effective drugs based on drug-susceptibility testing (DST) was associated with the highest odds of treatment success, and no single drug emerged as critical to a

favorable outcome. In another similar study, *in vitro* susceptibility to individual drugs used in the regimen was consistently and significantly associated with a higher probability of treatment success when compared with regimens that demonstrated resistance to one or more of the individual drugs in the regimen [5]. In this latter meta-analysis, encompassing 8,955 participants from 31 previously published cohort studies, DST provided clinically useful information associated with improved outcomes when used to guide drug selection in treatment regimens [5]. Other studies have also documented improved TB treatment outcomes in participants with MDR-/RR-TB with more aggressive therapy based on DST that was continued for a duration of at least 18 months; aggressive therapy in these studies was defined as use of at least five drugs in the regimen likely to be active based on baseline DST and treatment history, including a fluoroquinolone and at least one injectable second-line anti-TB drug [6-9].

Recent Experience with Shorter Course Treatment for MDR-/RR-TB

More recently, reports based on observational data and cohort studies conducted largely in Asia and sub-Saharan Africa, suggest that for select persons with MDR-/RR-TB, shorter course treatment with intensive regimens resulted in higher treatment success rates, as compared to historical controls who received longer courses of conventional regimens, with treatment success ranging from 83.4%-89.9% for those receiving shorter course regimens versus 61.7%-78.3% for those receiving conventional regimens (WHO Treatment Guidelines for drug-resistant tuberculosis – 2016 Update) [10, 11]. Shorter courses are generally defined as 9-12 months of treatment using variations of the "Bangladesh" regimen that include gatifloxacin (or moxifloxacin substituted for gatifloxacin), ethambutol, pyrazinamide, and clofazimine (CFZ) throughout with the addition of kanamycin, prothionamide, and high-dose isoniazid for the first 4 months [12]. Although the overall numbers of participants were small in many of the studies reviewed in the World Health Organization (WHO) analysis, and treatment success was lower in participants with pyrazinamide or fluoroquinolone resistance, based on their review of the data by an expert panel, the WHO recently issued new recommendations for shorter course treatment [10]. A WHO Rapid Communication published in August 2018 further refined these recommendations with the following new changes based on review of aggregated data from the Otsuka phase 3 randomized controlled trial of DLM, from the STREAM trial Stage 1 results, and from results of PK and safety data for DLM and bedaquiline (BDQ) in children [11]. The August 2018 recommendations indicated that a standardized shorter MDR-/RR-TB regimen may be considered for persons with MDR/RR-TB who do not have one or more of the following: "1) resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen; 2) exposure to one or more second line medicines in the regimen for more than 1 month unless susceptibility is confirmed; 3) intolerance to any medicine in the shorter MDR-TB regimen or at risk of toxicity; 4) pregnancy; 5) disseminated, meningeal or central nervous system TB or extrapulmonary TB in persons with HIV." The recommended regimens should include "at least five effective TB medicines during the intensive phase including four core second-line TB medicines – one chosen from group A, one from group B, and at least two from group C." If a regimen that includes a minimum of five effective drugs cannot be designed, then add-on drugs from group D2 and/or D3 may be added to total five effective drugs. The drugs in each group and their justification can be found in the WHO

publications as referenced above. More importantly, in this rapid communication, LZD had moved up to a Group A drug, DLM remained a Group C drug, and new recommendations emphasized a fully oral treatment regimen for most patients, that is, excluding injectable anti-TB drugs unless DST results indicate an effective regimen cannot be constructed without one. The guidance further emphasizes that optimal dose and duration of LZD is not known; the position of DLM needed to be reassessed pending additional data from clinical trials; shorter MDR-/RR-TB regimens were associated with a higher rate of treatment failure and relapse when resistance is present to one or more of the drugs in the regimen or when the comparator longer regimen used one or more of the Group A medicines [1].

Results from two additional clinical trials further support the treatment of MDR/RR-TB with shorter course regimens. The STREAM-1 trial, which compared the 9-11-month WHO recommended short-course regimen with a standard of care (SOC) long-duration regimen based on WHO 2011 recommendations, enrolled participants with MDR/RR-TB but with isolates sensitive to fluoroquinolones and at least one aminoglycoside [13]. The intensive phase could be extended by 4 or 8 weeks if sputum smear conversion had not occurred by 16 or 20 weeks, respectively. Among the 424 participants enrolled, 33% were coinfected with HIV and 62% had PZA resistance. A favorable outcome was defined as cultures negative for MTB at 132 weeks after randomization and at least one other occasion during the trial, with no intervening positive culture or other unfavorable outcome. Unfavorable outcomes included treatment extension beyond the permitted duration; starting ≥ 2 new drugs not included in the original randomized regimen; death; or positive culture at 132 weeks after treatment initiation or when last seen. Primary efficacy results demonstrated a 79.8% favorable outcome for those randomized to the long regimen versus 78.8% for the shorter regimen (P=0.02), which met the threshold for non-inferiority. One component of unfavorable outcome was bacteriologic failure, with 5.6% versus 10.5%, respectively, experiencing it. Similar outcomes occurred for those with HIV coinfection, although when compared with HIV uninfected participants, those with HIV infection had higher rates of unfavorable outcomes. The shorter course regimen was associated with higher rates of Grade 3 or 4 adverse events (AEs; 48.2% versus 45.4%) although there were differences in the types of AEs; however, there were fewer serious adverse events (SAEs) in the shorter course arm. Overall, more deaths occurred in those randomized to the shorter regimen (8.5% versus 6.4%), although the proportion of TB related deaths was the same in both arms (2.8% for both). The rate of occurrence of QTc interval prolongation was 11%, but most were managed with a reduction in the moxifloxacin dose or a switch to levofloxacin without clinical consequence. Severe hearing loss due to aminoglycosides was observed in approximately 6% of patients in both arms.

Recently published results of a study of a novel three-drug anti-TB regimen administered for 6-9 months have begun to challenge even the recent paradigm shifts in treatment for drug-resistant TB. The NixTB study was a prospective, single-arm study initiated based on *in vitro* and mouse model data demonstrating very potent antimycobacterial activity of the three drug combination of BDQ, pretomanid (a novel nitroimidazole drug), and LZD [14, 15, 16]. A total of 109 participants were enrolled with pulmonary XDR-TB or MDR-

TB unresponsive to or intolerant to MDR-TB treatment. BDQ was given in a standard loading dose of 400 mg given once daily for 2 weeks followed by 200 mg given 3 times weekly. Pretomanid was given in a 200 mg once daily dose and LZD was initially given in a 600 mg twice daily dose then later switched midway through the trial to 1200 mg once daily. All patients were treated for 26 weeks, although those who were culture positive between months 4 and 6 could continue treatment for an additional 12 weeks. The median age of enrolled participants was 35 years, 52% were male, 51% were people with HIV infection, 65% had XDR-TB, and 17% each had MDR-TB unresponsive to or intolerant to treatment. The median time from XDR- or MDR-TB diagnosis before enrolling in NixTB was 12.1 months with a range of 12.1-141 months. All patients had MTB isolates with a MIC below 1 mcg/mL for both LZD and BDQ.

Ninety percent of the Nix-TB participants had a favorable outcome at 6 months after the end of treatment (95% CI, 83%-95%). Importantly, no differences were observed between those with or without HIV infection and no differences were observed for those with XDR TB versus MDR-TB. The median time to sputum culture conversion was less than 6 weeks regardless of type of TB. There were seven deaths (six during treatment and one during follow-up due to an unknown cause), two relapses during follow-up, and one loss to follow-up. LZD associated peripheral neuropathy occurred in 81% of participants and myelosuppression occurred in 48%. These adverse effects were considered manageable although dose reductions and interruptions were common. Peripheral neuropathy related to LZD was generally observed after 3 months of treatment and plateaued during therapy. Myelosuppression tended to occur earlier than peripheral neuropathy, with anemia being the most common manifestation in 37% of participants; most anemia AEs were Grade 1 or 2 and only 8% developed neutropenia. Myelosuppression events resolved with dose reduction or discontinuation of LZD. Liver transaminase elevations occurred in 16% of participants; 8 participants interrupted treatment for liver AEs but all were able to resume and complete treatment. The U.S. FDA approved the combination of BDQ, pretomanid and LZD for treatment of XDR-TB in late 2019.

Another key update was published in December 2019 by the WHO as a Rapid Communication [1]. This latest update further addressed the benefits of short-course all oral anti-TB regimens, emphasized the recent finding that replacing injectable anti-TB drugs with BDQ was associated with improved treatment outcomes and treatment completion rates in people with MDR-/RR-TB without previous exposure to second-line drugs, and highlighted newly published data on the Nix-TB novel regimen of BDQ, pretomanid, and LZD in patients with XDR-TB [17a]. However, the recommendations for the latter indicate that the BPaL regimen should be used under operational research conditions in patients with XDR-TB not previously treated with either BDQ or LZD.

Finally, in the latest WHO update published in 2022, several regimens are now included as options for treatment of DR-TB. The choice of regimen should be based on DST results, prior drug treatment, patient history, drug-resistance profile of close contacts, age, extent and severity of TB disease, and presence and location of extrapulmonary disease [17b] The choices include: 1) a 6 month regimen of BPaLM (BDQ, pretomanid,

LZD, and moxifloxacin) with the option of removing the moxifloxacin for patients with FQ resistance; 2) a 9 month regimen that includes 6 months of BDQ in combination with 4 to 6 months of levofloxacin or moxifloxacin, ethionamide, high dose INH, PZA and CFZ, followed by a continuation phase of five months of one of the two fluoroquinolones, CFZ, EMB, and PZA (also noting that ethionamide can be replaced with two months of LZD), or; 3) longer individualized regimens of at least 18 months based on DST and prior drug tolerance. The BPaLM regimen is considered the "preferred" regimen [17b].

Despite these favorable advances, there are still relatively limited, although rapidly expanding, published data documenting longer term favorable outcomes associated with all oral short course MDR-/RR-TB regimens in diverse populations. Further information about the optimal use of LZD and DLM as part of these short course regimens and broader outcome data for short course regimens that combine BDQ with LZD and DLM, will be important in identifying their utility as part of any MDR-/RR-TB treatment regimen, especially as we move into the next generation of all oral regimens for treatment of drug-resistant TB.

Drug-Drug Interactions with Anti-TB Study Medications and Antiretroviral Therapy

Locations where drug resistant TB is prevalent overlap to a substantial degree with the prevalence of HIV and a substantial number of potential study participants are expected to have HIV coinfection. LZD, DLM, and CFZ are not expected to have clinically significant drug-drug interactions with most currently used antiretroviral drugs. However, several antiretroviral drugs should be used with caution during coadministration of BDQ. Potent inhibitors of CYP3A4 increase BDQ C_{max}, AUC, and trough concentrations, reduce concentrations of its major M2 metabolite, and may increase the risk of BDQ-related AEs [18]. In a healthy volunteer study, lopinavir/ritonavir given twice daily for 24 days followed by a single dose of 400 mg of BDQ increased BDQ AUC by 22% (bedaquiline package insert) [18]. Pharmacokinetic studies of chronic dosing of BDQ with lopinavir/ritonavir have not been done. This and other antiretroviral drugs that inhibit CYP3A4, including delavirdine, cobicistat, ritonavir and most other protease inhibitors, should be used with caution with careful monitoring during BDQ therapy [18]. Alternatively, CYP3A4 inducers have the potential to increase BDQ clearance and decrease C_{max} and AUC of the parent compound and its metabolites. In a healthy volunteer study, efavirenz (EFV) administered in a 600 mg daily dose until steady state concentrations were reached, followed by administration of a single 400 mg dose of BDQ reduced the AUC of BDQ by 20% but had minimal effect on C_{max} [19]. Subsequent modeling simulations using these data suggest that with chronic dosing of BDQ at 200 mg three times weekly together with EFV, BDQ AUC and C_{max} might be reduced by about 50% [20]. Such reductions would be clinically significant, particularly during early TB treatment in HIV coinfected individuals. Daily dosing of BDQ may mitigate the induction effect of EFV, but this has not been evaluated in clinical trials. Similar effects are anticipated with etravirine, thus EFV and etravirine should be avoided during BDQ treatment. Alternatively, drug interactions with nevirapine are not significant and nevirapine can be used with BDQ. Adverse drug interactions are not expected with integrase strand transfer inhibitors or nucleoside analogs. Integrase inhibitor based regimens are preferred for HIV and TB co-treatment in this setting.

2.2 Rationale

Rationale for A5356

There is currently no “standard of care” or single standardized treatment regimen recommended for all patients with MDR-/RR-/XDR-TB. Although newer TB drugs, including BDQ and DLM, have been approved for treatment of MDR-/RR-TB, scientifically rigorous well-controlled randomized clinical trials to evaluate how best to use these safely and durably in combination with each other or with other existing second-line anti-TB drugs, particularly in shorter courses of therapy excluding an injectable second-line drug, are limited. As the field has rapidly evolved toward use of shorter course treatment for MDR-/RR-TB, there is an urgent need to identify drugs with suitable antimycobacterial activity, appropriate PK, and safety profiles that will allow them to be safely combined to improve outcomes in the treatment of DR-TB. Recent WHO guidance no longer recommends use of injectable second-line drugs if DST results indicate that an initial regimen can be constructed to contain at least 4-5 active drugs without them [11]. This new recommendation is based in part on the very high rates of serious adverse reactions to injectable second-line anti-TB drugs, including permanent hearing loss in up to 25% of participants in clinical settings. Because LZD and BDQ are now included as core drugs in Group A that can be used as part of new shorter course treatment regimens, CFZ is included in Group B as an additional drug to be added if feasible, and DLM is included as an add-on agent in Group C, as previously described, it is imperative that more comprehensive data be developed to evaluate how these agents can be safely used together, and specifically to address optimal dosing for LZD in this context as the field moves toward even shorter durations of treatment. Data generated from this study will complement and extend the promising data from the NixTB trial of short course treatment for MDR-/RR-TB and XDR-TB, and data being generated in other ongoing randomized trials (ZeNix [NCT03086486], endTB [NCT02754765], endTB-Q [NCT03896685], SimpliciTB [NCT03338621], TB-PRACTECAL [NCT02589782]), and will add to the growing body of data from randomized clinical trials and PK modeling incorporated within them, to inform the field in identifying novel, safe and effective regimens to treat people with DR-TB. Furthermore, there are a number of other innovative approaches to treatment of DR-TB that are incorporated in A5356, including a modification of the BDQ dosing to a single daily dose regimen throughout (a dose that has not yet been extensively studied), the incorporation of DLM to replace pretomanid, a novel LZD dose of 1200 mg/d x 4 weeks followed by 1200 mg/d three times weekly, and the addition of CFZ as a fourth drug with the potential to further reduce emergence of resistance and add to the early mycobactericidal activity of the regimen. At this point in time, the team does not have access to pretomanid either through donation or purchase (although this may change) to allow a direct comparison of a pretomanid versus DLM short course regimen, regardless of the LZD dosing schedule. A5356 will provide useful data to historically compare to ZeNix, NixTB, and TB-PRACTECAL outcomes relative to the activity of a DLM versus a pretomanid regimen for treatment of DR-TB. The regimens being studied in A5356 have the potential to add to our knowledge about very short course treatment alternatives to pretomanid-based therapy for a broader

population of patients with DR-TB than those with pre-XDR-TB, XDR-TB, and treatment-unresponsive or treatment-intolerant MDR-TB.

Rationale for Intensive Evaluation of LZD

Because A5356 is focused in part on identifying effective alternative dosing schedules of LZD to maximize its antimycobacterial activity and to minimize adverse effects associated with its use, the following text highlights detailed information about the rationale for including LZD in regimens for treatment of DR-TB.

In vitro, Animal Model and Early Bactericidal Antimycobacterial Activity of LZD

LZD is an oxazolidinone antibiotic, approved for treatment of complex infections with Gram positive bacteria, that inhibits bacterial protein synthesis by binding 23S ribosomal RNA. LZD is active *in vitro* against MTB—including MDR and XDR-TB strains—at concentrations of 1 µg/mL or less. As a "first generation" oxazolidinone, LZD is less potent *in vitro* against MTB than its next generation counterpart, sutezolid; the minimum inhibitory concentration (MIC) for sutezolid is 25% to 33% lower than for LZD. Sutezolid has increased activity at acidic pH (5.9) and is approximately 15 times more potent than LZD against intracellular MTB. Further, it may have greater sterilizing activity in macrophages, although sutezolid and LZD were not compared at acidic pH [21]. Sutezolid is currently in development in phase 2-3 clinical trials and safety data is not available for its use in this context. LZD is also highly active against MTB [22]. In one study, 99% of 1447 MDR-TB strains, 58 of which were also XDR-TB, were susceptible to LZD at a MIC of <1 µg/mL [23]. In another study, only 5.9% of 201 MTB isolates, of which 59 were XDR-TB and 43 were pre-XDR-TB strains, had reduced LZD activity (MIC ≥1 µg/mL) [24].

The activity of novel antimycobacterial drugs alone and in combination in mouse models has been used as a predictive surrogate for establishing doses and combinations to evaluate in clinical trials. In a murine model comparing the activity of LZD with sutezolid, LZD demonstrated dose-dependent activity with a >90% reduction in colony forming units (CFUs)/lung compared with untreated controls over the first 4 weeks of treatment at doses of ≥100 mg/kg (the 100 mg/kg dose in mice produces an $AUC_{0\text{-}24h}$ comparable to the median AUC after a human dose of 1200 mg daily) [25]. In another study, LZD 100 mg/kg increased the 1-month bactericidal activity of BDQ or pretomanid (PA-824) monotherapy, and the bactericidal and sterilizing activity of the BDQ-pretomanid combination in mice. The BDQ-pretomanid-LZD combination cured mice 1 month earlier than the first-line regimen [14]. Studies combining different doses of LZD with BDQ and pretomanid demonstrated increasing activity with increasing doses of LZD in mice, with modestly greater sterilizing activity observed with sutezolid 50 mg/kg compared with LZD 100 mg/kg, although 0/15 mice relapsed after 3 months of treatment with either sutezolid or LZD [14]. The addition of LZD 100 mg/kg also increased the activity of the combination of pretomanid, moxifloxacin, and pyrazinamide (PZA), in both immunocompetent and immunocompromised (nude) mice [Nuermberger E, personal communication]. In nude mice, increasing benefit was observed when LZD was added for 1, 2, or 4 months, especially with regard to preventing the selection of pretomanid resistant mutants.

LZD has dose-dependent early bactericidal activity (EBA) in participants with pulmonary TB, suggesting the drug penetrates into tuberculous lesions and has bactericidal activity against rapidly growing bacilli in cavities. The EBA of LZD was evaluated in a randomized open-label trial in 30 participants with newly diagnosed smear-positive pulmonary TB; participants were assigned to receive LZD either 600 mg twice daily or 600 mg once daily for 7 days [24]. Mean EBA of LZD twice daily and once daily was 0.26 and 0.18 log10 CFU/mL, respectively, as measured for the first 2 days [26]. Preliminary analysis of a recently completed LZD dose-ranging, dose-fractionating 14 day EBA trial indicates a dose-response relationship, with EBA increasing with each daily dosage of 300, 600, and 1200 mg, and similar activity irrespective of whether 600 1200 mg is administered as a single daily dose or in two divided doses [26].

Pharmacokinetics of LZD

LZD is extensively absorbed after oral administration, with an absolute bioavailability of nearly 100%. A high-fat meal delays the T_{max} from 1.5 hours to 2.2 hours and reduces the C_{max} by 17%; however, the total exposure (area-under-the-concentration curve $[AUC]_{0\text{-}inf}$) is the same with or without food. Therefore, LZD may be administered with or without food [Zyvox® Package Insert, 2018]. LZD distributes well into tissues (volume of distribution 40 50 L) and approximately 31% is protein-bound in plasma. There are no known cytochrome P450 enzymes involved in LZD metabolism and it is not a cytochrome P450 enzyme inducer or inhibitor. LZD metabolism is not fully characterized, but it is metabolized by the liver via oxidation. Non-renal clearance accounts for approximately 65% of the total clearance of LZD; the rest is excreted in urine (30% as unchanged drug) and minimally in the feces (metabolites). LZD has a serum half-life of 4.3-5.4h; LZD elimination is non-linear with dose escalation, as described below [27].

Co-administration of rifampicin (RIF) with LZD reduced the LZD C_{max} 21% (90% CI: 15% to 27%) and LZD AUC 32% (90% CI: 27 to 37%). The mechanism of this interaction is unclear, but may be related to induction of LZD hepatic metabolism. LZD has not been investigated in combination with antiretroviral (ARV) drugs, but EFV may reduce LZD exposure due to similar mechanisms [Zyvox® Package Insert, 2018].

Data on the human PK of LZD in the treatment of TB disease are accumulating. Population PK of LZD in adults with pulmonary TB was evaluated in an EBA trial in which 19 adults were treated with LZD 600 mg once or twice daily. Using a one compartment model, the 600 mg twice-daily dose of LZD resulted in higher plasma free drug AUC to MIC (AUC/MIC) ratio and time above MIC [26]. Both regimens achieved free AUC/MIC ratios >100. Median times above the MIC for free drug were 100% for the twice-daily dose and 63% for the once daily dose [28].

In an open-label, prospective study of LZD PK in participants with MDR-TB, LZD was administered to 8 participants initially in a dose of 300 mg twice daily for 3 days followed by 600 mg twice daily [27]. In this study, the 300 mg dose was achieved by splitting a 600 mg tablet. The 300 mg twice-daily dose was selected to achieve similar steady state and cumulative concentrations of LZD to those observed with 600 mg once daily but

avoiding the high peak concentrations of the drug. After 3 consecutive days of LZD at 300 mg twice daily, samples were obtained to assess the AUC over 12 hours, and the dose was then increased to 600 mg twice daily. If an AUC_{24}/MIC ratio of >100 was observed, the dose was reduced to 300 mg twice daily. The median AUC_{12} was 57.6 mg•h/L for the 300 mg BID and 145.8 mg•h/L for the 600 mg BID dose schedule; the median AUC_{24}/MIC values were 452 (IQR 343-513) and 1151 (IQR 656-1500), respectively [27]. Based on the AUC_{24}/MIC ratio, treatment was continued at 300 mg twice daily for the duration of TB treatment. The median duration of LZD treatment was 56 days (IQR 44-82). No participants developed clinically significant adverse effects attributable to LZD, but TB treatment outcomes were not reported in this study.

Efficacy and Safety of LZD for Treatment of MDR-/RR-TB and XDR-TB

Two prospective, randomized clinical trials have evaluated LZD in multidrug regimens used to treat MDR-/RR- or XDR-TB. One was an open-label study that enrolled 41 participants with sputum-culture positive pulmonary XDR-TB who had no response to available SOC treatment regimens during the preceding 6 months [29]. In this study, participants were randomly assigned to start LZD, 600 mg daily, either immediately or after 2 months of continued therapy with the regimen they were already receiving. The primary endpoint was the time to sputum-culture conversion on solid media. LZD 600 mg daily was continued until participants were sputum-smear negative on consecutive testing for at least 2 weeks or until they had received at least 4 months of LZD, whichever came first, at which point a second randomization took place to continue LZD either at a dose of 600 mg daily or 300 mg daily for an additional 18 months. Nineteen participants were randomized to immediate LZD versus 20 to delayed LZD [29]. By 4 months, 15/19 (79%) in the immediate versus 7/20 (35%) in the delayed LZD group had sputum culture conversion (P=0.001). With data censored at 4 months, 12/19 (63%) in the immediate and 11/20 (55%) in the delayed start group had culture conversion on liquid medium (P=0.07). This study design effectively added LZD to a “failing regimen,” with the intent of the 2-month delay to assess the singular activity of LZD in the context of this failing regimen. A change in the “failing” regimen was allowed after participants had received at least 2 months of LZD. Of note, 34 of 38 participants who received at least one dose of LZD (89%) had sputum culture conversion on solid medium by 6 months after starting LZD, at a median of 75 days after starting treatment with LZD, regardless of their randomization. At the time of publication, 13 participants had completed therapy without relapse; 17 remained on treatment per protocol; eight withdrew from treatment early (four due to treatment failure, three for AEs), and four participants developed acquired resistance to LZD. Of the 38 participants who received LZD, 31 (82%) had clinically significant AEs possibly or probably related to LZD, but only three of these discontinued therapy [29]. Those receiving 300 mg daily after the second randomization had fewer AEs than those continuing on 600 mg daily. Treatment limiting AEs were optic neuropathy [2] and anemia [1]; seven episodes of myelosuppression occurred primarily within the first 7 months of treatment. Overall, other clinically significant AEs included optic neuropathy [7], peripheral neuropathy [25], and rhabdomyolysis [1]; all occurred in the first year of therapy. PK analyses demonstrated that plasma concentrations of free LZD were above the MIC for each MTB isolate during the entire dosing interval for nearly all of those treated with 600 mg daily, and nine

participants treated with 300 mg daily had trough levels lower than the MIC. LZD resistance developed in three participants with low free-LZD concentrations while receiving 300 mg daily [29]. There was no association between the time to culture conversion and either the C_{max} or C_{min} as measured after at least 2 weeks of LZD. Updated, longer-term follow-up data from this trial were recently published [30]. Among the 38 enrolled participants that received LZD, 27 had negative sputum cultures 1 year after the end of treatment (three were lost to follow-up; eight did not complete the study, and four from the earlier report failed LZD therapy). The median duration of LZD treatment for these 27 participants was 781 days; four of the 27 had a dose reduction from 600 mg to 300 mg daily of LZD before their second randomization and for the 13 remaining participants who were assigned to continue 600 mg daily of LZD, nine had a subsequent dose reduction to 300 mg daily due to AEs. In addition to the AEs reported in the initial publication, three additional participants developed optic neuropathies and one treatment-limiting anemia, all of which resolved after discontinuation of LZD [30].

In a second clinical trial conducted in China, 65 participants with XDR-TB were randomized to 24 months of individualized TB treatment regimens based on DST with or without LZD. HIV-infected participants were excluded from the study. Those randomized to the LZD group received an initial dose of 1200 mg daily (administered as 600 mg twice daily) for a period of 4-6 weeks, followed by a dose reduction to 300-600 mg daily. The proportion of participants with sputum culture conversion by 24 months in the LZD group was 78.8% versus 37.6% in the control group (P<0.001) [31]. The overall treatment success rate in the LZD group was 69.7%, which was significantly higher than the rate in the control group (34.4%) (P=0.004). Clinically significant AEs were observed in 81.8% of participants in the LZD group, most of which were possibly or probably related to LZD. Most resolved after reducing the dose or temporarily discontinuing LZD. A total of 12.1% of participants in the LZD arm and 9.4% in the control arm prematurely discontinued the trial. Rates of anemia, optic neuropathy, and peripheral neuropathy were 51.5%, 24.2%, and 18.2%, respectively. Hematologic AEs occurred generally between 2 weeks and 2 months after starting LZD treatment; peripheral neuropathy occurred between 2 and 4 months, and optic neuropathy occurred later, approximately 5-6 months into LZD therapy [31].

The majority of the data available reporting the safety and efficacy of LZD as part of multidrug regimens used for treatment of MDR-/RR-TB or XDR-TB has been derived from relatively small observational cohort studies, retrospective reviews, and meta-analyses of case series although numerous randomized clinical trials incorporating various doses of LZD are now underway. In previous studies, successful TB outcomes were reported in 61 100% of individuals. Varying doses of LZD were used with different dosing intervals and, based on retrospective or observational designs; it is difficult to discern the singular contribution of LZD or specific doses of LZD to the efficacy or toxicity of multidrug regimens. Many of these studies also addressed overall toxicity rates across the duration of treatment, often without consideration of time to event or treatment limiting toxicities, but reported overall high rates of “any” LZD-associated toxicity. In a meta-analysis of 12 studies from 11 countries that included 207 cases of MDR-TB (individual patient data were available from only 121 cases with a definite TB

outcome), the median duration of LZD treatment was 300 days and among the 121 participants with documented TB treatment outcomes, median and IQR time to sputum smear and culture conversion were 43.5 (21-90) and 61 (29-119) days, respectively, with an estimated 81.8% of the 121 participants successfully treated [32]. No significant differences in treatment outcomes were reported for those receiving 600 mg or less versus more than 600 mg daily. Sixty-three of 107 (58.9%) participants for whom data were available experienced AEs, and among 79 total AEs reported, 54 (68.4%) were major AEs that included anemia (38.1%), peripheral neuropathy (47.1%), GI disorders (16.7%), optic neuritis (13.2%), and thrombocytopenia (11.8%). The proportion experiencing AEs was significantly higher for those treated with LZD doses of greater than 600 mg daily (74.5% vs. 46.7%). In another systematic review and meta analysis of 11 studies, including 148 participants with MDR-/RR-TB and XDR-TB treated with LZD-containing regimens for a total duration ranging from 1-28 days, the pooled proportion with sputum culture conversion during LZD treatment was 98% (95% CI 95-100); the pooled proportion with treatment success was 68% (95% CI 58-79) [33]. The majority of studies reporting sputum culture conversion rates used a dose of 600 mg daily. There were no significant differences in treatment success comparing daily LZD doses of 600 mg or less versus more than 600 mg daily or a mean duration of LZD therapy of 7 months or less versus more than 7 months [33]. The pooled estimate for frequency of AEs was 61.48% (95% CI 40.15-82.80) with 36.23% (95% CI 20.67-51.79) discontinuing LZD due to AEs. The most commonly reported toxicities were peripheral neuropathy and anemia requiring transfusion. In a meta-analysis that included 120 participants all of whom had XDR-TB, 39 received LZD (25 were treated with 600 mg/daily or less and 14 received more than 600 mg/daily) [34]. The proportion of participants treated with LZD who experienced AEs was more than 60%. After a median duration of exposure to LZD of 315 days, peripheral neuropathy was seen in 55.2%, anemia in 31%, and optic neuritis in 20% [34].

Finally, the experience with LZD as part of the NixTB study, and the findings from the above studies and ongoing randomized clinical trials suggest that toxicity is associated both with dose and duration of LZD, but offer the potential that with appropriate monitoring and dose reduction strategies, a substantial proportion of individuals may be able to maintain LZD in the regimen at a dose that might further contribute to overall microbiologic efficacy. However, of the two published randomized clinical trials in persons with XDR-TB that have evaluated LZD dosing strategies, neither study provided sufficient information to fully assess the optimal dose of LZD to both maximize efficacy and minimize toxicity, nor the most appropriate strategy for dose adjustment in the setting of specific toxicities occurring in the context of multidrug therapies. There are additional studies ongoing that have included different dosing strategies for LZD in the setting of XDR-TB, pre-XDR-TB, and MDR-/RR-TB failing other therapies (NCT02333799; NCT03086486), and pharmacokinetic modeling based on early results from these suggest that starting with a daily dose of LZD of 300 mg/d is unlikely to provide sufficient antimycobacterial activity in combination regimens (Rada Savic, personal communication). Longer term outcomes associated with doses starting at either 600 mg/d or 1200 mg/d with dose modification in the setting of toxicities or intolerance are not yet available. Rigorous evaluation of the most safe and effective dose, the actual

exposure response relationships relative to TB outcomes, the singular contribution of LZD when added to other active drugs in a shorter course regimen, and the use of LZD together with other newer anti-TB drugs without injectable drugs in the background is extremely limited.

Rationale for LZD Dose Selection

Emerging evidence from *in vitro* and *in vivo* models and human studies suggest that more intermittent administration of higher doses of LZD may preserve efficacy while reducing the risk of toxicity. As against other pathogens, the exposure-response relationship governing the antimycobacterial activity of LZD correlates with the AUC/MIC ratio and time above the MIC ($T_{>MIC}$). AUC/MIC was the most highly correlated parameter in an *in vitro* hollow fiber model with acidified media [35] and a murine model [25], whereas $T_{>MIC}$ may be most predictive under active growth conditions in the hollow fiber model [34]. Based on the target free AUC/MIC ratio of 80-100 associated with bactericidal effect *in vitro* and *in vivo*, the data from the hollow fiber model suggest LZD doses of at least 600 mg or greater once daily will be required to achieve substantive antimycobacterial activity. While LZD-mediated suppression of bacterial subpopulations resistant to companion drugs should follow the same exposure-response relationship as other LZD-susceptible populations, the suppression of LZD-resistant mutants by LZD itself is most closely correlated with LZD C_{max} and follows, at least in the hollow fiber model, a nonmonotonic function or “U”-shaped pattern in which doses of 900-1200 mg are predicted to suppress LZD-resistant sub-populations more effectively than 300-600 mg doses [36]. Doses of 600 and 1200 mg once daily given for either 2 months or 6 months are now being evaluated in combination with BDQ and pretomanid in the ZeNix trial (NCT03086486) as are other dose reduction strategies to avoid toxicity in other ongoing trials. In contrast, mitochondrial toxicity (likely responsible for both the myelotoxicity and neurotoxicity of LZD) appears to be most closely associated with C_{min}. Observational studies and toxicodynamic modeling studies suggest that early myelotoxicity is associated with C_{min} >8-10 mg/L [37-39]. However, the C_{min} threshold associated with toxicity over longer treatment durations, particularly when used with other drugs that might contribute to toxicity, is likely lower. In a recent XDR-TB trial, the risk of mitochondrial toxicity was 100% if C_{min} was >2 mg/L and <50% if C_{min} was <2 mg/L [40**a**]. In an *in vitro* hollow fiber model of mitochondrial toxicity, toxicity correlated more closely with LZD C_{min} than AUC and greater toxicity was observed with a simulated 300 mg twice daily dose that maintained a steady-state LZD C_{min} of >1.2 mg/L compared with a 600 mg daily dose with a C_{min} <0.5 mg/L [36].

Considered in aggregate, available data indicate that a LZD dose of 300 mg daily, at least in initial therapy when maximized concentrations are needed to reach optimal antimycobacterial activity, has lower antimycobacterial efficacy and higher selection of LZD resistant mutants, while daily doses of 600 mg or more may be associated with greater antimycobacterial activity but with a higher risk of dose-limiting toxicity. A dose of 600 mg-1200 mg daily is the most common initial dose of LZD used in published human studies thus far and appears to have substantial antimycobacterial activity in humans and in mouse models. PK/PD data suggest that the time above the C_{min} is less when once daily dosing is used than with twice-daily dosing schedules such that toxicity may

be more manageable with careful monitoring and dose adjustment. Higher doses of LZD in the range of 900-1200 mg daily are clearly associated with increased antimycobacterial activity in mice, in vitro hollow fiber models, and in recent human EBA studies, but such daily doses may be associated with high rates of treatment-limiting toxicity unless the duration of exposure is limited or other alterations in dosing interval can lower the C_{min}, a hypothesis being tested in one of the ongoing clinical trials. Compared with a 600 mg daily dose, administering 1200 mg every other day may better balance the optimization of AUC/MIC and C_{max}/MIC for efficacy and resistance suppression, respectively, while minimizing the C_{min} to reduce toxicity. This study, therefore, will evaluate the safety and early antimycobacterial activity of two doses of LZD (600 mg daily and 1200 mg daily for 1 month followed by 1200 mg thrice weekly) in combination with BDQ, DLM, and CFZ, with careful monitoring and dose reductions for significant AEs. The rationale for the 1200 mg daily/intermittent regimen is to provide optimal early bactericidal activity for the first 4 weeks of treatment before transitioning to 1200 mg thrice weekly, which is expected to be equally efficacious to, and safer and better tolerated than the 600 mg daily dose for the remaining 20 weeks of combination therapy.

The findings from the recently completed ZeNix trial [40b], a follow-up study to the NixTB trial, prompted a reevaluation of the A5356 study design. The ZeNix trial was a four-arm, randomized, double-blind trial for the treatment of participants with XDR-TB, pre-XDR-TB, or treatment-intolerant or non-responsive MDR-TB. All participants received BDQ 200 mg daily x 8 weeks then 100 mg daily x 18 weeks, and pretomanid 200 mg daily for 26 weeks. In ZeNix, participants were randomized to one of four different doses of LZD including 1200 mg/d x 26 weeks, 1200 mg/d x 9 weeks, 600 mg/d x 26 weeks, or 600 mg/d x 9 weeks. Of the 181 participants enrolled, the majority had XDR-TB or pre-XDR-TB; 20% were people with HIV. Of the 177 evaluable participants, 89.3% had a favorable outcome, overall, with the distribution of favorable outcomes among the four arms of 93.2%, 88.9%, 90.9%, and 84.1% for the LZD arms 1200 mg/d x 26 weeks, 1200 mg/d x 9 weeks, 600 mg/d x 26 weeks, or 600 mg/d x 9 weeks, respectively. In the modified intention-to-treat analysis, the LZD 600 mg/d x 9 weeks arm did not perform as well as the other arms with regard to microbiologic efficacy. The LZD 1200 mg/d x 26 weeks arm was associated with a higher rate of Grade 3 or higher treatment-emergent AEs, although for all four arms, the AE rates were still relatively high: in excess of 20% of participants experiencing a Grade 3 or higher treatment-emergent AE. The proportion with at least one peripheral neuropathy event, the most common AE, was also relatively high, 37.8%, 23.9%, 24.4%, and 13.3%, respectively, with the lowest rate occurring in the LZD 600 mg/d x 9 weeks arm. Dose interruptions or modifications were highest in the two 1200 mg/d arms. After much deliberation, the team concluded that the ZeNix trial results, while extremely important, left room for additional studies to determine optimal LZD dosing in the setting of DR-TB, particularly when LZD is used with anti-TB drugs other than those studied in NixTB and ZeNix. Based on the relatively small sample size per arm in the ZeNix trial, the difference in patient populations studied from those proposed in A5356, the still substantial rates of peripheral neuropathy and other treatment-emergent AEs in all four arms of the ZeNix study, and the lower microbiologic efficacy observed with the lower doses and shorter durations of LZD, the

team concluded that the ZeNix trial results reinforce the novel elements of the A5356 study design and that the study should proceed as designed. The LZD dose of 1200 mg daily for 4 weeks followed by three times per week remains a novel and potentially effective dose that may further reduce the AEs observed in ZeNix, as the treatment-emergent AEs in that trial were not observed in the first 4 weeks of the 1200 mg/d dose. The novel intermittent dose of LZD after the 4-week high-dose lead-in might also improve the microbiologic efficacy (including reducing the emergence of drug resistance and potentially late relapse). Additional PK data using this dose in A5356, especially if pooled with data from NixTB and ZeNix, will provide very robust toxicodynamic modeling data that will complement the exposure-response relationships in ZeNix and other studies in the field, providing useful information about LZD dosing in regimens that do not contain pretomanid.

Rationale for the Combination of BDQ, DLM, and CFZ in OBT

Bedaquiline
BDQ is a diarylquinoline that inhibits the proton pump of MTB ATP synthase, and is active *in vitro* against both replicating and non-replicating bacilli. It has significant bactericidal and sterilizing activity in the murine model of TB infection. *In vitro*, it is equally active against drug-sensitive, MDR-/RR-TB and XDR-TB. The distinct target and mode of action of BDQ minimizes the potential for cross-resistance with existing anti-TB drugs [41].

BDQ is FDA-approved for the treatment of MDR-/RR-TB in combination with optimized background therapy (OBT). In prior studies and in clinical practice, a dose of 400 mg daily for 2 weeks, followed by 200 mg three times per week has been recommended. In independent randomized clinical trials, both BDQ and DLM have each been shown to improve sputum culture conversion rates when added to OBT versus OBT alone [42-46]. When BDQ was added to OBT for 8 weeks in a phase 2 clinical trial, 2-month sputum culture conversion rates increased from 9% to 48% versus OBT alone, and this effect was sustained after 6 months of treatment for MDR-TB [42, 43]. When BDQ was used in the regimen for a full 6 months, the overall culture conversion rate was improved as compared to an OBT regimen that did not contain BDQ. Similarly, in the phase 2 clinical trials of DLM with OBT alone versus two different dosing schedules (100 mg twice daily or 200 mg twice daily) plus OBT, the proportions with 2-month culture conversion were 29.6%, 45.4%, and 41.9%, respectively [44, 45]. Longer-term outcomes with DLM added to OBT for 6 months were also favorable. Based on these phase 2 trial results, both BDQ and DLM have received regulatory approvals in several countries. More recent experience combining these two drugs together with other anti-TB drugs have suggested that outcomes can be further improved in the treatment of DR-TB without incurring cross-resistance to 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. However, the combination of BDQ and DLM plus other anti-TB drugs has not yet been fully evaluated in randomized clinical trials.

Pharmacokinetics of BDQ
BDQ is well-absorbed with a T_{max} of 5h and an average terminal elimination half-life of 132 days (112 days for its M2 metabolite). Administration with food increases bioavailability by 95%. The drug is metabolized by oxidative metabolism via the CYP3A4 isoenzyme to its N-desmethyl metabolite, M2. The M2 metabolite has activity against MTB but is less potent than the parent compound [41].

Based on studies in human hepatocytes, BDQ appears to be an inducer of CYP2E1 and a weak inducer of CYP2C9 but does not induce other isoenzymes, and it demonstrates no inhibition of CYP activity. Coadministration of BDQ with ketoconazole, a CYP3A4 inhibitor, increases 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 EFV; with ritonavir-boosted lopinavir, single-dose concentrations are increased 22%, but at steady state, BDQ and M2 metabolite concentrations are likely to be substantially higher [40**a**]. Integrase inhibitors like raltegravir or dolutegravir have not been fully evaluated with BDQ, but based on the metabolism studies done to date, a clinically significant metabolic drug interaction is unlikely.

Safety of BDQ
In phase I trials of BDQ in healthy volunteers, the drug was safe and well-tolerated with the most common AEs being headache, nasopharyngitis, postural dizziness, and hyperuricemia. In a phase 2a trial, drug-related AEs included diarrhea, rash and somnolence. After 7 days of treatment, a mean 10ms increase in QTcF interval was seen. In the phase 2 trial of treatment with BDQ versus placebo plus OBT for MDR-TB, nausea was the only AE reported more frequently in the BDQ arm compared with the placebo arm (BDQ IB), although a 5-10ms increase in the QTcF interval compared to placebo was seen. However, during prolonged follow-up of participants enrolled in this trial, an increased risk of death was observed in the BDQ treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) at the 120-week visit; only one death occurred during the 24 weeks of BDQ administration. The imbalance in deaths remains unexplained as there was no obvious association between the deaths and sputum culture conversion or relapse rates, sensitivity to other drugs in the optimized background regimens, HIV status, or severity of disease. Review of combined data from all trials also indicated a higher rate of “erythema” among BDQ recipients, and more hepatic-related AEs were reported with the use of BDQ compared to other drugs used to treat TB without the addition of BDQ. Additional data from preclinical toxicity studies in dogs suggested there was an increased rate of conjunctival hyperemia, photophobia, or superficial corneal staining after 5 months of daily dosing. No ophthalmological side effects related to BDQ have been observed in other studies.

With regard to treatment emergent effects on the QT interval during study treatment in the phase II trial, 29.1% of participants had a QTcF of 450ms-479ms and only 1.3% each had intervals of 480ms-499ms or ≥500ms; 28.6% had an increase of <30ms and 58.4% had an increase of 30-60ms. Only 13% had an increase of >60ms. In Trial C208 Stage 2, the largest mean increase from baseline values in QTcF during the 24 week

BDQ treatment was 15.7ms at week 18, compared to 6.2ms 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 ≥10ms were seen from week 5 onwards and decreased after week 24 (when study drug was discontinued). Of note, many patients participating in the phase II trials of BDQ were also receiving other QT prolonging drugs (like moxifloxacin or CFZ).

Dose Justification for Once Daily Bedaquiline Dosing
Although the approved dosing for BDQ requires a 2-week lead-in of 400 mg daily followed by 200 mg three times per week, this schedule is challenging when other drugs in the regimen are taken once daily or according to other complex schedules. Because adherence to treatment is key to favorable outcomes, efforts to construct a once daily regimen for treatment of DR-TB has been a high priority. Current clinical trials are exploring a BDQ dose of 200 mg once daily for 8 weeks followed by 100 mg daily for the ensuing 20-22 weeks. A population PK model, based on data derived from 9 studies that included 480 persons and 5,222 specimens collected for PK monitoring over 24 weeks of dosing with BDQ for treatment of DS- and DR-TB, showed excellent concordance between observed and modeled PK data [47]. This model was used in a subsequent study to simulate multiple dosing schedules for BDQ 6-month regimens [48]. The dose of 200 mg daily for 8 weeks followed by 100 mg daily for the remainder resulted in exposures that were comparable to the standard dose schedule (<20% increase in cumulative or daily exposures for both BDQ and its M2 metabolite) at the end of treatment. Using a slightly different model with the same data set suggested that the simulated C_{max} of the M2 metabolite for the once daily regimen might be increased in nonblack participants, although in that simulation the difference was only a 4% increase. The conclusion from this study is that the safety and efficacy of this daily dose regimen is expected to be similar to those observed with the standard dose. This modified dose is also being studied in the ZeNix and SimpliciTB clinical trials and given that those two trials are ones with which we wish to have comparable data for the background regimen to be used in this study, we propose the once daily dose of 200 mg for 8 weeks followed by 100 mg for the remainder of the duration of treatment.

Delamanid
DLM is a nitro-dihydro-imidazooxazole anti-TB drug that inhibits mycolic acid synthesis and has potent *in vitro* activity against actively dividing and dormant mycobacteria, including drug-resistant strains of MTB with MICs ranging from 0.006-0.024 μg/mL [49]. DLM has been approved in the European Union, Japan, South Korea, Hong Kong, Turkey, India, the Philippines, Turkmenistan, China, Mongolia, and Ukraine for the treatment of MDR-TB as part of an appropriate combination regimen in adult patients. DLM is not currently recommended for use in children due to limited safety and efficacy data in controlled clinical trials. The drug demonstrates significant EBA from day 2 onward at all doses tested (i.e., 100-400 mg once daily), although EBA is greater at higher doses of 200-400 mg daily [44]. In a randomized, placebo-controlled trial, 481 participants with MDR-TB received DLM at a dose of either 100 or 200 mg twice daily or placebo plus background regimens based on WHO guidelines [45]. The primary endpoint of the study was sputum culture conversion rate in liquid broth medium at

2 months, which was 45.4%, 41.9%, and 29.6%, respectively, for the 100 mg, 200 mg, and placebo groups. The increase in sputum culture conversion rates compared with placebo was statistically significant for both DLM dose groups.

Pharmacokinetics of DLM
DLM absorption is enhanced by food and reaches a C_{max} at approximately four hours post dose. Exposure increases non-proportionally as doses increase from 50 to 400 mg. The drug is extensively protein-bound (>99.5%), as are its primary metabolites DM-6704, DM-6705, and DM-6706. It is metabolized by albumin, and CYP3A4 and CYP1A1 are involved in the subsequent metabolism of DLM metabolites. The main circulating metabolites are DM-6705 and DM-6706. The elimination half-life of DLM is 30-38 hours with a terminal half-life of the metabolites ranging from 121 to 425 hours. Steady-state concentrations of the parent compound are reached by 10 days but steady state for metabolites may not be reached until 6-8 weeks. About 89% of a single dose of DLM is excreted in feces and about 3% is eliminated in the urine. DLM exposures among participants with MDR-TB are similar to those in healthy participants [50].

DLM and its major metabolites do not show meaningful inhibition of CYP isoenzyme activity and are not inducers of CYP1A2, CYP2C9, or CYP3A4/5. Co-administration of DLM with a combination of first-line anti-TB drugs (INH, RIF, PZA, 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 1 hour. Co administration of DLM with lopinavir/ritonavir increased DLM and DM 6705 by about 25%, but DLM did not affect tenofovir, lopinavir, or ritonavir exposures and co-administration 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 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 [50].

Safety of DLM
As of the most recent delamanid Investigator's Brochure, a total of 1327 adult participants were exposed to oral doses of DLM in 21 completed trials in the United Kingdom, Japan, China, South Africa, Peru, Korea, Philippines, Egypt, European Union (EU), and the United States. Key safety data are summarized below.

In a 14-day EBA trial (Trial 242-06-101) in participants with drug-sensitive TB, 5 treatment-emergent AEs considered serious were reported: three participants with QT interval prolongation on electrocardiogram (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 [49].

In Trial 204, the randomized, double-blind trial evaluating DLM 100 mg or 200 mg BID orally in combination with an OBR versus placebo with OBR for 481 persons with MDR

TB, treatment-emergent AEs were reported for >90% of participants in all treatment groups (including the placebo + OBR group) [45]. Most were mild or moderate in severity and were similar for the DLM 100 mg BID plus OBR group and the placebo plus OBR group. Treatment-emergent AEs were higher in the 200 mg BID plus OBR group compared with the 100 mg BID plus OBR group and included 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 plus OBR group and the 200 mg BID plus OBR group (8.8% vs. 4.4%) compared with placebo plus OBR group.

Trial 208 was 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 [46]. Among the 213 participants from Trial 204 who continued follow-up in Trial 208, no new safety concerns were identified, although the incidence of some events in the DLM 100 mg BID plus OBR group was increased in Trial 208 relative to Trial 204, including 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 treatment emergent AE. Most were mild to moderate in severity, and the most frequently reported were hyperglycemia (6/10 participants; 60%), 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%) [51].

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 and one case of severe hepatic enzyme elevation 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 [49].

As of January 2021 neuropsychiatric side effects had occurred in six children taking open-label DLM as a preventive LTBI treatment in the PHOENIx/A5300B/I2003B study (Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant

Tuberculosis Patients (PHOENIx MDR-TB)). These have included hypnopompic or hypnogogic hallucinations of visual, auditory, or tactile nature, associated with insomnia or nightmares in the majority, and the development of acute psychosis in one participant. These side effects typically occurred within the first 2 weeks of starting DLM. No hallucinations were observed among more than 300 adult participants enrolled in PHOENIX study.

Neuropsychiatric adverse events have been reported in adults receiving DLM as part of their MDR-TB treatment regimens. In a prospective cohort of 122 South African participants (52.5% with HIV) with MDR-TB and poor prognosis, treatment outcomes and safety were compared in those who received a BDQ-based regimen (n=82) to those who received a BDQ + DLM-based combination regimen (n=40). There was an increased proportion of psychosis events in adults with MDR-TB receiving DLM + BDQ + optimized background regimen (OBR) compared to those who received BDQ + OBR (without DLM): 6 (15%) versus 3 (3.7%), p=0.02 [52].

In summary, DLM at doses of 100 mg BID and 200 mg BID is generally well tolerated among adults 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. Prolonged QTc intervals on ECG were observed in 9.9% of those receiving DLM 100 mg twice daily and in 13.1% of those receiving 200 mg twice daily versus 3.8% of placebo recipients. None of the episodes of QTc prolongation were associated with clinical symptoms or abnormalities. Only one of 161 Trial 204 participants receiving 100 mg BID and one of 160 receiving 200 mg BID of DLM 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 plus OBR group and 4% in the DLM 200 mg BID plus OBR group had QTcF >60 ms change from baseline compared with 0% in the placebo group. 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.

The WHO has issued interim guidance for the use of DLM in the setting of MDR/RR-TB [1]. Where it is available, DLM has been incorporated into OBT for MDR/XDR-TB and is being used in clinical practice for this purpose.

Dose Justification for 300 mg QD Delamanid
Dosing frequencies of once daily ([QD] or less frequent) are preferred for TB treatment regimens due to the need to maximize patient adherence and facilitate public health delivery where directly observed therapy is often needed. DLM is currently marketed outside the U.S. at 100 mg BID. PK/PD analyses using the EMA PK/PD guideline (European Medicines Agency, Science Medicines Health. Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal

products. London, England: European Medicines Agency; July 2016) were performed to determine whether QD is feasible, and if yes, at what dose.

The PK/PD driver for DLM has been determined to be the ratio of AUC/MIC in a mouse chronic TB model. Pharmacodynamic targets (PDTs) of AUC/MIC were obtained from various PK/PD analyses derived from mouse chronic TB model data, hollow-fiber system of tuberculosis (HFS TB) data, and human EBA clinical trials. The details of these analyses can be found in the attached unpublished manuscript titled: Cumulative Fraction of Response for Once- and Twice-Daily Delamanid in Pulmonary Multidrug Resistant Tuberculosis Patients (being reviewed by a journal). The mouse PDT was determined to be an AUC/MIC of 252 in a mouse chronic TB model, using nonlinear regression of AUC and efficacy (reduction of lung $Log_{10}CFU$). In the HFS-TB model, the plasma-equivalent PDTs were identified as an AUC/MIC of 211 and 218 in log-phase and low–pH (pH 5.8)-cultured bacteria, respectively. Finally, using DLM plasma AUC/MIC and sputum bacterial decline data from 2 EBA trials (7 14 day treatment) and employing a nonlinear mixed effects approach, the clinical PDT was calculated as an AUC/MIC = 171.

Next, the cumulative fraction of response (CFR) for the 100 mg twice daily (BID) dose (the currently recommended dose for MDR-TB) was determined. For the 100 mg BID dose, the CFR was determined to be above 95% in 2 trials of MDR-TB subjects, based on individual subject data from Trial 242-07-204 and Trial 242-09-213. The CFR for the 200 mg QD dose evaluated in Trial 242-09-213 was 89.3% based on the mouse PDT and above 90% based on the other 3 PDTs. These results are summarized in Table 2.2-1.

Table 2.2-1: CFR Following DLM 100 mg BID or 200 mg QD Dosing

	Mouse	**HFS-TB (Log phase)**	**HFS-TB (pH: 5.8)**	**Human EBA**
PDT	252	506	522	171
Plasma-equivalent PDT	252	211 [a]	218 [a]	171
100 mg BID-CFR in Trial 242-07-204 population (n = 104)	100%	100%	100%	100%
100 mg BID-CFR in Trial 242-09-213 population (n = 242)	95.9%	98.0%	98.0%	96.7%
200 mg QD-CRF in Trial 242-09-213 population (n = 242)	89.3%	95.9%	91.7%	91.3%

[a] Plasma-equivalent PDT was calculated by dividing the smallest Kp observed in animal studies (mouse Kp).

Therefore, the PDTs obtained using diverse study models were in a relatively narrow range of 171 to 252 and the CFRs ranged from approximately 89% or higher for the 200 mg QD dose to approximately 96% or higher for the 100 mg BID dose. These data suggest that 200 mg QD is a possible dose option because CFR is near 90% or higher depending on the PDT used in the MDR-TB populations studied.

For combination regimens designed to shorten treatment duration, the margin for treatment failure is narrower; therefore, the exposures chosen should be such that they maximize the chances of success. DLM 300 mg QD achieved 20 to 25% higher AUC than the 200 mg QD (Table 2.2-2). The maximum plasma concentration (C_{max}) following the 300 mg QD is similar to that of the 100 mg BID. Furthermore, in Trial 242 06-101, DLM 400 mg QD had a lower steady state area under the curve (AUC_{ss}) compared to the 300 mg QD and, therefore, this dose was not considered further.

Table 2.2-2: Delamanid C_{maxss} and AUC_{ss} Following Various DLM Regimens

DLM Dose	C_{maxss} (ng/mL)	AUC_{ss} (ng*h/mL)	Trial
100 mg BID	414	7925	242-07-204
200 mg QD	228	3551	242-06-101
200 mg QD	Not calculated	4625	242-17-256
300 mg QD	352	5489	242-06-101
300 mg QD	412	5840	242-08-211
400 mg QD	286	4877	242-06-101

C_{maxss} = steady state maximum plasma concentration.

From a safety perspective, the exposures of DLM and its metabolite DM-6705 following 300 mg QD were lower than that following the 100 mg BID dose, indicating that the 300 mg QD dose would likely have less of an effect on a key safety issue (i.e., QT prolongation) compared to the 100 mg BID dose. This is because the corrected QT interval (QTc) interval prolongation from DLM is primarily linked with its metabolite DM 6705, which has a much longer half-life than DLM.

Table 2.2-3: Delamanid C_{maxss} and AUC_{ss} Following Various DLM Regimens

Trial	Concentration of DLM (ng/mL)	Placebo-adjusted ΔQTc by DLM (ms [90%CI])	Concentration of DLM-6705 (ng/mL)	Placebo-adjusted ΔQTc by DLM-6705 (ms [90%CI])
242-06-101	363.5	6.47 [5.48-7.46]	47.93	3.36 [2.96-3.75]
242-08-211	412.0	7.33 [6.21-8.45]	61.70	4.32 [3.81-4.83]

Modeling and simulation indicated that the upper 90% confidence interval of the simulated QTc following 300 mg QD would be less than 10msecs (see Table 2.2-3 above), which is the threshold, in the ICH E14 QT guidance, to declare a drug as having a meaningful effect on QT. This indicates that DLM 300 mg QD dosing is not expected to result in significant QT prolongation.

Based on these data, particularly that the DLM 300 mg QD dose achieved a higher AUC than the 200 mg QD dose, and that DLM 300 mg QD is not expected to result in significant QTc prolongation, we propose to evaluate the 300 mg QD dose in A5356 as a potentially optimal dose to maximize antimycobacterial activity in the treatment of DR TB.

DLM in MDR-/RR-TB Treatment
A recent phase 3 trial of DLM, conducted at 17 sites in seven countries, enrolled 511 participants randomized to receive oral DLM 100 mg twice daily for 2 months followed by 200 mg once daily for 4 months or placebo, each in combination with optimized background therapy [53]. Among the 327 participants with culture confirmed MDR-TB at baseline (226 in the DLM and 101 in the placebo groups), the median time to sputum culture conversion was 51 days in the DLM group and 57 days in the placebo group and was not significantly different between the groups (HR 1.17 [95% CI 0.91-1.51; p=0.2157]), although the analysis considered any missing sputum data to be culture positive, among other such confounders, which has negatively impacted the results. The incidence of treatment emergent adverse events was also similar between the two groups.

In a retrospective analysis of treatment response in a select group of participants with MDR-TB who preferentially received DLM (as opposed to BDQ) as part of multidrug regimens at Medecins Sans Frontieres (MSF) supported programs before March 2016, 67.6% (25/37) of patients sputum culture converted by 6 months of treatment and 73.6% had a protocol-defined favorable treatment response [54]. DLM was prescribed via compassionate use for the cohort because the patients involved had fewer than 4 effective conventional second-line drugs available based on DST results.

BDQ and DLM in Combination for MDR-/RR-TB Treatment
In another retrospective cohort study, MSF evaluated 28 patients who received a combination of BDQ and DLM together with other second-line anti-TB drugs for treatment of MDR/XDR-TB [55]. All received standard doses of BDQ and DLM for six to 12 months. No patients had an increase in QTc interval of more than 500 ms, and none had to discontinue drugs due to prolongation of the QTc interval. Patients were treated with a median of seven drugs including BDQ and DLM; 79% (22/28) of patients had sputum culture conversion by 6 months of treatment.

A systematic review of published data on the combination of BDQ and DLM used together in the treatment of MDR-TB reported that among 87 patients, 41 of whom received them concomitantly; the sputum culture conversion rate was 81.4%. 71.4% reported treatment success, although the definitions and time period over which these occurred was not specified [56].

Lastly, a recently completed randomized clinical trial compared the safety, tolerability and efficacy of BDQ, DLM or both plus OBT (that excluded moxifloxacin, CFZ or other QTc prolonging anti-TB drugs) in 84 participants with MDR-TB [57]. Participants were treated for 24 weeks with their randomized regimen and then continued beyond week 24, if needed, on SOC treatment for MDR-TB. Participants were hospitalized for the first 8 weeks of treatment until an interim analysis established safety based on analysis of ECGs (done in triplicate) every 2 weeks. Data presented showed no Grade 3 or 4 QTcF prolongation, no cardiovascular AEs, and only a modest additive effect of an 8-20 ms increase in QTcF interval in the combination DLM/BDQ arm.

Recent data from Otsuka's DLM compassionate program reported that 84 patients with MDR/XDR-TB had initiated treatment with DLM in combination with BDQ; 67 of the 84 patients (79.8%) had not previously been treated with either drug, and 58 completed 24 weeks of treatment [58]. Of the 58 patients who completed 24 weeks of treatment with DLM and BDQ, 51 (87.9%) were culture negative at 24 weeks. Similar results were described among the subset of 35 patients who were HIV-infected. While 6% of participants experienced QT prolongation, only one patient who received CFZ in addition to BDQ and DLM had a QTc interval of >500 ms that required BDQ interruption, but was able to restart the drug without adverse effect.

Additional studies with DLM in a variety of settings used together with BDQ, LZD, and other second-line anti-TB drugs are ongoing in both children (NCT03141060) and adults in programmatic settings (NCT02619994; NCT02754765) to more fully assess the role of this drug in the treatment of MDR/RR-TB.

While the results of the large phase 3 trial of DLM plus OBT, as previously described, did not show a statistically significant difference between the DLM arm and OBT alone, overall the TB outcomes in both arms were generally better than historical data previously reported for MDR/RR-TB treated with conventional second-line anti-TB regimens. The combination of DLM with BDQ suggests further improvement in culture conversion rates and overall treatment success with this combination. The singular contribution of DLM (or LZD) to the antimycobacterial activity of such combination regimens remains to be determined.

Safety and PK data with the combination of DLM and BDQ is also being evaluated in ongoing clinical trials, although preliminary data from program-based studies and the results of the randomized clinical trial (DELIBERATE) suggest that for most patients this combination has not been associated with clinically problematic QTc interval changes [55-57].

Clofazimine

Clofazimine (CFZ) is a fat-soluble riminophenazine drug primarily used for the treatment of *Mycobacterium leprae*. The mechanism of action of CFZ is thought to be due to redox cycling and production of reactive oxygen species (ROS) superoxide and H_2O_2 coupled with increased lysophospholipid production resulting in inhibition of cellular uptake of potassium. These effects interfere with adenosine triphosphate production resulting in bacterial cell wall dysfunction and cell death [59]. In addition, CFZ is also thought to have anti-inflammatory effects due to decreased activation and proliferation of T-lymphocytes.

Although human EBA studies have not demonstrated significant antimicrobial activity, murine models show significant MTB killing activity, with cultures negative after 5 months in Balb/c mice treated with CFZ, amikacin, moxifloxacin, ethambutol, and PZA when compared with mice that received similar drugs without CFZ [60, 61]. In another mouse model study of DS-TB, the substitution of CFZ for ethambutol in the standard DS-TB

regimen of resulted in significantly faster clearance of organisms from the lungs, curing 100% of mice in 3 months [62].

Sequential cohorts treated with variations of the Bangladesh regimen had a 15% increase in overall cure rates when CFZ was included throughout the course [63]. A randomized trial evaluating CFZ (100 mg daily for 21 months versus placebo) included in OBT for treatment of MDR-TB demonstrated faster time to sputum culture conversion, cavity healing on chest CT, and higher treatment success rates (73.6% vs. 53.8%; p=0.035) in patients randomized to CFZ [64]. While a second smaller randomized trial including CFZ in individualized regimens to treat XDR-TB failed to demonstrate more rapid sputum culture conversion on solid medium, the drug was safe and not associated with increased rates of AEs [65]. Similarly, the short course regimen in STREAM-1, as previously described, included CFZ in the same Bangladesh regimen but with moxifloxacin substituted for gatifloxacin, and was associated with comparable treatment outcomes as the WHO standard-of-care long course regimen [10]. CFZ is now included in Group B in the most recent WHO recommendations, which indicate it should be added to Group A drugs to construct a regimen with 4-5 active drugs unless it cannot be added for safety or logistical reasons. Thus, there is support for the potential antimycobacterial activity of CFZ, and given the intent to construct a regimen with at least 4 active drugs for the treatment of DR-TB, CFZ is an appropriate addition to OBT.

Rationale for the Dose of CFZ
CFZ bioavailability after oral administration is variable (45-60%) and enhanced by co-administration with food [66, 67]. CFZ is primarily eliminated as unchanged drug in the in the GI tract due to biliary excretion and unabsorbed orally administered drug. CFZ is >99% protein bound, primarily to beta-lipoproteins but also alpha-lipoproteins in serum (Clofazimine Investigator's Brochure, Edition 2, August 31, 2016). CFZ distributes extensively to the reticuloendothelial system and adipose tissue. In humans, the half-life of CFZ is not fully understood. The plasma half-life of CFZ has been estimated to be 10.5 days, extending to 69 days after achieving steady state, which might take up to 110 days to achieve [67].

Studies suggest that CFZ is a cytochrome P450 (CYP) 3A4 inhibitor, possibly a weak inducer of CYP3A4, and an inhibitor of CYP2C8 and CYP2D6 (Clofazimine Investigator's Brochure, Edition 2, August 31, 2016). However, drug-drug interaction (DDI) studies are limited. A recent population PK modeling study failed to demonstrate a statistically significant PK DDI between CFZ and BDQ, a substrate of CYP3A4 [68]. Drug-drug interaction studies conducted by Novartis indicate that CFZ was a moderate inhibitor of EFV, RAL, and DTG metabolism, resulting increases in AUC ranging from 2-3.26 fold (Clofazimine Investigator's Brochure, Edition 2, August 31, 2016); however, based on current guidance these ARVs can still be used together with CFZ.

In the previously discussed EBA study of CFZ with BDQ, PZA and pretomanid, CFZ was administered as 300 mg orally for 3 days, followed by 100 mg orally daily through day 14, with a resulting median C_{max} range of 229-268 ng/mL and AUC_{0-24} range of 3742-4459 ng*h/mL [60]. Using intensive and sparse PK sampling, A5362 will be more fully

evaluating optimal dosing for CFZ. CFZ is available as 50 mg and 100 mg oral capsules. Adult dosing for multi-bacillary leprosy is 50 mg daily for 12 months in combination with RIF and dapsone. Severe type II leprae reactions unresponsive to corticosteroids can be treated with CFZ 300 mg daily.

Murine models indicate that loading doses of CFZ result in more rapid achievement of serum concentrations above the MIC for mycobacteria but do not result in more rapid killing. Because of its long half-life, the previously proposed dosing of CFZ in Novartis MDR-TB studies is 200 mg once daily for 18 weeks, followed by 100 mg once daily for the remaining 6 weeks of intensive therapy [69].

Novartis internal studies suggest the MIC_{99} for CFZ against drug-sensitive, clinical TB isolates ranges from 0.18 to 0.84 mcg/mL and for DR-TB from 0.3 to 1.18 mcg/mL [69]. However, because of the high intracellular concentrations CFZ achieves and the larger tissue volume of distribution, the serum concentrations of the drug may be only indirectly related to overall drug activity. Although loading doses were not associated with more rapid clearance of MTB from tissue, PK based on murine modeling suggests that loading doses of 300 mg daily for 2 weeks will reach appropriate concentrations of 250 ng/mL by the end of week 2, and that 100 mg daily throughout therapy will achieve appropriate steady state concentrations approximately 7 weeks into therapy [based on data generated by the A5362 protocol team, and personal communication, Rada Savic]. Therefore, the same loading and daily dose strategy will be used for A5356 to achieve comparable concentrations as suggested for A5362 (A Phase IIc Trial of Clofazimine- and Rifapentine-Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study).

Safety of CFZ
CFZ is well-tolerated in daily doses of 50 mg for the treatment of leprosy for more than 40 years and in doses of 100 mg daily used in the treatment of nontuberculous mycobacterial diseases. The most common toxicities are non-melanotic hyperpigmentation, phototoxicity, ichthyosis, and gastrointestinal distress. The reddish gray discoloration of the skin is slowly reversible after stopping treatment. In a recent clinical trial enrolling 2,912 participants with leprosy from India and China, CFZ related pigmentation of the skin during 6 months of treatment was usually short-lived and acceptable to patients [70]. There appears to be both geographic and racial differences in incidence and degree of hyperpigmentation. In meta-analyses of cohort studies of MDR-/RR-TB treatment that included CFZ in the regimens, the pooled proportion of AEs requiring discontinuation of CFZ was 0.1% of the cases [71].

CFZ has the potential to prolong the QTc interval and may exacerbate QTc prolongation when given with other anti-TB agents, including BDQ, DLM, and some fluoroquinolones. In the EBA study of CFZ with BDQ and pretomanid, CFZ alone was associated with a mean QTcF prolongation of ~13 ms although no patient had elevations above pre specified safety thresholds; no additive or synergistic QTcF prolongation was seen when CFZ was combined with BDQ or pretomanid after 2 weeks of combination dosing [60]. In

a 24-week study, synergistic QTcF prolongation of BDQ and CFZ was reported, but not associated with any clinically relevant dysrhythmia [72].

Pregnancy and LZD, BDQ, DLM, CFZ

BDQ is a Pregnancy Category B drug. While reproduction studies in rabbits and rats demonstrated no adverse effects on fetuses, there are no data evaluating BDQ in pregnant women. DLM is not FDA-approved in the U.S. DLM is not currently recommended for use in pregnant women as reproduction studies in rabbits suggested toxicity to fetuses at high doses. There are no studies of DLM use in pregnant women. LZD is a Pregnancy Category C drug. Reproduction studies suggested minor toxicities in rabbits. No adequate data are available regarding the use of LZD in pregnant women. CFZ is also a Pregnancy Category C drug based on the absence of adequate data in pregnant women. There are reports of skin pigmentation in infants born to pregnant women exposed to CFZ. Given the absence of adequate data regarding safety or appropriate dosing during pregnancy for any of the study medications, and cautionary animal data for DLM, LZD, and CFZ, women who become pregnant during the study will be discontinued from study medications and offered best available alternatives based on local standard of care, but followed on study for safety and pregnancy outcomes.

Summary of the Rationale for LZD, BDQ, DLM, and CFZ

In summary, each of the drugs proposed for inclusion in A5356 is expected to have broad and potent antimycobacterial activity against most isolates of DR-TB, including fluoroquinolone (FQ)-resistant isolates. LZD has also demonstrated the ability to restrict emergence of nitroimidazole resistance in murine models [Nuermberger E, personal communication]. LZD 100 mg/kg increased the 1-month bactericidal activity of BDQ or pretomanid (PA-824) monotherapy, and the bactericidal and sterilizing activity of the BDQ pretomanid combination in mice. Clinically significant drug-drug interactions are not expected based on the PK and metabolic profiles of each agent and there are few, if any, overlapping toxicities with the exception of the modest additive effect on QTc prolongation with BDQ, DLM and CFZ. BDQ and LZD are now recommended by the WHO as Group A drugs to be used in combination regimens for treatment of DR-TB, while CFZ and DLM are recommended in Groups B and C, respectively, as drugs to be added to construct a regimen with 4-5 active drugs. Although a FQ is also recommended for the intensive phase of initial therapy in those known to have FQ-susceptible isolates, the role of FQs in treatment shortening and in a regimen that already contains 4 active drugs has been recently questioned, particularly in light of the results of the OFLUTUB, ReMOX and RIFAQUIN trials of treatment shortening in drug-susceptible TB, in which the shorter course regimens containing a FQ substituted for one of the components of the 4-drug SOC regimen, did not result in increased efficacy and were associated with higher rates of unfavorable treatment outcomes, particularly relapse [73-75]. In addition, FQs are not without potential toxicities (recent FDA warnings about neuropsychiatric toxicities, tendonitis and tendon rupture, QTc prolongation, among others). Given the very promising results of the NixTB trial previously described, in which a 3-drug regimen that included LZD, BDQ, and pretomanid (a new drug in the nitro-dihydro-imidazooxazole class with DLM), resulted in rapid sputum culture conversion (nearly all participants on treatment had culture conversion by week 16) and favorable treatment

outcomes in 90% of patients enrolled with MDR-/RR-TB or XDR-TB, there is strong interest in evaluating another alternative regimen that excludes both an injectable agent and a FQ. The addition of CFZ as a fourth drug added to LZD, BDQ and DLM in this context may further enhance the activity of the regimen, particularly for participants enrolled with FQ resistance and achieve the goal of at least 4 active drugs in the regimen. Lower cost and generic formulations of LZD and other drugs continue to emerge, especially as more countries in resource limited settings adopt the new WHO shorter course therapy recommendations. How implementation of shorter course regimens that might utilize these agents in combination will perform as injectable drugs are phased out remains to be established in ongoing clinical trials; however, it is imperative that additional data be developed to evaluate how these agents can be safely used together in the treatment of DR-TB. There are several overarching questions this study hopes to address related to the use of LZD, BDQ and DLM in combination with CFZ for treatment of DR-TB in this context: 1) what is the most appropriate dose of LZD in a combination short course DR-TB regimen; 2) what dosing strategies for LZD might be exploited to reduce the risk of toxicity associated with LZD and maximize its antimycobacterial activity; and 3) what is the singular contribution of LZD to this novel combination of drugs? Thus, A5356 will address these questions and evaluate these four drugs in combination, with an emphasis on detailed PK/PD analysis of alternative dosing for LZD and BDQ, DLM, and CFZ in a novel treatment shortening trial that will complement and extend the data being generated in other ongoing trials for treatment of DR-TB.

Rationale for Excluding Adolescents

Considering safety data available for LZD [Zyvox® Package Insert, 2018] and to address limited safety and efficacy data in treatment of adolescents for MDR-/RR-TB, A5356 initially planned to enroll adolescents aged 16 and older. However, the enrollment criteria was changed to 18 and older as the safety profile of DLM, as outlined above, continues to be considered based on the PHOENIx study data.

Rationale for the Pharmacogenetics of TB Drugs

It is important to consider the impact of human genetic polymorphisms when studying the efficacy, safety and PK of TB drugs. Among TB drugs, the pharmacogenetics of isoniazid (INH) has been studied most extensively. Frequent polymorphisms in *NAT2* (which encodes N-acetyltransferase 2) predict increased plasma INH exposure [76-78], and have been associated with increased risk for INH hepatotoxicity in TB cohorts [79, 80]. Risk for INH induced neuropathy may also increase with *NAT2* slow acetylator alleles [81-83]. Regarding other TB drugs, rifampicin is a substrate for organic anion-transporting polypeptide 1B1 (coded by *SLCO1B1*) [84], and one study associated an *SLCO1B1* polymorphism with RIF bioavailability in South Africans [85]. Parenteral aminoglycosides such as streptomycin can cause sensorineural hearing loss [86-89], and mitochondrial DNA mutations in the gene that encodes 12S ribosomal RNA confer increased risk [86-91]. Given evidence that AEs such as neuropathy, myelosuppression, and hyperlactatemia with LZD may be the consequence of inhibition of mitochondrial protein synthesis, it will be important to examine whether mitochondrial polymorphisms affect susceptibility to AEs with LZD [92-97]. DLM is metabolized by albumin, CYP3A4 is

involved in the subsequent metabolism of DLM metabolites, and loss-of-function variants of CYP3A4 have been reported [98, 99].

Pharmacogenetics also affects a drug-drug interaction between the TB drug INH and the HIV drug EFV. RIF induces hepatic cytochrome P450 (CYP) 2B6, so should decrease plasma EFV exposure [100], but in some participants prescribed rifampicin with INH, plasma EFV exposure paradoxically increases, particularly if CYP2B6 and NAT2 polymorphisms are present [101-103]. This may be because high INH concentrations in *NAT2* slow acetylators inhibit CYP2A6, a necessary pathway for EFV clearance in *CYP2B6* slow metabolizers [102-105]. Therefore, to fully characterize study drug PK, pharmacogenetic samples will be collected.

3.0 STUDY DESIGN

A5356 is a phase II, prospective, randomized, open-label, two-arm, multicenter clinical trial in participants age 18 and older with drug-resistant (MDR-, RR-, pre-XDR-, and XDR-) TB, with or without HIV, to evaluate the efficacy, tolerability, and safety of two different dosing strategies of LZD plus BDQ, DLM, and CFZ. At entry, participants will be randomized to Arm A or B and will begin treatment with four TB drugs: LZD, BDQ, DLM, and CFZ. The only difference in treatment between the two arms is the dosing schedule for LZD.

<u>Arm A</u>
Weeks 1-26: LZD 600 mg once daily (QD)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

<u>Arm B</u>
Weeks 1-4: LZD 1200 mg QD
Weeks 5-26: LZD 1200 mg three times per week (TIW)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Table 3.0-1: A5356 Study Treatment Regimens

Arm	Drug and dose	Weeks				
		On-treatment				Follow-up
		1-2	3-4	5-8	9-26 Or 9-38[a]	27-72 Or 39-72[a]
Arm A	LZD 600 mg QD	X	X	X	X	Follow up with no further treatment
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	

Arm	Drug and dose	Weeks				
		On-treatment				Follow-up
		1-2	3-4	5-8	9-26 Or 9-38[a]	27-72 Or 39-72[a]
Arm B	LZD 1200 mg QD	X	X			
	LZD 1200 mg TIW			X	X	
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	

[a] Participants who do not achieve sputum culture conversion by 16 weeks of treatment will extend their treatment by an additional 12 weeks for a total treatment duration of 38 weeks.

The majority of participants will be on study-provided drugs treated for at least 26 weeks. In some cases, the duration may be up to 30, 38, or 42 weeks.

Participants whose TB drugs are held for any reason and who do not complete 26 weeks of treatment by week 26 will remain on study treatment through week 30, at which time they will have their final on-treatment visit.

Participants who do not achieve sputum culture conversion by 16 weeks of treatment will extend their treatment by an additional 12 weeks for a total treatment duration of 38 weeks. Participants who have their treatment extended to week 38 and for those whose TB drugs were held for any reason and who did not complete 38 weeks of treatment by week 38 will remain on study treatment through week 42 at which time they will return for their final on-treatment visit.

Upon completion of on-treatment duration, participants will be on study for 72 weeks.

Directly observed therapy (DOT) will be required at least five times weekly and will be administered by study personnel or their designates for all participants. Participant self report of ingested doses may be used for the other two days. For example, DOT might be administered on 5 days during the week and participant self-report recorded for 2 weekend days. Adherence to study TB drugs and ARVs (when applicable) will be assessed at each visit throughout study follow-up.

TB treatment outcome will be assessed at weeks 26 (and 38 for those who extend treatment for an additional 12 weeks) and 72 and at the premature discontinuation of TB treatment. Treatment-related AEs will be assessed at weeks 2, 4, 6, 8, 12, 16, 20, and 26 (and 38 for those who extend treatment for an additional 12 weeks) and at the discontinuation of TB treatment.

Participants will have intensive, abbreviated, or sparse PK sampling as described in section 11.0.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Aged ≥18 years of age at screening.

4.1.2 Newly diagnosed pulmonary drug-resistant TB (DR-TB), with resistance to at least RIF as determined by either molecular genotypic testing (such as Cepheid Xpert MTB/RIF, Cepheid Xpert MTB/RIF Ultra, Cepheid Xpert MTB/XDR, Hain GenoType MTBDR*plus*, Hain GenoType MTBDR*sl*, or other WHO-endorsed rapid diagnostic test) or with the results of culture-based phenotypic drug susceptibility testing (DST) from a sputum specimen collected within 60 days prior to entry.

NOTE: DR-TB diagnosis for purposes of meeting inclusion criteria can be from a network-approved study testing laboratory or from an outside laboratory.

4.1.3 HIV-1 infection status 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. Two or more HIV-1 RNA viral loads of >1,000 copies/mL are also acceptable as documentation of HIV infection.

NOTE A: 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.

NOTE B: WHO and US 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.

4.1.4 For participants living with HIV, either currently on an ART regimen or willing and able to start ART within 30 days after entry.

NOTE: For a list of excluded ARV medications, refer to Appendix I.

4.1.5 Efavirenz or etravirine must be discontinued prior to a participant's starting anti TB medications. For participants on efavirenz or etravirine, they must be willing and able to discontinue these at least 7 days prior to initiating study TB medications.

4.1.6 For participants living with HIV, CD4+ cell count ≥50 cells/mm^3 obtained within 60 days prior to study entry at any network-approved non-US laboratory that is Immunology Quality Assurance (IQA) certified.

4.1.7 For females of reproductive potential, negative serum or urine pregnancy test at any network-approved laboratory or clinic that operates in accordance with Good Clinical Laboratory Practices (GCLP) and participates in appropriate external quality assurance programs.

NOTE: Urine test must have a sensitivity of ≤25 mIU/mL.

4.1.8 Females of reproductive potential who are participating in sexual activity that could lead to pregnancy must agree to use two of the following forms of birth control while receiving TB study medications and for 30 days after stopping study medications:

- Male or female condoms
- Diaphragm or cervical cap (with spermicide, if available)
- Intrauterine device (IUD) or intrauterine system (IUS)
- Hormone-based birth control (e.g., oral contraceptives, Depo-Provera, NuvaRing, implants)

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

4.1.9 The following laboratory values obtained within 14 days prior to entry at any network-approved laboratory that operates in accordance with Good Clinical Laboratory Practice (GCLP) standards and participates in appropriate external quality assurance programs:

a. Creatinine ≤1.5 x upper limit normal (ULN)
b. Absolute neutrophil count (ANC) ≥800/mm^3
c. Hemoglobin level of >8.5 gm/dL for females and >9.0 gm/dL for males
d. Platelet count ≥100,000 cells/mm^3

e. Alanine aminotransferase (ALT) <2.5 x ULN
f. Alkaline phosphatase (ALP) <2.5 x ULN; ≥2.5 – 8.0 x ULN may enroll per the investigator's discretion after discussion with the team
g. Total bilirubin ≤2.0 x ULN, or ≤1.50 x ULN if AST, ALT or ALP is above the ULN but no higher than a Grade 1 level
h. Potassium level ≥3.4 mEq/L
i. Negative for HBsAg and HCV antibody
j. Calculated creatinine clearance (CrCl) >50 mL/min, as estimated by the Cockcroft-Gault equation, or other ACTG-accepted equation or algorithm **(e.g., Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation)**.

NOTE A: Calculator for the Cockcroft-Gault equation is available at https://www.frontierscience.org/apps/cfmx/apps/common/Portal/index.cfm.

NOTE B: Any laboratory value that excludes the candidate may be repeated to confirm eligibility. The repeated laboratory value will be excluded from the required >24 hour window between screening and entry.

4.1.10 Karnofsky performance score ≥50 within 30 days prior to entry.

4.1.11 Ability and willingness of candidate and/or legal guardian/representative to provide informed consent and meet requirements for the study.

4.1.12 Chest X-ray obtained within 30 days prior to entry.

4.2 Exclusion Criteria

4.2.1 Documentation of clinically significant (as judged by the site investigator) active infections (including HIV-related opportunistic infections) other than TB and HIV requiring treatment within 30 days prior to entry.

4.2.2 Evidence of clinically significant (as judged by the site investigator) metabolic, gastrointestinal, cardiovascular, musculoskeletal, ophthalmological, pulmonary, neurological, psychiatric, endocrine diseases, malignancy, or other abnormalities (other than the indication being studied) that would interfere with study medications or procedures.

4.2.3 Inability to take oral medications.

4.2.4 Suspected or documented TB involving the central nervous system, clinically significant renal TB or TB pericarditis, or current extrapulmonary TB involving other organ systems that might interfere with study medications or procedures, as judged by the site investigator.

4.2.5 Prior treatment with LZD, DLM, BDQ, or CFZ at any time in the past for an episode of DR-TB that is not the qualifying episode of DR-TB.

4.2.6 For the qualifying episode of DR-TB, any presumptive TB treatment, including any regimen containing one or more of LZD, DLM, BDQ or CFZ for more than 7 cumulative days within the 30 days prior to entry.

4.2.7 History of allergy or hypersensitivity to any of the study drugs or medications in the same class as the study drugs.

4.2.8 Known or suspected current alcohol and/or drug abuse that is, in the opinion of the site investigator, sufficient to compromise the safety and/or cooperation of the participant.

4.2.9 Receipt of any investigational drugs within 60 days prior to entry.

4.2.10 Known history of prolonged QT syndrome or current QTcF interval >450 ms on screening ECG.

4.2.11 Known history of clinically significant cardiac arrhythmia requiring medication or 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 or prolongation of the QRS complex interval over 120 ms.

4.2.12 Pregnancy or current breastfeeding, or intent to become pregnant and/or breastfeed while on study treatment.

4.2.13 Current use of monoamine oxidase inhibitors or use within 30 days prior to entry.

4.2.14 Current use of serotonergic agents including SSRI/SNRI antidepressants or prior use within 30 days prior to entry.

4.2.15 Known history of optic neuropathy of any grade as diagnosed by an ophthalmologist.

4.2.16 Current peripheral neuropathy Grade ≥2.

4.2.17 Weight <35 kg.

4.2.18 Currently taking other prohibited medications.

NOTE: Refer to Appendix I for a list of prohibited medications.

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.

For any protocol amendments, upon receiving final IRB/EC and any other applicable RE approval(s) as well as meeting any additional study-specific requirements as determined by the protocol team, 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 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 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) Study Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of candidates for enrollment.

4.3.3 Randomization/Participant Registration

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

Candidates who meet the enrollment criteria will be randomized to the study according to standard ACTG DMC procedures.

4.4 Co-enrollment Guidelines

If sites are participating in the A5300B PHOENIx study, sites are encouraged to recruit participants from among the index cases and household contacts with newly diagnosed pulmonary DR-TB (INH arm only) in the A5300B PHOENIx trial and/or to refer participants from A5356 to the A5300B PHOENIx trial, as appropriate. Co-enrollment of participants will be allowed should participants otherwise meet all eligibility criteria for both studies.

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management Section.

5.0 STUDY TREATMENT

Study treatment is defined as linezolid (LZD), bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ).

The study-provided drugs are LZD, BDQ, DLM, and CFZ.

Participants must not be on any locally provided OBT or any other anti-TB medication other than study-provided drugs during study treatment.

For participants living with HIV, ART is required, but will not be provided through this study. Site clinicians, in conjunction with participants, should determine the optimal ART regimen for each participant. For participants not on an ART regimen, they must be able to start ART within 30 days after entry.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

At entry, all participants will be randomized 1:1 to one of two treatment arms (Arm A or Arm B). The only difference in treatment between the two arms is the dosing schedule for LZD, as shown below. Also refer to Table 3.0-1.

Arm A
Weeks 1-26: LZD 600 mg once daily (QD)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Arm B
Weeks 1-4: LZD 1200 mg QD
Weeks 5-26: LZD 1200 mg three times per week (TIW)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Participants will be followed for 72 weeks for the outcomes of efficacy and tolerability. Participants will be monitored closely for adverse events. LZD doses will be adjusted or discontinued as needed based on the dose reduction algorithm described in the Toxicity Management section 8.2.

5.1.2 Administration

Linezolid
LZD 600 mg will be administered as one 600 mg tablet orally once daily in the morning for Arm A.

LZD 1200 mg will be administered as two 600 mg tablets orally once daily in the morning for 4 weeks, then once daily three times per week (Monday-Wednesday-Friday) in the morning for Arm B.

Bedaquiline
BDQ 200 mg will be administered as two 100 mg tablets orally once daily in the morning for 8 weeks, then one 100 mg tablet orally once daily in the morning.

Delamanid
DLM 300 mg will be administered as six 50 mg tablets orally once daily in the morning.

Clofazimine
CFZ will be administered as three 100 mg capsules orally once daily in the morning for 2 weeks, then one 100 mg capsule orally once daily in the morning.

5.1.3 Regimen Administration

Study TB drugs of LZD, BDQ, DLM, and CFZ should be taken with a meal or within 15-30 minutes after a meal. The study drugs should generally be taken together. However, it is acceptable if some are taken with a meal and other immediately (within 15-30 minutes) after a meal.

NOTE: A meal is meant to be the equivalent of a breakfast, lunch or dinner meal based on local standards and should be more than a few crackers or single piece of fruit.

5.1.4 Treatment Duration

Participants in both study arms will remain on study treatment for a minimum of 26 weeks. If a participant has missed doses for any reason, participants will have 210 days (30 weeks) from entry to complete 182 doses of treatment; any missed doses should be made up with the same combination of drugs that were missed.

A partial missed dose, where some but not all study drugs are taken, will be considered a full missed dose and will need to be made up.

For participants who experience vomiting after taking study drugs, if this occurs >1 hour after ingestion, they are considered to have completed their scheduled dose. If vomiting occurs <1 hour after a dose (partial or complete dose), this will be considered a missed dose and will need to be made up. For safety reasons, participants should not immediately repeat the dose due to the risk of overdose.

Study medications may be extended by 12 weeks if a participant has failed to culture convert by week 16, for a total of 38 weeks of treatment. These participants will have 294 days (42 weeks) to complete 266 doses, unless otherwise directed after discussion with the team. Participants who do not complete doses in durations specified above will still be followed until the completion of therapy.

NOTE: Study treatment can be extended beyond 210 days to complete 182 doses and beyond 294 days to complete 266 doses with concurrence of the A5356 CMC (e.g., due to either interruptions of a study drug for an AE or non-adherence). However, this study treatment extension to complete all doses means the participant will not meet the definition of "completion of all doses of TB medication" for the Favorable TB Treatment Outcome (Cure) defined in section 6.3.18. On the eCRF, select "Favorable TB Treatment Outcome (study treatment extension to complete study treatment)" instead.

5.2 Study Product Formulation and Preparation

5.2.1 Linezolid: LZD will be supplied as 600 mg film coated tablets for oral administration. Store at 25°C (77°F), excursions permitted between 15 and 30°C (59-86°F). Protect from light. Keep bottles tightly closed to protect from moisture.

5.2.2 Delamanid: DLM will be supplied as 50 mg film-coated tablets in blister packs for oral administration. Store at 25°C (77°F); excursions permitted between 15 and 30°C (59-86°F). Dispense in original container.

5.2.3 Bedaquiline: BDQ will be supplied as 100 mg tablet. Store at 25°C (77°F); excursions permitted at 15-30°C (59-86°F). Keep in the original container and keep out of light. **Store tablets dispensed outside of the original container in a tight light-resistant container with an expiration date not exceeding 3 months and protect from light.**

5.2.4 Clofazimine: Clofazimine will be supplied as 100 mg capsules. Do not store above 30ºC (86ºF). Protect from light and moisture.

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Supply

5.3.1.1 Linezolid: LZD manufactured by Pfizer, Inc. will be supplied by Pfizer, Inc.

5.3.1.2 Delamanid: DLM manufactured by Otsuka Pharmaceutical Co., Ltd. will be supplied by Otsuka Pharmaceutical Co., Ltd.

5.3.1.3 Bedaquiline: BDQ manufactured by Janssen will be supplied through the study with funding support from the ACTG.

5.3.1.4 Clofazimine: Clofazimine manufactured by Novartis will be supplied through the study with funding support from the ACTG.

5.3.2 Study Product Distribution

Linezolid, delamanid, and clofazimine will be available through the NIAID Clinical Research Products Management Center (CRPMC). Bedaquiline will be available through the NIAID International Clinical Research Products Management Center (ICRPMC).The site pharmacist should obtain the study products for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

5.3.3 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. 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 ACTG Precautionary and Prohibited Medications Database located at https://www.ppmdb.org/PPMD.

5.4.1 Required Medications

For participants living with HIV, ART (non-study provided).

5.4.2 Prohibited and Precautionary Medications

For a list of prohibited and precautionary medications, see Appendix I.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening -14 Days, Unless Otherwise Specified (see section 4.1)	Entry/ Day 0 Week 0	Post-Entry Evaluations (Weeks)									Post Study Treatment Evaluations (Weeks)				Suspected MTB IRIS	Following Dose Reduction of LZD Due to Toxicity	Suspected or Confirmed TB Treatment Failure OR Possible TB Recurrence	Premature Treatment or Study Discontinuation
			Visit Window ±7 days																
			2	4	6	8	12	16	20	26	30 [1] (see section 6.2.3)	38	42 [1] (see section 6.2.3)	52	72				
Documentation of HIV-1 Status	X																		
Medical History	X																		
Medication History	X	X																	
Complete Physical Exam	X [2]	X [2]																	
Karnofsky Performance	X																		
Targeted Physical Exam		X [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
TB Evaluations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant Medications(including ART if HIV+)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Evaluation	Screening -14 Days, Unless Otherwise Specified (see section 4.1)	Entry/ Day 0 Week 0	Post-Entry Evaluations (Weeks)									Post Study Treatment Evaluations (Weeks)				Suspected MTB IRIS	Following Dose Reduction of LZD Due to Toxicity	Suspected or Confirmed TB Treatment Failure OR Possible TB Recurrence	Premature Treatment or Study Discontinuation
			Visit Window ±7 days																
			2	4	6	8	12	16	20	26	30 [1] (see section 6.2.3)	38	42 [1] (see section 6.2.3)	52	72				
Antiretroviral Medications Modifications (if HIV+)			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
TB Medication Modifications			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
ACTG Brief Peripheral Neuropathy Assessment	X			X		X	X	X	X	X	X	X	X	X	X		X		X
Chest X-Ray	X									X						X		X	X
Vision Screening		X		X		X	X	X	X	X	X	X	X				X (**as clinically indicated**)		X
12-Lead ECG (Resting)	X	X	X	X	X	X	X	X	X	X	X	X	X						X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Liver Function Tests and Blood Chemistries	X	X		X		X	X	X	X	X	X	X	X			X			X
Calculated Creatinine Clearance	X	X		X		X	X	X	X	X	X	X	X			X			X

Evaluation	Screening -14 Days, Unless Otherwise Specified (see section 4.1)	Entry/ Day 0 Week 0	Post-Entry Evaluations (Weeks)									Post Study Treatment Evaluations (Weeks)				Suspected MTB IRIS	Following Dose Reduction of LZD Due to Toxicity	Suspected or Confirmed TB Treatment Failure OR Possible TB Recurrence	Premature Treatment or Study Discontinuation
			Visit Window ±7 days																
			2	4	6	8	12	16	20	26	30 [1] (see section 6.2.3)	38	42 [1] (see section 6.2.3)	52	72				
Hepatitis B and C Serology	X																		
TSH		X																	
Pregnancy Test	**X**	X	as clinically indicated																
Sputum AFB Smear and Culture [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X
Rapid Genotypic DST [4]	X	X					X	X	X	X	X	X	X	X	X			X	X
Culture Based Phenotypic DST [5]	X	X					X	X	X	X	X	X	X	X	X			X	X
CD4+ Cell Count (if HIV+)	X									X				X		X		X	X
Plasma HIV-1 RNA (if HIV+)	X									X				X		X		X	X
Intensive or Abbreviated PK				X													X		
Sparse PK Sampling			X		X	X	X	X	X	X	if still on treatment							X	X
Stored Serum		X				X		X		X		X				X		X	X
Stored Plasma		X				X		X		X		X				X		X	X

Evaluation	Screening -14 Days, Unless Otherwise Specified (see section 4.1)	Entry/ Day 0 Week 0	Post-Entry Evaluations (Weeks)									Post Study Treatment Evaluations (Weeks)				Suspected MTB IRIS	Following Dose Reduction of LZD Due to Toxicity	Suspected or Confirmed TB Treatment Failure OR Possible TB Recurrence	Premature Treatment or Study Discontinuation
			Visit Window ±7 days																
			2	4	6	8	12	16	20	26	30 [1] (see section 6.2.3)	38	42 [1] (see section 6.2.3)	52	72				
Stored PBMCs		X				X		X		X		X				X		X	X
Stored Sputum		X				X		X		X	X	X	X					X	
TB Treatment Status Determination										X	X	X	X		X			X	X
Adherence Assessment and Directly Observed Therapy Review			X	X	X	X	X	X	X	X	X	X [1]	X			X		X	X
Dispense Study Medication		X	X	X	X	X	X	X	X	as indicated									
Stored Whole Blood for Pharmacogenetic Testing (Optional)		X [6]																	

1 Only for participants whose treatment is extended to week 38, or for those who take 30 or 42 weeks to complete treatment.
2 See section 6.3.4.
3 Two sputum samples at least 15 minutes apart should be obtained for AFB smear and mycobacterial culture; each sputum sample should be submitted for culture on both solid and in liquid media.

4 Rapid DST for detection of RIF, INH, fluoroquinolones, and injectable aminoglycosides/cyclic peptides may be performed by molecular genotypic tests (e.g., Cepheid Xpert MTB/RIF, Cepheid Xpert MTB/RIF Ultra, Cepheid Xpert MTB/XDR, Hain GenoType MTBDR*plus* and MTBDR*sl*).

5 Culture-based phenotypic DST will be performed only if sputum specimens obtained at the time of the visit are positive for MTB. DST for detection of LZD, DLM, BDQ, and CFZ will require sputum culture-based phenotypic methods, which can also detect RIF, INH, fluoroquinolone and injectable aminoglycoside resistance. See section 6.3.11 for details. The DST must be culture-based phenotypic testing at the time of treatment failure (see section 6.2.3).
See section 6.3.17.

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

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

Screening evaluations to determine eligibility must be completed within 14 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 an ACTG Screening Failure Results form and keyed into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified and must be completed before initiating treatment. Participants must begin treatment within 72 hours after randomization.

6.2.3 Post-Entry Evaluations

The window for all study visits is ±7 days.

On-Treatment Evaluations
Participants who do not take all required doses of their 26 weeks of treatment by week 26 will remain on study treatment up to week 30, at which time they will have their final on-treatment visit.

Participants who have their treatment extended to week 38 because they did not achieve culture conversion by week 16 will remain on study treatment through week 38, at which time they will return for their final on-treatment visit. However, any of these participants who did not take all required doses of study treatment by week 38 will remain on study treatment up to week 42 at which time they will have their final on-treatment visit.

Post Study Treatment Evaluations
Post study treatment visits will include TB evaluations per section 6.3.5, toxicity assessment for TB treatment if continuing on local SOC treatment and TB treatment status determination as indicated in section 6.3.18. The TB evaluation information may be obtained through local clinic chart review and laboratory and clinical data obtained from the participant's local TB program or provider and must be recorded on the eCRFs when received.

MTB IRIS
Participants who develop symptoms consistent with MTB IRIS at any time while on study treatment should have the evaluations listed in the SOE **(Table 6.1-1)**

within 7 days after presentation. See the ACTG definition of MTB IRIS on the ACTG website under Protocol Support Resources https://actgnetwork.org.

Reporting of an MTB IRIS event includes recording information concerning any invasive procedures and hospitalizations related to the MTB IRIS episode on the AE log along with any other appropriate eCRFs, as well as subsequently recording eventual resolution of that event.

Dose Reduction of LZD Due to Toxicity
This visit is for any participant who undergoes a dose reduction of LZD according to section 8.2, and remains on LZD. The visit should occur 2-4 weeks after the dose reduction.

Suspected or Confirmed TB Treatment Failure
A participant must undergo the evaluations within 14 days after the site's becoming aware of a suspected or confirmed TB treatment failure as indicated below.

Suspected TB Treatment Failure
TB treatment failure should be suspected for participants whose signs and symptoms related to the qualifying episode of TB have not improved or resolved by week 16, or those with a persistently positive AFB smear in sputum or other body fluid or tissue sample after week 16 (or week 20 for those who extended treatment for an additional 12 weeks).

Confirmed TB Treatment Failure
See section 6.3.18.

Possible TB Recurrence
A participant must undergo the evaluations as soon as possible (but within 14 days) of the site's becoming aware of a possible TB recurrence as indicated below.

TB recurrence is considered a possibility for participants whose signs and symptoms related to the qualifying episode of TB have resolved and who have two consecutive MTB-negative mycobacterial cultures by week 16 (or 20 if TB treatment has been extended for an additional 12 weeks) and have completed treatment, but who subsequently have a recurrence of clinical or radiographic deterioration consistent with active TB. Any **MTB-**positive sputum culture should be stored at the site or at the local TB laboratory per site procedures.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit.

Premature TB Treatment Discontinuation Evaluations
Participants who prematurely and permanently discontinue any study-provided TB drug will have the discontinuation evaluations performed as noted in the SOE **(Table 6.1-1)** within 4 weeks after the discontinuation.

If the participant prematurely discontinues any study-provided TB drug, they will continue on the remaining TB drugs and the date of the discontinuation of the study-provided TB drug and the reason for discontinuation will be entered on the eCRF.

If the participant prematurely discontinues all study-provided TB drugs, the date of the last dose of study-provided TB drug and the reason for discontinuation should be entered on the eCRF.

If the participant discontinues all study-provided TB drugs prematurely, they will be referred to their national TB program or local clinic for treatment of their DR-TB according to local SOC, but will be encouraged to continue on study, off study treatment, and receive all evaluations per the SOE **(Table 6.1-1)** through week 72, with the exception of PK assessment and adherence assessment (i.e., PK and adherence assessments are not required if all study-provided TB drugs are prematurely discontinued, but the participant remains on study).

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue from the study for any reason will have the study discontinuation evaluations performed as noted in the SOE **(Table 6.1-1)** prior to being taken off the study.

Evaluations for Participants Who Die
All eCRFs must be completed and keyed for the period up to the death week.

6.3 Instructions for Evaluations

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

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 website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf. **Direct data entry cannot be performed for this study.**

All stated evaluations are to be recorded unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity

of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) and AE reporting of adverse events requirements.

6.3.1 Documentation of HIV-1

Section 4.1.3 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the previous 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (oral history accepted)
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis, including extrapulmonary TB
- Chronic hepatitis C
- Chronic hepatitis B
- Hearing loss
- Peripheral neuropathy
- Optic neuropathy
- Cardiac history including history of arrhythmias, coronary artery disease, and heart failure, transient ischemic attack, cerebrovascular accident)/stroke, myocardial infarction
- Hypothyroidism
- COVID-19
- Psychiatric conditions, including history of hallucinations or acute psychosis

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

Documentation of historical information for all prior TB episodes (including extrapulmonary TB) will include any available information about diagnosis dates from results of TB cultures, AFB smear results (including smear grade defined as 1+, 2+, or 3+ positive), TB drug-susceptibility testing, and TB treatment information (estimated start and stop dates allowed if actual start and stop dates are unavailable). Any other available information about prior TB episodes that is not listed above should be documented only in the source documents.

6.3.3 Medication History

A medication history must be present, including start and stop dates. Alternative therapies and dietary supplements should be recorded on source documents only. Table 6.3.3-1 lists the medications that must be included in the history.

Table 6.3.3-1: Medications To Be Included in Medication History

Medication Category	Complete History or Timeframe
TB therapy for the qualifying episode	Complete history
Prior TB treatment	Complete history
ARVs (for participants living with HIV only)	Within 12 months prior to study entry
Immune-based therapy	Within 30 days prior to study entry
Blinded study treatment	Complete history
Prescription drugs, including for treatment and/or prophylaxis of opportunistic infections	Within 30 days prior to study entry
Alternative therapies	Currently being taken
Dietary supplements	Currently being taken
Sex-hormone medications or sex-hormone analogues or antagonists*	Last 12 months except as noted below

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxif**e**ne, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.4 Clinical Assessments

All clinical assessments described below will be performed as indicated in the SOE (**Table 6.1-1**), except as noted.

Complete Physical Exam

A complete physical examination will be performed at either screening or entry, and is to include, at a minimum, an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema. The complete physical exam will also include signs and symptoms, diagnoses, height, weight, and vital signs (temperature, pulse, respiration rate, and blood pressure). A targeted physical exam, as indicated below, should be done at entry if a complete physical examination was performed at screening.

Karnofsky Performance Score
The Karnofsky performance score will be assessed at screening only.

Targeted Physical Exam
Targeted physical examination will be performed at entry and after entry visits and is to be driven by any previously identified or new signs or symptoms including diagnoses or adverse events (AEs) that the participant has experienced since the last visit. At the discretion of the site investigator, components of a complete physical exam can be performed again as needed at the entry visit.

The targeted exam, at a minimum, will include vital signs (temperature, pulse, respiration rate, and blood pressure); weight; presence of lymphadenopathy, presence of rash, and lung examination.

Refer to section 7.2 for AE collection requirements.

Concomitant Medications
Post-entry, the following new and discontinued concomitant medications must be recorded:

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.3 for examples).
- All prescription medications, excluding TB medications, started or stopped since the last study visit.

Nonprescription medications must be present only in the source documents.

Antiretroviral Medications
For participants living with HIV, all modifications to antiretroviral medications will be recorded, including actual start dates and stop dates, initial doses, and inadvertent and deliberate interruptions of more than 7 days at each visit. Record any permanent discontinuation of ARVs. Selection and dosing of ART in combination with the TB regimen should adhere to local guidelines at each site.

TB Medication Modifications
At each visit, all TB medications started or stopped since the last study visit must be recorded, including actual start dates and stop dates, initial doses, participant initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions. Record any permanent discontinuation of medications.

6.3.5 TB Evaluations

A review of all reported results from evaluations for the qualifying episode of TB performed at the local clinic or TB program site must be completed for all participants. At each study visit, any diagnostic, laboratory and radiology results, and treatment information available regarding the qualifying (current) episode of TB, including any updates not previously available from the local TB clinic, must

be recorded when received. Two sputum specimens separated by, at least, 15 minutes should be obtained at entry and at the time of study visits as indicated in the SOE **(Table 6.1-1)** and sputum samples should be submitted for culture as performed on both solid and in liquid media. Evaluations will include TB-related radiologic results, including most recent chest X-ray (as indicated in section 6.3.7), AFB smear (including smear grade defined as 1+, 2+, or 3+ for positive results) and mycobacterial culture results as above, with speciation (*M. tuberculosis* or other mycobacterial species) and DST (as indicated in section 6.3.11), and other evaluations related to TB diagnosis and evaluation of TB status. The DST must be culture-based phenotypic testing at the time of treatment failure (see section 6.2.3). Any new or worsening of previous findings identified from repeated radiologic evaluations must be documented on the eCRF.

6.3.6 ACTG Brief Peripheral Neuropathy Assessment

A brief peripheral neuropathy assessment, consisting of participant-elicited symptoms of peripheral neuropathy, testing of vibratory sensation, and deep tendon reflexes will be performed per the SOE **(Table 6.1-1)**.

For post-entry assessments, record all peripheral neuropathy events of Grade 2 or higher. Refer to section 7.2 for AE collection requirements.

6.3.7 Chest X-Ray

A chest X-ray must be performed within 30 days prior to study entry and per the SOE **(Table 6.1-1)** thereafter. The chest X-ray projection will be posterior anterior (PA). Extent of disease (limited to one lobe or region, unilateral, bilateral, or diffuse) and cavitation status (cavities present or absent, and if present, location and estimated number) will be documented. Interpretation of the chest X-ray must be performed by either a site clinician or a local radiologist and the interpretation recorded as indicated on the eCRF. A copy of the interpretation if performed by a local radiologist outside the study should be filed with source documentation.

6.3.8 Vision Screening

Vision screening for optic neuritis by signs and symptoms, Snellen chart, and Ishihara Plates will be performed at the local site for all participants per the SOE **(Table 6.1-1)**.

NOTE: Signs and symptoms of optic neuritis may include but are not limited to one or more of the following: eye pain, vision or visual acuity loss in one or both eyes, visual field loss in one or both eyes, loss of color vision, and flickering/flashing lights.

For post-entry assessments, record all diagnoses of optic neuritis regardless of grade. Refer to section 7.2 for AE collection requirements.

6.3.9 12-Lead ECG (Resting)

The screening ECG must be performed within 14 days prior to the entry ECG. ECGs will be read and interpreted locally.

Because of the diurnal variation of QTcF interval, ECGs for each participant should be done at approximately the same time of day throughout the study.

At week 4 where ECG testing and blood draws for intensive or abbreviated sampling PK assessments are scheduled together, the participant should have ECGs performed prior to TB medication dosing and blood draws.

For post-entry ECG testing, record all values of Grade 2 or higher for QTcF prolongation.

6.3.10 Laboratory Evaluations

At screening and entry, all laboratory values must be recorded.

For post-entry assessments, record all laboratory values of Grade 2 or higher for hemoglobin, absolute neutrophil count, platelet count, ALT, total bilirubin, and lactate. Refer to section 7.2 for AE collection requirements.

Hematology
Hemoglobin, white blood cell count (WBC), differential WBC (to include only neutrophils, lymphocytes, and monocytes), absolute neutrophil count (ANC), and platelet count will be performed in real time at the local laboratory.

Liver Function Tests
AST [SGOT], ALT [SGPT], total and direct bilirubin, alkaline phosphatase and albumin levels will be performed in real time at the local laboratory.

Blood Chemistries
Serum potassium, calcium, magnesium, creatinine, glucose, and a lactate level will be performed in real time at the local laboratory.

NOTE: A routine lactate level should be obtained at entry, regardless of symptoms, to assess the baseline value. Post-entry, lactate levels should only be obtained if there are signs and symptoms suggestive of lactic acidosis (see section 8.2.13).

Calculated Creatinine Clearance
Calculated CrCl is required as estimated by Cockcroft-Gault equation or other ACTG-accepted equation **(e.g., Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI])**. This requires the recording of all serum creatinine values regardless of grade.

NOTE: Calculator for the Cockcroft-Gault equation is available at https://www.fstrf.org/apps/cfmx/apps/common/Portal/index.cfm.

Hepatitis B and C Serology
HBsAg and HCV antibody will be performed by a DAIDS approved laboratory or its equivalent. HBsAg and HCV antibody results are not be recorded on the eCRF.

Thyroid Stimulating Hormone (TSH)
TSH will be performed at the local laboratory.

Pregnancy Test
For women of reproductive potential: Serum or urine β-HCG may be used (urine test must have a sensitivity of ≤25 mIU/mL). Record pregnancy and pregnancy outcome per section 8.3.

6.3.11 TB Laboratory Diagnostics and Microbiology

Sputum AFB Smear and Mycobacterial Culture will be performed per the SOE **(Table 6.1-1)**. Sputum AFB smear grade (1+, 2+, or 3+ positive) should be recorded. Two sputum samples separated by, at least, 15 minutes should be collected for smear and mycobacterial cultures to be performed in both solid and liquid media per the SOE **(Table 6.1-1)**. Sputum samples should be collected according to the ACTG/IMPAACT network SOP for collecting sputum. It is recognized that participants who have completed 4 or more weeks of therapy or who have completed anti-TB treatment may no longer be able to produce sputum, therefore, inability to produce sputum with or without induction is considered a MTB-negative culture. MTB-positive cultures (i.e., the actual MTB isolates) from study samples will be stored at the site laboratory or the local TB laboratory performing the TB testing (as appropriate to the site procedures) unless shipment to a central lab is requested).

Post-entry DST will be performed only in a study site testing laboratory and will use either culture-based phenotypic resistance tests for all first and second line drugs or a combination of molecular genotypic (e.g., Cepheid Xpert MTB/RIF, Cepheid Xpert MTB/RIF Ultra, Cepheid Xpert MTB/XDR, Hain GenoType MTBDR*plus*, Hain GenoType MTBDR*sl*, or other WHO-endorsed rapid diagnostic tests) and culture-based phenotypic tests as needed. Molecular tests can be done directly on a sputum specimen or on culture. The DST must be culture-based phenotypic testing at the time of treatment failure (see section 6.2.3).

DST for detection of LZD, DLM, BDQ, and CFZ will generally require sputum culture-based phenotypic methods, which can also detect RIF, INH, fluoroquinolone and injectable aminoglycoside resistance. Pre- and post-entry DST for LZD, DLM, BDQ, and CFZ may not be routinely available in many TB laboratories. Therefore, TB DST for these drugs will be assessed as an exploratory objective and may be performed in a local TB program laboratory, national TB laboratory, or at a central laboratory to be designated by the ACTG and may use either phenotypic resistance tests alone or a combination of molecular genotypic tests and phenotypic tests as per the SOE **(Table 6.1-1)**. Any MTB isolates recovered in culture from sputum specimens for DST as indicated in the SOE **(Table 6.1-1)** should be stored at the local TB testing laboratory until DST assays can be done either in a local TB program laboratory, national TB laboratory, or a central laboratory designated by the ACTG. Culture-based phenotypic resistance testing for first and second line anti-TB drugs and/or LZD, DLM, BDQ and CFZ should be done only if a sputum culture is MTB positive.

Screening DST for at least RIF for to establish a DR-TB diagnosis for purposes of meeting inclusion criteria 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.

6.3.12 Immunologic Studies

CD4+ (for participants living with HIV only)
Obtain absolute CD4+ count within 60 days prior to study entry and per the SOE **(Table 6.1-1)** at a laboratory that possesses the IQA certification.

6.3.13 Virologic Studies

Plasma HIV-1 RNA (for participants living with HIV only)
Obtain HIV-1 viral load within 60 days prior to entry and then per the SOE **(Table 6.1-1)**. All on-study quantifications must be performed in real time using a licensed assay at a network-approved laboratory that possesses the Virology Quality Assurance (VQA) certification.

6.3.14 Pharmacokinetic (PK) Studies

Details for intensive, abbreviated, and sparse PK sampling are described in section 11.0.

6.3.15 Blood Serum, Plasma, and PBMCs

Serum, plasma, and viable PBMC specimens will be collected per the SOE **(Table 6.1-1)** and stored for future use. PBMCs must be processed at a DAIDS-IQA certified laboratory prior to storage.

6.3.16 Stored Sputum

Two sputum specimens will be collected as indicated in the SOE **(Table 6.1-1)** for culture and DST per section 6.3.11. At least one aliquot from one of the sputum samples should be stored for future use. If insufficient volume of sputum is available for aliquoting for storage, the sample should be prioritized for culture and DST. See the Laboratory Processing Chart (LPC) on the PSWP for details regarding processing and shipping of sputum for storage.

6.3.17 Stored Whole Blood for Pharmacogenetic Testing (Optional)

A single whole blood sample will be obtained from participants who consent to this collection. This sample will be obtained preferably at entry or week 2; however, at a subsequent visit will be acceptable as well. The sample will be used for genotyping of polymorphisms in human genes that may affect metabolism, disposition, and toxicity of study drugs as well as concomitant medications. See the LPC for details regarding processing and shipping.

6.3.18 TB Treatment Status Determination

TB treatment status determination (see section 5.1.4 for definitions of treatment completion based on number of doses completed) must be assessed at week 26 (week 30 if TB drugs are extended through week 30 to complete 26 weeks of treatment) or week 38 if TB drugs were required to be extended due to a MTB-positive culture at week 16 (or week 42 if TB drugs are extended through week 42 to complete 38 weeks of treatment), and week 72 and recorded.

TB treatment status determination should also be documented at the time of suspected TB treatment failure or TB relapse/recurrence, premature TB treatment discontinuation, premature study discontinuation, or death.

TB treatment status determination will be classified according to the descriptions noted below. For determination, the following should be performed as appropriate. **Two** sputum samples, **separated by at least 15 minutes and preferably by 60 minutes,** should be obtained for AFB smear, mycobacterial cultures **in both solid and liquid media,** and phenotypic TB DST. A chest X-ray should also be performed. Any results from repeated sputum and chest X-ray evaluations must be documented. Any information that is provided by the local TB clinic or program related to TB treatment failure must be recorded when

received. Any **MTB-**positive sputum culture should be stored at the site or at the local TB laboratory as appropriate to site procedures.

Favorable TB Treatment Outcome (Cure): Completion of all doses of TB medication (see section 5.1.4) and evidence of a bacteriological response (defined as last two consecutive mycobacterial cultures from sputum specimens collected by week 26 are MTB-negative with no other MTB-positive cultures thereafter and with no evidence of treatment failure or unfavorable TB treatment outcome). Inability to produce sputum with or without induction is considered a MTB-negative culture.

NOTE: If a participant has an MTB-positive culture at week 16, they will go on extended therapy, so they will still have the opportunity to convert to MTB-negative with a favorable outcome. They might be suspected of treatment failure if they have a sputum that remains MTB-positive at week 20, as per section 6.3.18. But if their next culture at week 26 is MTB-negative and they remain on treatment through week 38 and their sputum culture remains MTB-negative by week 38 (because they are on extended treatment), they then have two negative cultures between week 26 and week 38, so this will count as a favorable outcome.

NOTE: If a participant is without signs or symptoms of ongoing active TB and is unable to produce sputum with or without induction at week 26 (or week 38 if on extended treatment) or produces a sputum specimen that is contaminated in two consecutive cultures without evidence of TB at week 26 (or week 38 if on extended treatment), they will be considered as having a favorable TB treatment outcome if they have no evidence of previous or subsequent treatment failure or unfavorable outcome (any of those described below).

NOTE: The TB treatment outcome of participants who fail to complete all doses of study treatment within the protocol-defined time period outlined in section 5.1.4 due to having a study treatment extension to complete all doses (e.g., due to either interruptions of a study drug for an AE or non-adherence), but ultimately complete all doses of study medications and have a favorable TB outcome as defined above will be classified as "Favorable TB Treatment Outcome (study treatment extension to complete study treatment)" on the eCRF".

Unfavorable TB Treatment Outcome (Absence of Cure): Meeting one or more of the following:

- Participant with confirmed microbiologic TB treatment failure defined as the presence of a MTB-positive mycobacterial culture from a sputum sample obtained at or after week 16 (or week 20 for those who extend therapy for another 12 weeks) and that is confirmed by a second sputum sample that is MTB culture positive by end of treatment. A single

MTB-positive sputum culture in isolation will not be considered a confirmed microbiologic TB treatment failure.

NOTE: If a participant has an MTB-positive culture at week 20 and then at week 26, this will be considered a failure regardless of whether the participant is on extended therapy. The participant will stop current treatment and will be referred to their national TB program or local clinic for treatment of their DR-TB according to local SOC, but will be encouraged to continue on study, off study treatment, and receive all evaluations per the SOE (**Table 6.1-1**) through week 72.

- Participants who fail to complete study treatment (treatment regimen is terminated or permanently changed to a new regimen or treatment strategy) or require extension of study treatment beyond the study-prescribed treatment duration due to clinically inadequate response. Extension of study treatment to make up missed doses will not count as unfavorable.
- Participants who had a**n MTB-**positive sputum culture at their last study visit, whether confirmed by a second sputum sample or not, unless determined to have been reinfected with a new strain of *Mtb*.
- Participants who die from any cause during study treatment, except from violent or accidental cause (e.g., road traffic accident).
- Participants failing to complete study treatment and not assessable at the end of the follow-up period.

Unevaluable Outcome

- Participants still undergoing study treatment for *Mtb*.
- Participants lost to follow-up during study treatment or post-treatment follow-up with their last culture being negative for *Mtb*.
- Violent or accidental death.
- Participants with recurrent TB due to a new strain of *Mtb* confirmed by conventional molecular genotyping (as defined by MIRU and IS6110 typing).
- Women who become pregnant during their assigned active treatment and stop their assigned treatment.

6.3.19 Adherence Assessment and Directly Observed Therapy (DOT) Review

DOT is required at least five times weekly and should be administered by study personnel or their designates for all participants. Methods used to conduct DOT may be according to local SOC practices and may include video-DOT, use of community health workers, or other strategies used locally for delivering observed therapy. Participant self-report of ingested doses may be used for the other two days. For example, in-person DOT may be administered on Monday, Wednesday, Friday, video-DOT used on Tuesday and Thursday, and participant self-report on Saturday and Sunday.

Adherence to study TB drugs and ARVs (when applicable) must be assessed at each visit throughout study follow-up. TB medication cards, such as those provided by local TB control programs, may be used if available. The estimated number of observed and self-administered doses based on DOT and self-report for study-provided TB drugs (i.e., LZD, DLM, BDQ, and CFZ) will be recorded. Participants will be also asked to report on whether they took their LZD, DLM, BDQ, and CFZ doses with food (see section 5.1.3 for information related to food).

6.3.20 Dispense Study Medications

Study medication will be dispensed per the SOE **(Table 6.1-1)**.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

All AEs must be reported if any of the following criteria have been met:

- Grade ≥3
- Diagnoses of optic neuritis regardless of grade
- Targeted AE of Grade ≥2 for peripheral neuropathy, anemia/hemoglobin, absolute neutrophil count, platelet count, ALT, total bilirubin, lactate, and QTcF prolongation
- Targeted AE of anemia/hemoglobin ≥25% decline from entry/baseline
- AE that led to a change in study treatment regardless of grade
- New or worsening neuropsychiatric signs or symptoms
- AE meeting SAE definition or EAE reporting requirements

  NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC Web site: https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

The DAIDS AE Grading Table provides grading for creatinine values based on both absolute value and change from baseline. For this study, only the grading based on absolute value should be used. This grading is shown as follows:

Severity Grading for Creatinine

Severity Grade	Creatinine Values
Grade 1	1.1 to 1.3 × ULN
Grade 2	> 1.3 to 1.8 × ULN
Grade 3	> 1.8 to < 3.5 × ULN
Grade 4	≥ 3.5 × ULN

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is another important medical event (that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the events listed above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

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

The DAIDS Adverse Experience Reporting System (DAERS) 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. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting. For questions about DAERS, please contact 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.

Sites where DAERS has not been implemented must submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/safety-office-expedited-adverse-event-form. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

7.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study through 4 weeks after completing study provided drugs. For the remainder of the trial, only SAEs that are judged by the site as having a reasonable possibility of being related to study drug should be reported (SUSAR).

- The study agents for which expedited reporting are required are: linezolid (LZD), bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ).
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are:
  - Episodes of ventricular tachycardia or fibrillation, syncope, and seizure.
  - Grade 3 QTcF prolongation and results of repeated ECGs after holding study-provided drugs associated with QTcF prolongation.
  - Grade 3 pancreatitis.
  - Grade 3 rash.
  - Grade ≥2 hallucinations.
  - Any Grade 4 event, including laboratory values.
  - Deaths.

7.3.3 Grading Severity of Events

DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC web site at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

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

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

7.4 Study Monitoring

The A5356 Clinical Management Committee (CMC) will monitor the conduct of the study via regular summaries of screening failures, accrual, data completeness, and specimen collection compliance. The CMC will be provided with and monitor aggregated AEs and participants who did not have at least one MTB-positive sputum culture at entry on a monthly basis. This information will be pooled across randomized arms. The A5356 CMC

consists of the A5356 Protocol Chairs, Statisticians, DAIDS Clinical Representative, DAIDS Pharmacist, Data Managers, Clinical Trials Specialist, and other protocol team members selected by the A5356 Protocol Chairs.

The DAIDS Clinical Representative will review and assess EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs, as applicable. Additionally, the DAIDS Clinical Representative will review aggregated AE summaries by pooled across randomized arms prepared every 3 months by the Statistical and Data Management Center (SDMC).

The study will undergo interim review at least annually by the TB TSG Study Monitoring Committee (SMC). The first interim review will occur approximately 6 months after the enrollment of the first study participant or after 30 participants have enrolled into the study, whichever occurs first. An interim review may also be convened if a concern is identified by the DAIDS Clinical Representative, the study chairs, or study statistician in consultation with the CMC. See section 10.5 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study Progress, Data, and Safety Monitoring Plan (SPDSMP) developed by the SDMC prior to enrollment of the first participant.

8.0 MANAGEMENT ISSUES

Except for QTcF prolongation, A5356 will use the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected Version 2.1, July 2017, as a guideline for grading toxicities.

This section provides guidelines for management of specific toxicities related to study provided drugs. 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 8.1.

Every attempt should be made to continue to follow participants who discontinue study provided drugs because of a Grade 3 or Grade 4 AE at least until resolution of the AE can be documented and through the end of the study, if possible.

Whenever applicable in the following subsections, study TB drug dose reductions should follow the table below to allow flexibility in overall management of toxicities potentially associated with linezolid. The table shown below refers only to LZD dosing.

Table 8.0-1: LZD Dose Reduction Schedules

Treatment Arm (LZD Dose)	Arm A 600 mg QD Weeks 1-26 (38)	Arm B 1200 mg QD Weeks 1-4	Arm B 1200 mg TIW Weeks 5-26 (38)
Dose Reduction #1	300 mg QD	600 mg QD	600 mg TIW
Dose Reduction #2	None	300 mg QD	None

The A5356 CMC (actg.cmca5356@fstrf.org) is available to discuss toxicity management of study-provided drugs with investigators.

8.1 Toxicity Management

Many anti-TB drugs, including the study-provided drugs, may cause abnormal lab work and clinical signs/symptoms. Participants entering this trial will have active TB, may be seriously ill, and may have underlying HIV disease that contributes to their signs and symptoms. Therefore, changes in lab work and signs/symptoms should be evaluated within the clinical context of the abnormalities. Site investigators may decide to hold or discontinue ART as part of the overall toxicity management for participants with HIV. Site investigators are encouraged to consult with the A5356 CMC regarding the complex participant management issues that will arise during the course of this study.

The A5356 CMC must be contacted for all AEs that lead to study treatment hold or discontinuation.

The following guidance is for toxicities not specifically described in section 8.2.

Grade 1 or Grade 2
Participants who develop a Grade 1 or Grade 2 AE or toxicity not described in section 8.2 may continue study-provided drugs without alteration of the dose. 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
Participants who develop a Grade 3 AE that the site investigator determines is not related or unlikely to be related to one of the study-provided drugs, dosing may continue at the discretion of the site investigator.

Participants who develop a Grade 3 AE that the site investigator determines to be possibly related or probably related to one or more study-provided drugs, will have all study-provided drugs temporarily held for up to 14 ±2 days. The participant will be evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in

need of such frequent monitoring as determined by the CMC. Sites will contact the A5356 CMC to discuss relatedness of the AE to the study-provided drugs and to develop an individualized plan for restarting TB drugs in a step-wise manner depending on the clinical situation.

If the Grade 3 toxicity is felt to be due to one or more study-provided drugs does not improve to Grade ≤2 within 14 ±2 days or Grade 3 or greater toxicity recurs after reintroduction of study-provided medications, the study-provided drug(s) most likely to be associated with the AE should be discontinued. If this results in at least 3 active study provided drugs remaining in the regimen, the participant will continue on the remaining study-provided drugs and followed on study. If the resulting regimen no longer retains at least 3 active study-provided drugs, the participant will be discontinued from study-provided drugs and will be referred to their national TB program or TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

Grade 4

Participants who develop a Grade 4 AE that the site investigator determines to be not related or unlikely to be related to one of the study-provided drugs, dosing may continue at the discretion of the site investigator; the A5356 CMC must be notified. The participant will be evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring as determined by the CMC.

Participants who develop a Grade 4 AE that the site investigator determines as possibly or probably related to one or more of the study-provided drugs will have all study-provided drugs temporarily held for up to 14 ±2 days. Sites will contact the A5356 CMC to discuss the relatedness of the AE to the study-provided drugs, and to develop a plan for reintroducing individual study-provided drugs not likely to be related to the AE, depending on the clinical situation. The participant will be evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring. If the Grade 4 toxicity does not improve to Grade ≤2 within 14 ±2 days or recurs after reintroduction of study-provided medications, the study-provided drug most likely to be associated with the AE should be permanently discontinued. If this results in at least 3 active study-provided drugs remaining in the regimen, the participant may continue on the remaining study-provided drugs and followed on study. If the resulting regimen no longer retains at least 3 active study-provided drugs, all study-provided drugs will be permanently discontinued, and the participant will be referred to their national TB program or TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

Referral to local clinic or healthcare provider

In the event that safety testing reveals an abnormal result (e.g., abnormal ECG, abnormal vision screening, evidence of worsening peripheral neuropathy) that requires further investigation and treatment, the participant will be referred to their local clinic or healthcare provider for management.

8.2 Specific Management of Toxicities Related to Study-provided Drugs

8.2.1 QTcF Prolongation

Participants will receive TB drugs (BDQ, DLM, CFZ) that have the potential to prolong the QTcF interval. Table 8.2.1-1 indicates grading based on the ECGs at each visit.

Sites should report the following events to the study team and to DAIDS immediately: 1) Grade 3 or 4 QTcF prolongations, 2) deaths possibly related to QTcF prolongation, and 3) results of repeated ECGs after holding study-provided drugs associated with QTcF prolongation.

Table 8.2.1-1: QTcF Prolongation Grading

Grade 1	Grade 2	Grade 3	Grade 4
(1) Absolute QTcF >480 ms 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 ms and ≤60 ms.	(2) Absolute QTcF ≤480 ms and QTcF change from baseline >60 ms.	(2) Absolute QTcF >480 ms and QTcF change from baseline >60 ms.	

Grade 2 QTcF prolongation:
The participant will be monitored more closely, with once weekly ECG testing, and correction of electrolytes where necessary. If potassium or magnesium levels are below the normal range, supplementation should be initiated to return and maintain the levels of these electrolytes to within normal ranges (for potassium to at least 3.6 mEq/L or its equivalent).

Grade 3 QTcF prolongation:
Temporarily discontinue all anti-TB drugs known to be associated with QTcF prolongation (BDQ, DLM, CFZ). Sites will contact the A5356 CMC to inform them of the event. Hospitalization is strongly recommended to closely monitor the participant until the abnormality decreases to Grade ≤2.

Participant will have their electrolytes checked (at a minimum, potassium, sodium, magnesium, chloride, and calcium should be checked) and corrected where necessary. If potassium or magnesium levels are below the normal range, supplementation should be initiated to return and maintain the levels of these electrolytes to within normal ranges (for potassium to at least 3.6 mEq/L or its equivalent). The ECG will be repeated **(**after electrolyte correction, if indicated**)** and within 24 hours of the Grade 3 event.

- **In cases of Grade 3 QTcF prolongation <u>defined as >500 ms</u>:**
  CFZ will be permanently discontinued. In consultation with the A5356 CMC, the site investigator will decide whether continuing on the remaining study drugs would be in the participant's best interests. If remaining on study treatment is an acceptable option and once the repeated QTcF reading is Grade ≤2, BDQ and DLM may be restarted sequentially at the discretion of the site investigator. The drugs must be reinitiated one at a time, separated by at least 24 hours between added drugs. ECGs will be repeated within 24 hours after adding back each drug and weekly after reinitiation of these drugs. If the QT grade is ≤2 on repeat ECGs, the next drug may be reinitiated.

  If any subsequent ECG after drug reinitiation has a Grade ≥3 QT reading, all study drugs will be permanently discontinued, and the participant will be referred to the national TB clinic/provider for SOC treatment. The participant will continue to be followed on-study, but off study-provided drugs.

- **In cases of Grade 3 events <u>defined as absolute QTcF 481-500 ms and QTcF change from baseline >60 ms</u>:**
  In consultation with the A5356 CMC and at the discretion of the site investigator, BDQ, DLM, and CFZ may be reintroduced after repeat QTcF readings are Grade ≤2. Study drugs must be reinitiated one at a time, separated by at least 24 hours between adding each drug. If the QT grade is ≤2 on repeat ECGs, the next drug may be reinitiated. Additional ECGs will be repeated within 24 hours after adding back each drug and weekly after reinitiation of these drugs.

  If the QTcF again increases to Grade 3 defined as absolute QTcF 481-500 ms and QTcF change from baseline > 60 ms on repeat ECGs after all study drugs are restarted, CFZ will be permanently discontinued, and BDQ and DLM held. The ECG should be repeated within 24 hours and daily after, withholding BDZ and DLM. At the discretion of the investigator and in consultation with the A5356 CMC, BDQ and DLM may be restarted sequentially after QTcF returns to Grade ≤2 and remains Grade ≤2. If any QTcF Grade 3 event occurs after reinitiating treatment, all study drugs will be permanently discontinued, and the participant will be referred to the national TB clinic/provider for SOC treatment. The participant will continue to be followed on-study, but off study-provided drugs.

NOTE: If at any time in the management of QTcF prolongation, the resulting regimen no longer contains two or more study-provided drugs (e.g., if LZD has been discontinued for protocol required toxicity management and the CFZ has been permanently discontinued due to QTcF prolongation), the participant will be discontinued from study-provided drugs and will be

referred to their national TB program or TB clinic/provider for SOC treatment and will be followed on-study but off study-provided drugs.

Grade 4 QTcF prolongation:
The participant should be hospitalized and permanently discontinued from study-provided drugs. Sites will contact the A5356 CMC to inform them of the event. Participants will have their electrolytes checked (at a minimum, check potassium, sodium, magnesium, chloride, and calcium) and corrected where necessary. The ECG will be repeated after electrolyte correction if indicated and within 24 hours of the Grade 4 event. Participants will be referred to their National TB clinic/provider for SOC treatment and will be followed on-study but off study drug.

8.2.2 ALT or Total Bilirubin Elevation

Many anti-TB drugs, including the study-provided drugs, may cause abnormalities in liver chemistry tests. Also, participants entering this trial will have active TB, may be seriously ill, and may have underlying HIV disease that contributes to their signs and symptoms. Therefore, elevations in liver chemistry tests are not unexpected. Concomitant illnesses, including HIV infection, and other medications, such as antiretroviral (ARV) medications, may also alter these laboratory parameters. Therefore, changes in liver chemistry tests (ALT, bilirubin) should be evaluated within the clinical context of the abnormalities. Liver chemistry tests will be checked regularly for all study participants, as per the SOE **(Table 6.1-1)**.

Grade 3 ALT only:
All participants who have new Grade 3 elevation of ALT should be evaluated for hepatitis B and C virus infection and have their INR checked. Study-provided drugs may be continued at the discretion of the site investigator after discussion with the A5356 CMC. If there is documented acute viral hepatitis, the sites should contact the A5356 CMC regarding management of study medications.

Grade 3 ALT and/or Total Bilirubin:
Participants with asymptomatic or symptomatic Grade 3 elevations that the site investigator determines are not related or unlikely to be related to one of the study-provided drugs, dosing may continue at the discretion of the site investigator.

Participants who develop a Grade 3 elevation that the site investigator determines to be possibly related or probably related to one or more study provided drugs, will have all study-provided drugs temporarily held. The participant will have their liver function tests (ALT, AST, Alk phos, and total Bili) evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring. Sites will contact the A5356 CMC to discuss relatedness of the AE to the study-provided drugs and to develop an

individualized plan for restarting TB drugs in a step-wise manner depending on the clinical situation and the drug(s) most likely to be related to the abnormality.

Grade 3 ALT or Total Bilirubin Persisting for >14 ±2 days or Repeat Grade 3 ALT or Total Bilirubin Elevation:
Participants who develop a recurrent Grade 3 ALT or total bilirubin after restarting study-provided drugs and OBT (and/or ART, if applicable), or if the Grade 3 toxicity does not resolve to Grade ≤2 within 14 ±2 days, **the site will then recontact the A5356 CMC to further discuss relatedness of the AE to study-provided drugs and to develop an individualized plan to either restart or to permanently discontinue one or more study-provided drugs.** Participants **who permanently discontinue two or more study-provided drugs** will be referred to their National TB clinic/provider for SOC treatment and will be followed on-study but off study drug.

Grade 4 ALT or Total Bilirubin:
Sites will contact the A5356 CMC to inform them to the event. The participant will have their liver function tests (ALT, AST, Alk phos, and total Bili) evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring as determined by the CMC. **Once the Grade 4 elevation of ALT or Total Bilirubin has resolved according to these measures, the site will then recontact the A5356 CMC to further discuss relatedness of the AE to study-provided drugs and to develop an individualized plan to either restart or to permanently discontinue one or more study-provided drugs.** Participants **who permanently discontinue two or more study-provided drugs** will be referred to their National TB clinic/provider for SOC treatment and will be followed on-study but off study drug.

8.2.3 Acute Allergic Reaction

Grade 1 or 2 Acute Allergic Reactions
Participants may continue study-provided drugs for Grade 1 or Grade 2 acute allergic reactions at the discretion of the site investigator. The participant should be advised to contact their site investigator 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.

Grade 3 or Higher Acute Allergic Reactions
Participants with Grade ≥3 acute allergic reactions that are considered to be possibly or probably related to a study-provided drug should permanently discontinue the implicated study-provided drug. Sites will contact the A5356 CMC to inform them of the event and to discuss the attribution of the event and management issues for the remaining drugs in the regimen. The participant will be treated as clinically appropriate by the site investigator until the participant is stable and until resolution of the AE.

Participants who develop a Grade 4 acute allergic reaction that the site investigator determines as possibly or probably related to one of the study-provided drugs should permanently discontinue the implicated study-provided drug. Sites will contact the A5356 CMC to inform them of the event. Other study provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator together with the CMC determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue all study-provided drugs. The participant will be treated as is clinically appropriate by the site investigator until stable and until resolution of the AE. The participant will be referred to the national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. The participant will continue to be followed on study, but off study-provided drugs.

8.2.4 Neutropenia/Absolute Neutrophil Count (ANC)

Participants entering this trial will have active TB and some will have HIV. Neutropenia is common in these participants. Neutropenia is also one of the possible AEs associated with LZD and some ARVs.

Grade 2 or 3 Neutropenia

For participants receiving LZD, if neutropenia of Grade ≥2 or an increase of at least one grade above the value at entry/baseline occurs, the LZD dose will be lowered according to the dose reduction schedules outlined in **Table 8.0-1 above**. All participants experiencing Grade ≥2 neutropenia/ANC or an increase of at least one grade from entry/baseline values will have their CBC with differential counts checked weekly until the ANC returns to Grade <2 or the entry/baseline value.

If a Grade 3 neutropenia/ANC occurs, and there is compelling evidence that the neutropenia has NOT been caused by LZD or other study-provided drugs, dosing of LZD may continue at the reduced dose. Consideration should be given to other medications, including ARVs, that might be causing neutropenia. The site will contact the A5356 CMC to discuss relatedness of the AE to LZD or other study-provided drugs and to develop an individualized plan to either continue the reduced LZD dose or increase the LZD dose back to the prior level. If, after discussion with the **A5356** CMC, the site investigator and the CMC determines neutropenia is possibly or probably related to LZD or other study-provided drugs (or ART drugs, if applicable) then LZD or other study-provided drugs if possibly or probably related (and ARVs, where applicable) will be temporarily held for up to 14 ±2 days or until levels return to Grade ≤2 or entry/baseline levels, at which time therapy may be reintroduced with LZD dosing adjusted to the reduced dose, as indicated above. If the reduced dose of LZD is tolerated without a further increase in neutropenia grade for ≥14 ±2 days, at the discretion of the site investigator after discussion with the A5356 CMC, the LZD dose may be increased to the original dose.

If a Grade 3 abnormality continues for ≥14 ±2 days or if a Grade 3 abnormality recurs, then further reduction of LZD dose according to Table 8.0-1 should be considered.

Grade 3 Neutropenia Persisting for ≥14 ±2 days, Recurrent Grade 3 Neutropenia After LZD Dose Reductions or Grade 4 Neutropenia
After reducing the LZD dose, if a Grade 3 abnormality continues for ≥14 ±2 days or if a Grade 3 abnormality recurs **after subsequent LZD dose reductions outlined in Table 8.0-1**, or (regardless of LZD dose reduction) if any Grade 4 abnormality occurs, LZD should be permanently discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator together with the CMC determines that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study provided drugs, and will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. The participant will continue to be followed on study, but off study-provided drugs.

All participants experiencing Grade ≥2 neutropenia/ANC or an increase of at least one grade from entry/baseline values will have their CBC with differential counts checked weekly until the ANC returns to Grade <2 or the entry/baseline value.

8.2.5 Thrombocytopenia/Platelets

Participants entering this trial will have active TB and some will have HIV. Thrombocytopenia is also one of the possible AEs associated with the LZD and some ARVs.

Grade 2 or 3 Thrombocytopenia
For participants receiving LZD, if Grade ≥2 thrombocytopenia or an increase of at least one grade above the value at entry occurs, the LZD dose will be lowered according to the dose reduction schedules outlined in **Table 8.0-1**. All participants experiencing Grade ≥2 thrombocytopenia or an increase of at least one grade from the entry/baseline value will have their CBC with differential counts checked weekly until the platelet count returns to Grade <2 or to the entry/baseline value.

If a Grade 2 or 3 thrombocytopenia or an increase of at least one grade above the value at entry occurs, and there is compelling evidence that the thrombocytopenia has NOT been caused by LZD, dosing of LZD may continue at the reduced dose. The site will contact the A5356 CMC to discuss relatedness of the AE to LZD or other study-provided drugs and to develop an individualized plan to either continue the reduced LZD dose or increase the LZD dose back to the prior level. If, after discussion with the **A5356** CMC, the site investigator and the CMC determines thrombocytopenia is possibly or probably related to LZD

then LZD (and ART drugs, if applicable) will be temporarily held for up to 14 ±2 days or until levels return to Grade ≤2 or to the entry/baseline value, at which time therapy may be reintroduced with LZD dosing adjusted to the reduced dose, as indicated above, and other study drugs may be continued as appropriate. If the reduced dose of LZD is tolerated without a further increase in thrombocytopenia grade for ≥14 ±2 days, LZD will continue at the reduced dose.

If a Grade 3 abnormality continues for ≥14 ±2 days or if a Grade 3 abnormality recurs, then further reduction of LZD dose according to Table 8.0-1 should be considered.

Grade 3 Thrombocytopenia Persisting for ≥14 ±2 days, Recurrent Grade 3 Thrombocytopenia After LZD Dose Reduction or Grade 4 Thrombocytopenia
After reducing the LZD dose, if a Grade 3 abnormality continues for ≥14 ±2 days or if a Grade 3 abnormality recurs **after subsequent LZD dose reductions outlined in Table 8.0-1**, or (regardless of LZD dose reduction) if a Grade 4 thrombocytopenia occurs, LZD should be permanently discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study provided drugs, and will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. The participant will continue to be followed on study, but off study-provided drugs.

All participants experiencing Grade ≥2 thrombocytopenia or an increase of at least one grade from the entry/baseline value will have their CBC with differential counts checked weekly until the platelet count returns to Grade <2 or to the entry/baseline value.

8.2.6 Anemia/Hemoglobin

Participants entering this trial will have active TB and some will have HIV, both of which can be associated with anemia. Anemia is also one of the possible AEs associated with LZD and with some ARVs.

If there is a decline in hemoglobin of ≥15% as compared to the entry/baseline level, but not yet a decline of Grade ≥2 or ≥25% as compared to the entry/baseline level, and the relationship to LZD cannot be excluded, hemoglobin levels should be checked weekly until hemoglobin is stabilized or increasing, and monitoring should then return to the schedule in the SOE (Table 6.1-1). If the hemoglobin level continues to decline, then follow the steps outlined below.

Grade 2 or 3 Anemia
For participants receiving LZD, if the participant experiences a new Grade ≥2 hemoglobin abnormality, an increase of one grade above the entry/baseline

value for those who enter with a Grade 2 hemoglobin, the LZD dose will be reduced according to the dose reduction schedules outlined in **Table 8.0-1**.

The participant should have a CBC with differential counts repeated at least weekly until no further decline is observed, and then monitoring should return to the schedule in SOE **(Table 6.1-1)**.

If the participant experiences a Grade 3 hemoglobin abnormality or if the hemoglobin declines by ≥25% as compared to entry/baseline, the site will contact the A5356 CMC to discuss relatedness of the AE to LZD or other study-provided drugs. If, after discussion with the **A5356** CMC, the site investigator and the CMC determine the anemia is possibly or probably related to LZD, then LZD (and any implicated ART drugs, if applicable) will be temporarily held for up to 14 ±2 days. A CBC with differential counts should be repeated at least weekly until levels return to Grade ≤2 or the entry/baseline value, at which time therapy may be reintroduced with a reduced LZD dose according to **Table 8.0-1**, as indicated above. Other study drugs may be continued as appropriate.

If there is compelling evidence that the Grade 3 hemoglobin or the decline in hemoglobin by **≥**25% from entry/baseline is not related to LZD or other study-provided drugs, then the LZD dose should be reduced according to the schedules in **Table 8.0-1** and dosing continued; hemoglobin levels should be checked weekly until hemoglobin is stabilized or increasing, and then monitoring should return to the schedule in the SOE (Table 6.1-1). If the reduced dose of LZD is tolerated without a further increase in grade of hemoglobin abnormality for ≥14 ±2 days, LZD will continue at the reduced dose.

If a Grade 3 hemoglobin abnormality or a ≥25% decline from entry/baseline persists for ≥14 ±2 days or recurs, then further reduction of LZD dose according to Table 8.0-1 should be considered.

Grade 4 Anemia or Persistent or Recurrent Grade 3 Anemia or Hemoglobin Decline of **≥**25% from Entry/Baseline

After reducing the LZD dose as described above, if a Grade 4 hemoglobin abnormality occurs or if a Grade 3 hemoglobin abnormality or a ≥25% decline from entry/baseline persists for ≥14 ±2 days or recurs **after subsequent LZD dose reductions outlined in Table 8.0-1**, LZD should be permanently discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, the participant will permanently discontinue LZD and other study-provided drugs, and will be referred to the national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. The participant will continue to be followed on study, but off study-provided drugs.

NOTE: As above, for all participants experiencing Grade ≥2 anemia, an increase of at least one grade from the entry/baseline hemoglobin value, or a ≥25% reduction in hemoglobin from the entry/baseline value will have their CBC with differential counts checked weekly until the hemoglobin returns to Grade <2 or to the entry/baseline value.

NOTE: If the reduced dose of LZD is tolerated without a further increase in grade of hemoglobin abnormality or if the grade of hemoglobin abnormality returns to Grade ≤2 or the entry/baseline value for ≥14 ±2 days, after discussion with the A5356 CMC, the LZD dose may be increased to the previously assigned dose.

8.2.7 Rash/Cutaneous Reaction

Moderate to severe rash potentially related to drug hypersensitivity may occur with any of the study-provided drugs as well as other drugs the participants may be taking. It may not be possible to determine which, if any of the study-provided drugs is the cause.

Participants receiving clofazimine are expected to have skin pigmentation changes. These should be differentiated from a generalized rash; participants with skin pigmentation changes will be continued on their treatment regimen.

Grade 1 and Grade 2 Rash/Cutaneous Reactions
Participants with a Grade 1 or Grade 2 rash may continue study-provided drugs at the site investigator's discretion. Participants should be advised to contact the site investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Grade >3 Rash or Grade >2 Rash Accompanied by Mucosal or Systemic Signs, Symptoms and/or ALT or Total Bilirubin Elevations
Participants with a Grade ≥3 rash alone that the site investigator determines is not related or unlikely to be related to one of the study-provided drugs, study-provided drugs may be continued or temporarily held for up to 14 ±2 days until the rash resolves at the discretion of the site investigator. Participants should be advised to contact the site investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with a Grade ≥3 rash that the site investigator determines is possibly or probably related to study-provided drugs, or any Grade ≥2 rash that is associated with any of the following: increase in ALT or bilirubin of at least one grade above baseline, Stevens-Johnson syndrome, toxic epidermal necrolysis, or severe hypersensitivity reaction that includes: fever, blisters, oral lesions, eye

inflammation, facial swelling, swelling of the eyes, lips, mouth, breathing difficulty, and/or signs and symptoms of liver abnormalities as previously described (e.g., jaundice, dark or tea-colored urine, pale-colored stools/bowel movements, accompanied by nausea and/or vomiting of at least one grade above baseline, or right upper quadrant abdominal pain) should have all study-provided drugs withheld until the AE resolves. The participant should be evaluated weekly until the rash returns to Grade ≤1. If further evaluation indicates that the etiology of the rash can be diagnosed as definitely being unrelated to study-provided drugs and due to a specific medical event or a concomitant non-study medication, study-provided drugs may be restarted at the discretion of the site investigator and after discussion with the A5356 CMC. Routine management should be performed and documentation of the diagnosis provided. If an alternative diagnosis is not made, then study-provided drugs will be permanently discontinued. Participants taken off study-provided drugs for rash will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.2.8 Nausea, Vomiting and/or Diarrhea Not Associated with Hyperlactatemia

Although common, nausea, vomiting and/or diarrhea following initiation of therapy with TB medications and/or ARV medications usually subsides or resolves during the first few weeks of treatment. For some participants, nausea can persist for a long period of time. Participants experiencing nausea, vomiting and/or diarrhea should have their hydration status monitored and supportive therapy administered as recommended by the site investigator. See section 8.2.13 for symptoms that may be deemed due to hyperlactatemia.

Grade 1 or 2 Nausea, Vomiting and/or Diarrhea
Participants who develop Grade 1 or 2 nausea, vomiting and/or diarrhea may continue study-provided drugs at the discretion of the study investigator. Steps in the management of nausea include taking the medication with food and administration of antiemetics. Antiemetics can only be used if they do not have drug-drug interactions with the study-provided drugs and if they do not have overlapping toxicities with the study-provided drugs. Steps in the management of diarrhea include use of antidiarrheals (e.g., loperamide) but these may be used only if they do not have clinically significant drug-drug interactions or overlapping toxicities with the study-provided drugs.

Grade 3 or 4 Nausea, Vomiting and/or Diarrhea
Participants with Grade ≥3 nausea, vomiting and/or diarrhea should have their hydration status assessed and be referred to appropriate local medical care for monitoring and volume resuscitation if clinically indicated depending on site-specific standard practices. Participants will have their study-provided drugs held for up to 14 ±2 days regardless of relatedness. Participants will be monitored until the symptoms return to Grade ≤2. Sites will contact the A5356 CMC to

discuss relatedness of the AE to the study medications and to develop an individualized plan for restarting study-provided drugs in a step-wise manner depending on the clinical situation. If the symptoms do not reach Grade ≤2 within 14 ±2 days or if Grade 3 or Grade 4 nausea, vomiting and/or diarrhea occur after reintroduction of study-provided drugs, if applicable, then study-provided drugs should be permanently discontinued and the participant referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study provided drugs.

8.2.9 Peripheral Neuropathy

Participants will be screened for peripheral neuropathy using the ACTG Brief Peripheral Neuropathy Scale. Participants who develop any new grade of neuropathy will be monitored weekly using the ACTG scale.

LZD and some ARVs have been associated with the development of peripheral neuropathy. Some participants may have Grade 1 or 2 peripheral neuropathy at entry related to the prior use of other medications or underlying medical conditions known to be associated with peripheral neuropathy.

Grade 1 Peripheral Neuropathy
If a participant develops new Grade 1 peripheral neuropathy or an increase of one grade from their entry/baseline level, LZD may continue at the randomized dose and other study-provided drugs may be continued at the discretion of the investigator. The participant will undergo investigation for other treatable causes of the impairment and be treated symptomatically according to local standards.

New Grade 2 or Worsening of Peripheral Neuropathy from Entry/Baseline
Participants who develop new Grade 2 peripheral neuropathy, the LZD dose will be reduced according to the dose reduction schedules outlined in **Table 8.0-1**.

If the participant does not have symptom improvement to Grade ≤**1** after the LZD dose is reduced, then dose will be **further reduced according to Table 8.0-1, if possible OR** LZD will be permanently discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study-provided drugs.

New Grade 3 Peripheral Neuropathy
If a Grade 3 peripheral neuropathy occurs, LZD (and any possibly or probably related ART drug, if applicable) will be temporarily held for up to 14 ±2 days or until symptoms improve by one grade, at which time therapy may be reintroduced with LZD dose reduced, as indicated above. If the participant does not have symptom improvement of one grade within 14 ±2 days after the LZD

dose is reduced, then **further reduction can be considered according to Table 8.0-1 or** the LZD will be permanently discontinued. Other study provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study provided drugs.

Grade 4 Peripheral Neuropathy
Any participant developing Grade 4 peripheral neuropathy will have LZD (or ART drugs, if applicable) permanently discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study-provided drugs.

All participants permanently discontinued from study-provided drugs will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.2.10 Neuropsychiatric Symptoms

Some anti-TB drugs and ARVs have rarely been associated with development of neuropsychiatric side effects that may include headache, somnolence, irritability, acute mental status or behavior changes, depression, psychosis, seizures, suicidal ideation, hallucinations, or other neuropsychiatric symptoms. Although the category “neuropsychiatric symptoms” is not found in the DAIDS Toxicity Tables, individual symptoms as described above may occur and may be graded as appropriate.

Grade 2 or 3 Neuropsychiatric Symptoms
If a participant develops new Grade 2 or 3 neuropsychiatric side effects as described above (excluding peripheral neuropathy) or an increase in grade of neuropsychiatric side effects from entry/baseline, that, in the opinion of the site investigator, are likely due to study-provided drugs (or ARVs) during the course of the study, the relevant drug should be temporarily held for up to 14 ±2 days. If Grade 2 or 3 symptoms resolve after interruption of study-provided drugs, then study-provided drugs may be restarted in a stepwise manner at the discretion of the site investigator after consultation with the A5356 CMC. Should symptoms worsen or fail to resolve, then the drug in question should be discontinued. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator, together with the CMC, determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study provided drugs.

Grade 4 Neuropsychiatric Symptoms
If any Grade 4 symptoms occur individually or in combination and fail to resolve after discontinuation of the study-provided drugs (or ARV) thought to be responsible for the symptoms, then all study-provided drugs (or ARVs, if applicable) should be held until symptoms resolve. If Grade 4 symptoms resolve after interruption of all study-provided drugs, then study-provided drugs determined as unlikely to be associated with the AE may be restarted in a stepwise manner at the discretion of the site investigator after consultation with the A5356 CMC. If Grade 4 symptoms recur or fail to resolve after interruption of study-provided drugs (and ARVs, if applicable), then all study-provided drugs will be permanently discontinued.

All participants permanently discontinued from study-provided drugs will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.2.11 Serum Creatinine

Elevations of serum creatinine may occur in people with renal TB and rarely in association with some anti-TB drugs, **and particularly** CFZ **in the context of study provided drugs**. For this study, only the grading based on absolute value of creatinine should be used. See section 7.2 for more information regarding grading.

Grade 1 or 2 Serum Creatinine Elevation
Participants who develop Grade 1 or 2 serum creatinine elevation may continue study-provided drugs at the discretion of the site investigator. Supportive care should be given and an alternative cause for the elevation should be investigated.

Grade 3 or 4 Serum Creatinine Elevation
If Grade 3 or 4 elevation of serum creatinine occurs and, after discussion with the CMC, the site investigator determines that Grade 3 or 4 serum creatinine elevation is possibly or probably related to **one or more of the** study-provided drugs, then **those** study-provided drugs will be temporarily held for up to 14 ±2 days and the participant will have their serum creatinine evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring. Sites will contact the A5356 CMC to discuss relatedness of the AE to the study-provided drugs and to develop an individualized plan for restarting study-provided drugs in a step-wise manner depending on the clinical situation.

Grade 3 or 4 Serum Creatinine Elevation for >14 ±2 days or Recurrent Grade 3 or 4 Serum Creatinine Elevation

If a Grade 3 or 4 abnormality continues for 14 ±2 days or more, or if a Grade 3 or 4 abnormality recurs after restarting study-provided drugs, **CFZ (or other study drugs if determined the toxicity is not related to CFZ but likely related to one or more of the other study-provided drugs)** will be permanently discontinued. Participants permanently discontinued from **CFZ may continue other** study-provided drugs**, at the discretion of the site investigator together with the CMC.**

Participants permanently discontinued from all study-provided drugs will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.2.12 Optic Neuritis/Visual Changes

Optic neuritis is a known AE of LZD. Participants who develop Grade ≥2 visual changes (compared with entry/baseline), will be referred to an ophthalmologist. If another more likely cause for the change in vision is identified (e.g., cataracts, diabetic retinopathy), LZD may be continued. If the visual changes are considered likely due to LZD, then the LZD will be permanently discontinued and the A5356 CMC should be informed. If LZD is discontinued, the participant should be evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator together with the CMC determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study-provided drugs, and will be referred to their national TB program or local TB clinic/provider for treatment of their DR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.2.13 Lactic Acidosis Attributed to LZD

LZD and some ARVs have been associated with development of lactic acidosis. Lactic acidosis was identified post-marketing as a relatively uncommon toxicity associated with LZD. Symptoms of hyperlactatemia and lactic acidosis may be non-specific but usually include nausea, vomiting, abdominal pain, sudden weight loss, extreme fatigue, exertional dyspnea, hyperventilation, arrhythmias, and in very severe cases, liver failure. Lactic acidosis attributed to LZD should be considered if participants have a constellation of two or more of these symptoms that are not explained by other causes or other concomitant medications. If symptoms are present, participants should have a serum lactate measured according to the procedure described in the LPC and Manual of Procedures (MOPS).

NOTE: If the lactate is not measured correctly, false elevation of lactate levels may be observed.

Routine measurement of lactate levels in asymptomatic participants is not recommended. If symptoms are present as described above, and a lactate level appropriately obtained and measured is elevated, the site investigator should evaluate whether any concomitant medications (e.g., nucleoside reverse transcriptase inhibitor-type antiretroviral drugs) may be associated with the symptoms and elevated lactate level and consider pausing other concomitant drugs that could be responsible until the symptoms and hyperlactatemia resolves. If the symptoms and elevated lactate levels are not otherwise explained and the investigator determines these are possibly or likely to be secondary to LZD toxicity, the following management strategies should be utilized.

Grade 1 Lactate Attributed to LZD
Participants who develop a Grade 1 lactate level may continue study-provided drugs without dose adjustment and will be managed at the discretion of the site investigator.

Grade ≥2 Lactate Attributed to LZD
Participants receiving LZD who develop a new Grade 2 or higher lactate level or who have symptoms as described above and an increase of one grade from entry/baseline lactate level that is considered likely to be secondary to LZD will have LZD temporarily held for up to 14 ±2 days, and the participant will have their symptoms and serum lactate levels evaluated weekly until the AE returns to Grade <2 or until stabilized and no longer in need of such frequent monitoring. Sites will contact the A5356 CMC to discuss relatedness of the AE to LZD and to develop an individualized plan for restarting LZD depending on the clinical situation. If symptoms and a Grade ≥2 lactate level or an increase of one grade above the entry/baseline lactate level abnormality continue for 14 ±2 days or more, or if symptoms and a Grade 2 or increase of one grade above entry/baseline or higher abnormality recur after restarting LZD then LZD will be permanently discontinued and the site should inform the A5356 CMC of the event. If LZD is permanently discontinued, the participant should be evaluated weekly until the AE returns to Grade ≤2 or until stabilized and no longer in need of such frequent monitoring. Other study-provided drugs may continue at the discretion of the site investigator after discussion with the A5356 CMC. If the site investigator together with the CMC determine that continuation of other study-provided drugs would not be advisable, participants will permanently discontinue LZD and other study-provided drugs and will be referred to their national TB program or local TB clinic/provider for treatment of their MDR-TB or RR-TB according to local SOC. These participants will continue to be followed on study, but off study-provided drugs.

8.3 Pregnancy

If a participant becomes pregnant during the study, the participant will be discontinued from study-provided drugs and referred to her national TB program or local TB clinic/provider for treatment of her DR-TB according to local SOC and to a prenatal care program for management of her pregnancy according to local SOC. The participant will continue to be followed on study, but off study-provided drugs. She will be followed through the end of the study period. At the end of the pregnancy, the pregnancy outcome and AEs for the participant will be recorded on an eCRF. Any known or reported AEs for the infant should be recorded in the source document.

If a 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 an eCRF at the end of the pregnancy.

Pregnancies that occur on study in participants 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 910-256-0637; Phone: 910-679-1598.

8.4 Breastfeeding

Breastfeeding is exclusionary; if a participant begins breastfeeding during the study, the participant will be discontinued from study-provided drugs and referred to her national TB program or local TB clinic/provider for treatment of her DR-TB according to local SOC and to a pediatric or post-natal care program for management of breastfeeding according to local SOC. The participant will continue to be followed on study, but off study-provided drugs. She will be followed through the end of the study period. At the end of the study period, the outcome of TB treatment and AEs for the participant will be recorded on the appropriate eCRFs.

8.5 HIV-Infection

If an HIV-uninfected participant seroconverts while on study, the participant will be referred to their local clinic for management of HIV and initiation of ART. Should the participant still be receiving study medication, the CMC will recommend to the clinic an appropriate regimen in the context of drug-drug interactions, and the participant will continue to be followed through to the end of the study period.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Drug-related toxicity (see sections 8.1 and 8.2).
- Pregnancy or breastfeeding (see sections 8.3 and 8.4).
- Requirement for prohibited concomitant medications (see Appendix I).

- 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.
- **Pending baseline susceptibility testing showed resistance to one or more study medications.**

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the site investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the ACTG, 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.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5356 is a phase II, prospective, randomized, two-arm, open-label, multicenter clinical trial evaluating the efficacy and safety/tolerability of an injectable-free short course regimen for treatment of DR-TB comparing two dosing strategies of linezolid (LZD) combined with bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ). The trial will randomize 132 participants with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB. Participants will be on study medications for at least 26 weeks. Participants who do not have sputum culture conversion by 16 weeks of treatment will extend their treatment by an additional 12 weeks for a total treatment duration of 38 weeks. All participants are followed for TB outcomes and safety to 72 weeks.

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be described in the study's primary Statistical Analysis Plan, which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript(s) and results reporting to ClinicalTrials.gov. Outcome measures related to other objectives intended for subsequent publications are listed under Other Outcome Measures and will be described in separate secondary statistical analysis plans.

The outcome measures will be described for each of the randomized arms.

10.2.1 Primary Outcome Measures

10.2.1.1 The primary efficacy outcome measure is time from randomization date to collection date of the sputum corresponding to the first MTB negative culture (i.e., sputum culture conversion) up through week 26.

Sputum culture conversion is defined as at least two consecutive MTB negative sputum cultures obtained at least 7 days apart and no subsequent **MTB-**positive cultures. Inability to produce sputum with or without induction is considered a MTB-negative culture. A participant is MTB positive at a visit if at least one of the liquid cultures is MTB positive. A participant is MTB negative at a visit if both cultures are MTB negative or if one culture from the visit is MTB negative and the other is missing or contaminated. If the first MTB-negative culture is the last available culture at week 26, then sputum culture conversion has been met.

10.2.1.2 The primary tolerability outcome measure is proportion of participants with permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death by the end of treatment.

Intolerance is defined as permanent discontinuation of at least one anti-TB drug due to side effects that do not lead to a protocol-required discontinuation as described in section 8.0, due to participant non-compliance with at least one anti-TB drug or study visits, or due to participant request.

10.2.2 Secondary Outcome Measures

10.2.2.1 Proportion of participants with sputum culture conversion in liquid media at weeks 8, 16, 26, and 38.

10.2.2.2 Proportions of participants with permanent discontinuation of LZD due to AEs, intolerance, or death; temporary discontinuation of LZD for any reason; and dose reduction of LZD by the end of treatment.

10.2.2.3 Proportion of participants with treatment-related AEs by the end of treatment.

10.2.2.4 Proportions of participants with unfavorable TB treatment outcome at weeks 26, 38 (for those who extend treatment by 12 weeks), and 72.

Unfavorable TB treatment outcome is defined in section 6.3.18.

10.2.2.5 LZD PK parameters at week 4.

10.2.2.6 DLM PK parameters at week 4.

10.2.2.7 Proportion of doses taken during the treatment period.

10.2.3 Other Outcome Measures

10.2.3.1 Participants with MTB IRIS.

10.2.3.2 Gene polymorphism results as described in section 11.3.2.

10.2.3.3 LZD, BDQ, DLM, and CFZ blood levels at week 4 (intensive PK subset) and all sparse PK sampling visits.

10.3 Randomization and Stratification

At study entry, participants will be randomized in approximately equal numbers. The randomization will be balanced by site and will use a permuted blocks design. There will be no stratification at randomization.

10.4 Sample Size and Accrual

10.4.1 Overall Sample Size

A5356 has two primary objectives: efficacy and tolerability. The sample size calculations are based on the primary efficacy outcome measure. Using this sample size, the precision for estimating the tolerability outcome measure is presented.

Efficacy
Based on the STREAM trial Stage 1 [74] and the NixTB study, the team is assuming the true median time to sputum culture conversion in this population is 6 weeks in the 600 mg LZD arm and will be shorter in the 1200 mg LZD arm. The sample size calculations were based on a two-sided log rank test, with 10% alpha and 90% power, 104 weeks (24 months) to accrue, and 72 weeks (18 months) of follow-up. As shown in Table 10.4.1-1 below, a sample size of 59 is sufficient to differentiate between a median of 6 weeks to sputum culture conversion in the 600 mg LZD arm and a median of 3.4 weeks in the 1200 mg LZD arm; this translates to a hazard ratio of 1.75. These calculations were done in PASS 15, which used time measured on a continuous scale. Since time in this study will be measured on a discrete scale (cultures every 2, 4, or 6 weeks through week 26), simulations were done to assess any effect this has on power of the log rank test. Simulations when the visits are measured on continuous time versus discrete time show inconsequential effects on power: power decreased from 90.84% (continuous time) to 90.29% (discrete time).

Table 10.4.1-1: Sample Size for a Range of Design Assumptions for the Primary Efficacy Objective

N per Arm	Hazard Ratio (600 mg LZD Arm/ 1200 mg LZD Arm)	Median Weeks to Sputum Culture Conversion	
		600 mg LZD Arm	1200 mg LZD Arm
108	1.5	4	2.67
108	1.5	6	4
108	1.5	8	5.3
108	1.5	12	8
59	1.75	4	2.29
59	1.75	6	3.43
59	1.75	8	4.57
59	1.75	12	6.86
39	2.0	4	2
39	2.0	6	3
39	2.0	8	4
39	2.0	12	6

Tolerability

Based on Singla et al., the team is assuming the true proportion of participants who permanently discontinue at least one anti-TB drug due to AEs, intolerance, or death by week 26 is between 20% and 30% [106]. This is assuming that LZD is driving the permanent discontinuations. As shown in Table 10.4.1-2 below, if the observed proportion is 25% in 59 participants, then the 95% confidence interval would be sufficiently precise at a width of 0.216.

Table 10.4.1-2: 95% Wilson Confidence Interval Widths for a Range of Design Assumptions for the Primary Tolerability Objective

N per Arm	Observed Proportion of Participants Who Permanently Discontinue at Least One Anti-TB Drug Due to AEs, Intolerance, or Death by Week 26	95% Confidence Interval	Width of 95% CI
59	0.20	(0.118, 0.319)	0.201
59	0.25	(0.157, 0.373)	0.216
59	0.30	(0.198, 0.426)	0.228
59	0.35	(0.241, 0.477)	0.237
59	0.40	(0.285, 0.527)	0.243

Overall Sample Size

Accounting for the possibility of unevaluable participants who did not have DR-TB or were otherwise deemed clinically ineligible for the study, use of Greenwood's formula for calculating SEs, and interim analyses, sample size per arm was boosted by 10%. Thus, the total sample size is 66 participants per arm for a total of 2 x 66 = 132 participants.

10.4.2 Intensive PK Sample Size

In each arm, 20 participants will undergo an intensive PK sampling visit at week 4. Because there are a number of PK parameters to be estimated based on the these PK data, the size of the subset was determined based on the width of the 95% confidence interval as estimated in relation to the observed standard deviation (SD).

Table 10.4.2-1: Intensive PK Sample Size per Arm for a Range of Design Assumptions

Sample Size per Arm	Width of 95% Confidence Interval
N=13	0.604 x SD
N=17	0.514 x SD
N=21	0.455 x SD

Thus, requiring 17 participants randomized to each arm to undergo an intensive PK sampling visit at week 4 will provide sufficient precision in the estimation of the PK parameters. For example, Lee, et al. published AUC data on LZD 600 mg daily. With an AUC SD of 89 for LZD 600 mg daily, a sample size of 17 would yield a 95% CI with a width of 45.7 (or 157.6-203.3 using their mean AUC of 180.4) [20].

Participants who miss the week 4 intensive PK visit or the 24-hour sampling time will be replaced in the intensive PK subset. Accounting for participants who become unevaluable for the PK study, the sample size per arm will be increased by 3 per arm. Thus, a total of 2 x (17+3) = 40 participants will undergo an intensive PK sampling visit at week 4.

10.4.3 Overall Accrual

The team estimates the study will fully accrue 132 participants within 24 months (104 weeks) after the enrollment of the first participant.

10.5 Data and Safety Monitoring

Section 7.4 described study monitoring, including details of reviews by the TB TSG Study Monitoring Committee (SMC). In this section, the statistical considerations of stopping guidelines and interim analysis are described.

10.5.1 Interim Monitoring Guidelines

The TB TSG SMC will review an interim analysis of the primary objectives at every review. Each interim analysis will include all participants who have completed 26 weeks of potential follow-up (i.e., follow-up based on

randomization date and the expected week 26 study visit, regardless of whether the participant is still on study). The purpose of each interim analysis is to determine if either of the arms has an unacceptable proportion of participants with:

1) MTB-positive culture at week 16; or
2) Permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death within the first 26 weeks of follow-up.

Efficacy

The SMC will be provided the one-sided lower 90% confidence bound for the true proportion of participants with MTB-positive cultures at week 16 within each arm. The lower 90% confidence bound provides the minimum possible true proportion of participants with MTB-positive cultures at week 16 in the respective arm. A hard stopping guideline has not been chosen since there are not enough data to support one. The confidence bounds will be discussed at each interim review.

Tolerability

The SMC will be provided the one-sided lower 90% confidence bound for the true proportion of participants who prematurely discontinue TB treatment due to AEs, intolerance, or death by week 26 within each arm. The lower 90% confidence bound provides the minimum possible true proportion of participants who prematurely discontinue TB treatment due to AEs, intolerance, or death by week 26. A lower 90% confidence bound within an arm that is at least 35% at an interim review would be consistent with an unacceptably large proportion of participants prematurely discontinuing TB treatment due to AEs, intolerance, or death by week 26.

The SMC and the DAIDS Clinical Representative will determine whether the combined efficacy, tolerability, and safety data warrant discontinuation of the applicable arm or the entire study, and will follow ACTG SOP-124.

10.5.2 Analysis Plan

For all annual SMC reviews, the SMC will be provided detailed information on efficacy (including culture results), safety/tolerability (including mortality, adverse events, and premature treatment discontinuations), and administrative aspects (including accrual, retention, and compliance with study requirements).

In the interim analysis of the primary efficacy objective, the cumulative proportion of participants with MTB-positive cultures or death at week 16 will be calculated using Kaplan-Meier estimators. Participants will be censored at the sputum collection date for their last culture with non-MTB-negative evaluable results. The associated one-sided lower 90% confidence bounds will be calculated using standard errors (SEs) based on Greenwood’s formula.

In the interim analysis of the primary tolerability objective, the cumulative proportion of participants with permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death within the first 26 weeks of potential follow-up will be calculated using Kaplan-Meier estimators. Participants will be censored at the date of the last clinic visit by week 26. The associated one-sided lower 90% confidence bound will be calculated using standard errors (SEs) based on Greenwood's formula and compared against the 35% stopping rule.

10.6 Analyses

A detailed Statistical Analysis Plan that addresses the primary and secondary objectives will be developed by the time the study starts enrolling participants. The following describes the general approach to analysis that will be taken.

10.6.1 Analysis Sets

- Efficacy Analysis Set: All randomized participants **who had at least one MTB-positive sputum culture at baseline (based on cultures from screening, entry, and week 2)**, except those who did not have pulmonary DR-TB or were otherwise deemed clinically ineligible for the study
- Safety Analysis Set: All randomized participants who took at least one dose of study drug
- PK Analysis Set: All randomized participants who completed the intensive PK sampling visit and met PK inclusion criteria in section 11.2.1

10.6.2 Primary Efficacy Objective

Analysis Set = Efficacy Analysis Set

Participants will be censored at the sputum collection date for their last culture with non-MTB-negative evaluable results by week 26; deaths for all causes except trauma will be censored at week 72 in order to rank them as the worst possible event. The results will be displayed graphically using Kaplan-Meier-type plots of the cumulative incidence between randomization date and collection date of the sputum corresponding to the first MTB-negative culture. Data summaries will include descriptive statistics of the time to sputum culture conversion and hazard ratios. Statistical comparison of randomized treatments will be undertaken using the log rank test. If there is evidence of a significant departure from proportional hazards, a non-parametric Restricted Mean Survival Time analysis will be undertaken, which will include providing restricted mean survival time curves and conducting a homogeneity test of whether the restricted mean survival times at time t = 26 weeks differ.

Supplementary Analyses
Sputum culture conversion based on solid and liquid cultures will also be analyzed. In this analysis, a participant is MTB positive at a visit if at least one of

the cultures (solid or liquid) is MTB positive. A participant is MTB negative at a visit if all cultures are MTB negative or if some cultures from the visit are MTB negative and others are missing or contaminated.

If there are large numbers of premature study discontinuations or deaths by week 26, competing risks analyses of the primary efficacy objective may be undertaken.

10.6.3 Primary Tolerability Objective

Analysis Set = Safety Analysis Set

The cumulative proportion of participants with permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death at the end of treatment will be calculated using Kaplan-Meier estimators. Participants will be censored at the date of the last clinic visit on or before the end of treatment. Data summaries will include within-arm cumulative proportions with two-sided 95% confidence intervals calculated using standard errors (SEs) based on Greenwood's formula.

Supplementary Analyses
Permanent discontinuations by treatment arm will be compared using a Z test.

An analysis of time to permanent treatment discontinuation of at least one anti-TB drug due to AEs, intolerance, or death will be undertaken using an approach similar to that used for the primary efficacy objective. Participants will be censored at the date of the last clinic visit on or before the end of treatment.

10.6.4 Secondary Objectives

The secondary objectives will be analyzed as follows.

- Efficacy analyses (i.e., sputum culture conversion and unfavorable TB treatment outcome):
  - Analysis Set = Efficacy Analysis Set
  - Analyzed using an approach similar to that used for the primary tolerability objective
  - Treatment comparisons will be made using a Z test
- Tolerability and safety analyses (i.e., treatment modifications and adverse events):
  - Analysis Set = Safety Analysis Set
  - Analyzed using an approach similar to that used for the primary tolerability objective
  - Treatment comparisons will be made using a Z test
- Pharmacokinetic analyses (i.e., LZD and DLM PK parameters):
  - Analysis Set = PK Analysis Set
  - PK parameters will be summarized

- Adherence analyses:
  - Analysis Set = Safety Analysis Set
  - Proportions will be summarized
  - Treatment comparisons will be made using a Fisher's Exact Test

Supplementary Analyses

The sputum culture conversion objectives will also be analyzed based on solid and liquid cultures using the definition provided in the primary efficacy objective supplementary analyses.

The cumulative proportions of participants with sputum culture conversion at weeks 2, 4, 6, 12, 20, 30, 42, 52, and 72 will be summarized and compared using an approach similar to that used for the secondary efficacy objectives.

The permanent discontinuation of LZD due to AEs, intolerance, or death outcome measure will also be analyzed as time to permanent treatment discontinuation using an approach similar to that used for the primary efficacy objective.

The temporary discontinuation of LZD for any reason outcome measure will also be analyzed as time to temporary treatment discontinuation using an approach similar to that used for the primary efficacy objective.

The dose reduction of LZD outcome measure will also be analyzed as time to dose reduction using an approach similar to that used for the primary efficacy objective.

The treatment-related AEs outcome measure will also be analyzed as time to treatment-related AEs using an approach similar to that used for the primary efficacy objective, except it will be an mITT analysis as described above.

The unfavorable TB treatment outcome measure will also be analyzed as time to unfavorable TB treatment outcome using an approach similar to that used for the primary efficacy objective.

The PK parameters by treatment arm will be compared using a Wilcoxon test.

Risk-benefit analysis may be undertaken by creating a composite outcome ranking for pre-specified outcome measures of efficacy, safety, and/or tolerability. The summary ranking/scoring will be compared between study arms.

10.6.5 Exploratory Objective of Comparison with Contemporaneous Clinical Trials

This exploratory objective will include comparisons of both efficacy (e.g., favorable TB treatment outcome) and safety (e.g., treatment-related AEs) outcome measures. The efficacy analysis will be modified intent-to-treat (mITT), excluding participants who did not have DR-TB or were otherwise deemed

clinically ineligible for the study. The safety analysis will be intent-to-treat (ITT), including all randomized participants.

Contemporaneous clinical trials may include, but not be limited to, STREAM-1, NixTB, or ZeNix.

If the analysis of the respective A5356 efficacy or safety objective indicates a treatment difference between arms, each A5356 arm will be separately compared to the comparator trial. If there is no treatment difference, both the pooled A5356 arms and each A5356 arm will be separately compared to the comparator trial.

The comparisons will be undertaken using approaches similar to those described above.

10.6.6 Exploratory Objective of Baseline Prognostic Risk Factors for Unfavorable TB Treatment Outcome

In order to inform a future phase III study, baseline characteristics will be examined in relation to unfavorable TB outcome treatment outcome at week 72 (18 months).

This exploratory objective will be modified intent-to-treat (mITT), excluding participants who did not have DR-TB or were otherwise deemed clinically ineligible for the study. The outcome measure is the proportion of participants with unfavorable TB outcome treatment outcome at week 72. Participants missing the week 72 determination of TB outcome treatment outcome (e.g., due to premature study discontinuation) will use their last determination (e.g., at the time of premature study discontinuation). Proportions and associated 90% confidence intervals will be calculated and analyzed according to one of the following two schemes.

- If the analysis of the primary efficacy objective indicates a treatment difference between arms, the difference in the proportions between arms and its associated 90% confidence interval will be calculated. Variables (or sub-ranges of variables) will merit further examination if the 90% confidence interval excludes 0%.
- Otherwise, the data will be pooled and the proportion and its associated 90% confidence interval will be calculated. Variables (or sub-ranges of variables) will merit further examination if the 90% confidence interval lies above 25%.

The results will be summarized using a forest plot.

Baseline variables will include, but not be limited to, sex, categorized age (e.g., <30 years versus ≥30), categorized body mass index (BMI; e.g., <17 kg/m^2 versus ≥17), HIV immune status (e.g., HIV-negative, HIV-positive and CD4<250 cells/mm^3, versus HIV-positive and CD4≥250 cells/mm^3), smear grade,

cavitation status, categorized cavitary lesions (e.g., <4 cm versus ≥4), TB disease status (unilateral versus bilateral), and TB-drug resistance status (RR-, MDR-, pre-XDR, versus XDR-TB). Categorized baseline variables may be grouped into two or more levels and analyzed separately.

Variables undergoing further examination will be combined to create hard-to-treat and/or easy-to-treat subtypes. A training dataset consisting of a 70% random sample of the mITT population will be used to calculate the proportions with unfavorable TB outcome treatment status/outcome at week 72. Those variables that best meet the analysis conditions above will be further examined as hard-to-treat and easy-to-treat subtypes in a validation dataset consisting of the remaining 30% of the population. The results of the training and validation datasets will summarized in separate forest plots.

Additional analyses will include summaries of the time to unfavorable TB treatment outcome within the hard-to-treat and easy-to-treat subtypes and proportion of the participants in the hard-to-treat subtype who needed the 12 week treatment extension.

This analysis may be repeated for treatment-related AEs using the hard-to-treat and easy-to-treat subtypes from the unfavorable TB outcome treatment status/outcome at week 72 analysis.

11.0 PHARMACOLOGY PLAN

A combined intensive, abbreviated, and sparse sampling strategy will be used to characterize the LZD and DLM and metabolite (referred to throughout as DLM) PK. Intensive or abbreviated sampling at week 4 will describe the disposition of LZD at each proposed dosing strategy, as well as DLM given as 300 mg daily, in our population of interest. Sparse sampling will enrich these data and provide exposure over the study duration to assess the relationship between drug exposure and study-related outcomes. Characterizing LZD exposure-response is the primary pharmacology objective, but secondarily, PK of DLM will be characterized. Additionally, other TB regimen components may be assessed from the same samples collected for LZD analysis in order to better characterize the total regimen exposure-response relationship.

11.1 Pharmacology Objectives

See section 1.0 for objectives.

11.2 Pharmacology Study Design

11.2.1 Week 4 PK Schedule:

For Arm B participants, the week 4 visit must occur while the participant is still receiving LZD 1200 mg once daily.

The times of the last three doses of the TB regimen prior to the week 4 PK visit will be recorded. Confirmation of LZD, DLM, BDQ, and CFZ administration with food (yes/no) for the dose immediately prior to the PK sample should be recorded. The PK visit should be rescheduled only if the participant has missed any of the last three doses of LZD or DLM.

For the PK visit, participants should be instructed to bring all anti-TB medications to the clinic and await instruction from site staff before taking their morning dose of anti-TB therapy. Follow instructions for regimen administration in section 5.0.

The exact times of blood collection, morning food intake, and administration of each medication in the TB regimen during the PK visit should be recorded. Confirmation of LZD, DLM, BDQ, and CFZ administration with food (yes/no) for the dose administered during the PK visit should be recorded.

11.2.1.1 Intensive PK visit: Twenty participants in each arm will undergo an intensive PK sampling visit. LZD concentrations will be measured in all intensive PK participants (total n=40). DLM concentrations will be assessed in 20 intensive PK participants (10 from Arm A and 10 from Arm B), selected as the first 10 PK-evaluable participants within each arm.

Participants who are not evaluable (miss the week 4 PK visit or the 24 hour sampling time) will be replaced for the PK evaluation sample size but may remain on study. The exact times of specimen collection will be recorded.

The sample collection times are all based upon the time of LZD administration. LZD and DLM should be administered at the same time, or as near as possible, during intensive PK visits. Plasma to assess LZD and DLM concentrations will be collected pre-dose (less than 30 minutes prior to a morning dose of LZD) and then 1, 2, 4, 8, and 24 hours after the observed LZD dose. The 24 hour sample should be collected before the next dose of LZD or DLM is administered. Participants may leave the clinical site after the 8-hour sample is collected, as long as they are able to return prior to the scheduled 24-hour plasma collection.

11.2.1.2 Abbreviated PK visit: For participants enrolled in each arm who do not have the intensive PK visits: Participants will have timed plasma samples collected during an abbreviated PK study visit surrounding their morning dose of LZD. LZD and DLM should be administered at the same time, or as near as possible, during abbreviated PK visits. The plasma sample should be collected pre-TB therapy (specifically less than 30 minutes prior to the morning dose of LZD or DLM) and then 1,

2, and 4 hours after the observed LZD dose. The exact times of specimen collection will be recorded.

11.2.2 Additional PK Sampling (Intensive or Abbreviated) after LZD Dose Reduction

Participants who reduce the LZD dose due to toxicity, but remain on LZD therapy will be asked to undergo an additional intensive PK sampling visit approximately 2-4 weeks after the dose adjustment. Plasma to assess LZD concentrations will be collected pre-dose (less than 30 minutes prior to the morning dose of LZD) and then 1, 2, 4, and 8 hours after the observed LZD dose. The exact times of specimen collection will be recorded.

Participants who reduce the LZD dose due to toxicity and cannot participate in the additional intensive PK sampling visit will be asked to undergo an abbreviated PK sampling visit approximately 2-4 weeks after the dose adjustment. Plasma samples should be collected pre-dose (less than 30 minutes prior to the morning dose of LZD) and then 1 hour and 2 hours after the observed LZD dose.

At intensive or abbreviated sampling, the times of the last three doses of the TB regimen prior to the PK visit will be recorded. Confirmation of LZD, DLM, BDQ, and CFZ administration with food (yes/no) for the dose immediately prior to the PK sample should be recorded. The PK visit should be rescheduled only if the participant has missed any of the last three doses of LZD.

For the PK visit, participants should be instructed to bring all anti-TB medications to the clinic and await instruction from site staff to take their morning dose of anti TB therapy. Follow instructions for regimen administration in section 5.0.

The exact times of blood collection, morning food intake, and administration of each medication in the TB regimen during the PK visit should be recorded. Confirmation of LZD, DLM, BDQ, and CFZ administration with food (yes/no) for the dose administered during the PK visit should be recorded.

11.2.3 Sparse Sampling PK

All participants will have a single blood sample collected at visits outlined in the SOE **(Table 6.1-1)**. Ideally, in Arm A these samples should be collected 23-25 hours after the last LZD dose and before the next daily LZD, BDQ, DLM, and CFZ doses are administered, but can be obtained irrespective of times since last dose. Ideally, in Arm B these samples should be collected 23-25 hours after the last LZD dose during daily LZD administration, or 47-73 hours after the last LZD dose during the thrice weekly LZD administration, and before the daily LZD, BDQ, DLM, and CFZ doses are administered, but can be obtained irrespective of times since last dose.

The time of the last three doses of LZD and other TB medications will be recorded. Documentation of the exact time of the dose immediately prior to the PK sample collection is necessary. Confirmation of DLM, BDQ, and CFZ administration with food (yes/no) for the dose immediately prior to the PK sample should be recorded. The sample should be collected regardless of missed doses prior to this visit.

11.2.4 Optional Pharmacogenetic Sampling

A single, whole blood sample will be collected from all participants who consent to the pharmacogenetic sampling. The sample preferably should be collected at entry or week 2; however, at any subsequent study visit will be acceptable. Participation in pharmacogenetic testing is optional. Participants who choose not to participate in pharmacogenetic sampling may still participate in the study.

11.3 Primary and Secondary Data, Modeling, and Data Analysis

11.3.1 PK Analyses

The primary PK characteristics of interest for LZD and DLM are: C_{min}, C_{max}, T_{max}, area under the concentration-time curve (AUC), and apparent oral clearance (CL/F). The elimination half-life ($T_{1/2}$) and volume of distribution (Vd) is considered a secondary PK parameter and will be determined when possible. Standard noncompartmental techniques will be used to determine PK parameters from the studies conducted at week 4 and separately at the time of LZD dose reduction. The software package Phoenix WinNonLin (Certara Corporation) will be used for this analysis.

This noncompartmental analysis may be supplemented with a compartmental analysis and/or a nonlinear mixed effects population PK analysis as necessary.

For the compartmental analysis, the concentration-time data will be graphically inspected. A series of compartmental models, beginning with a one-compartment first-order elimination model and progressing to two- and three-compartment models, will be fitted to the concentration-time data with maximum likelihood estimation (ADAPT; Biomedical Simulations Resource, University of Southern California, Los Angeles). A proportional variance model will be used to describe the output error associated with the concentration-time data (variance model). Each observation will be inversely weighted by the model-based estimated variance (of the corresponding predicted value), assuming the variance is proportional to the predicted value and coefficient of variation for the assay. The final PK model that best describes the data will be selected using the principle of parsimony and based on residual analysis and calculation of the Akaike information criterion. The estimated PK parameters will depend upon the final model, but will include the Vd and elimination rate constant (k_e);

apparent oral clearance (CL/F), $T_{1/2}$, and AUC will be calculated from these parameters using standard equations.

Because LZD and DLM are taken as part of a complete TB regimen, other TB medication pharmacokinetics may be analyzed from the same plasma samples to characterize the complete TB regimen drug exposure.

11.3.2 Pharmacogenetic Analyses

- Evaluation of study drug efficacy, safety, and PK in relation to polymorphisms that may affect metabolism, disposition, and toxicity of study drugs and concomitant medications.
- Status for polymorphisms in genes relevant to study drugs (e.g., *NAT2* for INH, mitochondrial genes for LZD) and concomitant medications (e.g., *CYP2B6* for efavirenz) obtained at study entry from participants enrolled to all study arms.

11.3.3 Pharmacodynamic Analyses

The objective and intended outcome of this analysis is to investigate relationships among the plasma concentrations of LZD, DLM, or other TB medications with any patient characteristics that influence the PK of the medications and relationships with treatment outcomes (parameters of TB response and safety). Conventional measures of exposure will be obtained from the pharmacokinetic analyses, including, for example, AUC, C_{max} and C_{24}. In addition, other measures of exposure integrating information drug susceptibility testing may be calculated, such as the AUC_{24} to MIC ratio, and the C_{max} to MIC ratio. These measures will be used in the PD analyses and models. These PD models may be in the form of a linear or a sigmoid E_{max} relationship where, for example, higher concentrations are related to medication associated AEs. In addition to this pharmacologic assessment of PK-PD, PK measures will be used in the statistical analysis (see section 10.0) to evaluate the study outcomes associated with the two arms.

For this analysis, we may determine the population PK characteristics of LZD, DLM, and other TB medications. This would be approached using NONMEM (GloboMax, Hanover, MD), which uses mixed effects (random and fixed) regression to estimate population means and variances of PK parameters and to identify patient characteristics (covariates) that may influence these parameters, including the influence of concomitant medications. Base models will be developed using first-order conditional estimation with interaction (FOCE-I). A stepwise procedure will be used to determine whether a 1- or 2-compartment model best fits the plasma data under the principle of parsimony. An exponential error distribution will be assumed for the description of both interpatient and intrapatient (residual) PK parameter variability. Residual error will be modeled as an additive plus proportional error model. If necessary, poorly identified structural

parameters, such as the absorption rate constant, may be fixed to usual adult values. Covariates including sex, age, weight, race, and genetic characteristics of drug metabolizing enzymes and transporters will be investigated. The influence of each covariate on the PK characteristics of the drug will be tested sequentially. At the end of the analysis, all covariates that show an influence on the parameters will be evaluated again by comparison of the full model (with all factors included) with a model from which each of the factors is deleted sequentially. NONMEM uses extended least squares to calculate the objective function and the difference in the value of the objective function between models is approximately chi squared distributed. A difference in objective function of greater than 6.6 is considered significant (6.6 corresponds to a chi square for p=0.01 with 1 degree of freedom) when one parameter is added or the covariate (e.g., body weight, HIV-1 RNA) is replaced. This is analogous to the commonly used F test to select among regression models.

After the model that best describes the plasma PK characteristics of LZD or other TB medications is identified, we will next develop a linked PK and PD model to investigate relationships among the PK parameters of the drug, and measures of safety and tolerance and TB outcomes.

11.4 Anticipated Outcomes

The pharmacologic evaluations will provide information on the steady-state PK of the LZD, DLM, and other TB regimen components in both study arms. The measures of drug exposure determined from the PK data will be used to evaluate the relationship between the PK parameters achieved in two study arms and study outcomes.

12.0 DATA COLLECTION AND MONITORING AND ADVERSE EVENT REPORTING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.2 Role of Data Management

12.2.1 Instructions for entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

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

12.3 Clinical Site Monitoring and Record Availability

12.3.1 Site monitors under contract to the NIAID will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, 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.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of or in addition to onsite visits to ensure the safety of study participants and data integrity [107]. The site must make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage sites to use the DMC-provided Medidata RSR platform but other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, and direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

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

12.4 Reporting Protocol Deviations

This protocol follows the requirements to report protocol deviations per ACTG-153. The site principal investigator and personnel are responsible for identifying, and reporting deviations. Once protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be sent to the IRB/EC per their guidelines.

Protocol deviations must be recorded on the study protocol deviation eCRF.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol, 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 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, and this fact will be documented in the participant's record.

13.2 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, and other government agencies as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

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

14.0 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 supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and **other biological** 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 the transmission of TB can occur through contact with participants and specimen handling, appropriate infection control precautions are recommended for all personnel in direct contact with participants or biological specimens.

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.

16.0 REFERENCES

1. World Health Organization. WHO Global Tuberculosis Report 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.
2. Johnston JC, Shahidi MC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 2009;4:e6914.
3. Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J 2013;42:156-68.
4. Migliori GB, Sotgiu G, Gandhi NR, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J 2013;42:169-79.
5. Bastos ML, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. Clin Infect Dis 2014;59:1364-74.
6. Mitnick CD, Franke MF, Rich ML, et al. Aggressive regimens for multidrug-resistant tuberculosis decrease all-cause mortality. PLOS One 2013;8:e58664.
7. Franke MF, Appleton SC, Mitnick CD, et al. Aggressive regimens for multidrug-resistant tuberculosis reduce recurrence. Clin Infect Dis 2013;56:770-6.
8. Tierney DB, Franke MF, Becerra MC, et al. Time to culture conversion and regimen composition in multidrug-resistant tuberculosis treatment. PLOS One 2014;9:e108035.
9. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:153-61.
10. WHO Treatment Guidelines for drug-resistant tuberculosis – 2016 Update. https://apps.who.int/iris/bitstream/handle/10665/250125/9789241549639-eng.pdf;sequence=1.
11. WHO Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis [MDR/RR-TB]. License: CC BY-NC-SA 3.0 IGO; August 2018.
12. Aung KJM, 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;18:1180-87.
13. Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin resistant tuberculosis. New Engl J Med 2019; 380:1201-13.
14. Tasneen R, Betoudji F, Tyagi S, et al. Contribution of oxazolidinones to the efficacy of novel regimens containing bedaquiline and pretomanid in a mouse model of tuberculosis. Antimicrob Agents Chemother 2015;60:270-7.
15. Li S-Y, Tasneen R, Tyagi S, et al. Bactericidal and sterilizing activity of a novel regimen with bedaquiline, pretomanid, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. Antimicrob Agents Chemother 2017;61(9).
16. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382:893-902.

17a. WHO Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. License: CC BY-NC-SA 3.0 IGO; December 2019.
17b. WHO Operation Handbook on Tuberculosis. Module 4: Treatment - Drug-Resistant Tuberculosis Treatment; 2022 Update. Geneva: World Health Organization; 2022.
18. Van Heeswijk RP, Dannermann B, Hoetelmans RM. Bedaquiline: a review of human pharmacokinetics and drug-drug interactions. J Antimicrob Chemother 2014;69:2310-8.
19. Dooley KE, Park JG, Swindells S, et al. Safety, tolerability, and pharmacokinetic interactions of the antituberculous agent TMC207 (bedaquiline) with efavirenz in healthy volunteers: AIDS Clinical Trials Group Study A5267. J Acquir Immune Defic Syndr 2012;59:455-62.
20. Svensson EM, Aweeka F, Park JG, et al. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. Antimicrob Agents Chemother 2013;57:2780-7.
21. Yip PCW, Kam KM, Lam ETK, Chan RCY, Yew WW. In vitro activities of PNU-100480 and linezolid against drug-susceptible and drug-resistant *Mycobacterium tuberculosis* isolates. Int J Antimicrob Agents 2013;42:96-7.
22. Zhu T, Friedrich SO, Diacon A, Wallis RS. Population pharmacokinetic/ pharmacodynamic analysis of the bactericidal activities of sutezolid (PNU-100480) and its major metabolite against intracellular Mycobacterium tuberculosis in ex vivo whole-blood cultures of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 2014;58:3306-11.
23. Chaiprasert A, Srimuang S, Tingtoy N, et al. Second-line drug susceptibilities of multidrug-resistant tuberculosis strains isolated in Thailand: an update. Int J Tuberc Lung Dis 2014;18:961-3.
24. Ahmed I, Jabeen K, Inayat R, Hasan R. Susceptibility testing of extensively drug-resistant and pre-extensively drug-resistant Mycobacterium tuberculosis against levofloxacin, linezolid, and amoxicillin-clavulanate. Antimicrob Agents Chemother 2013;57:2522-5.
25. Williams KN, Stover CK, Zhu T, et al. Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. Antimicrob Agents Chemother 2009;53:1314-19.
26. Dietze R, Hadad DJ, McGee B, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. Am J Respir Crit Care Med 2008;178:1180-5.
27. Alffenaar J-WC, van Altena R, Harmelink IM, et al. Comparison of the pharmacokinetics of two dosage regimens of linezolid in multidrug-resistant and extensively drug-resistant tuberculosis patients. Clin Pharmacokinet 2010;49:559-65.
28. McGee B, Dietze R, Hadad DJ, et al. Population pharmacokinetics of linezolid in adults with pulmonary tuberculosis. Antimicrob Agents Chemother 2009;53:3981-4.
29. Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med 2012;367;1508-18.
30. Lee, M, Cho SN, Barry CE, et al. Linezolid for XDR-TB – final study outcomes. N Engl J Med 2015;373:290-1.
31. Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J 2015;45:161-70.

32. Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J 2012;40:1430-42.
33. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. Int J Tuberc Lung Dis 2012;16:447-54.
34. Sotgiu G, Centis R, D'Ambrosio LD, et al. Linezolid to treat extensively drug-resistant TB: retrospective data are confirmed by experimental evidence. Eur Respir J 2013;42:288-90.
35. Srivastava S, Magombedze G, Koeuth T, et al. Linezolid dose that maximizes sterilizing effect while minimizing toxicity and resistance emergence for tuberculosis. Antimicrob Agents Chemother 2017;61:e00751-17.
36. Brown AN, Drusano GL, Adams JR, et al. Preclinical evaluations to identify optimal linezolid regimens for tuberculosis therapy. MBio 2015;6(6):e01741-15.
37. Cattaneo D, Orlando G, Cozzi V, et al. Linezolid plasma concentrations and occurrence of drug-related haematological toxicity in patients with gram-positive infections. Int J Antimicrob Agents 2013;41:586-9.
38. Pea F, Viale P, Cojutti P, Del Pin B, Zamparini E, Furlanut M. Therapeutic drug monitoring may improve safety outcomes of long-term treatment with linezolid in adult patients. J Antimicrob Chemother 2012;67:2034-42.
39. Matsumoto K, Takeshita A, Ikawa K, et al. Higher linezolid exposure and higher frequency of thrombocytopenia in patients with renal dysfunction. Int J Antimicrob Agents 2010;36:179-81. doi:10.1016/j.ijantimicag.2010.02.019. Epub 2010 Apr 13.
40a. Song T, Lee M, Jeon HS, et al. linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. EBioMedicine 2015;2:1627-33.
40b. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid. IAS 2021, 18-21 July 2021. https://theprogramme.ias2021.org/Abstract/Abstract/2405.
41. Bedaquiline Investigator Brochure, Janssen Pharmaceuticals, Inc., 2015.
42. Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360:2397-405.
43. 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.
44. Diacon AH, Dawson R, Hanekom M, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis 2011;15:949-54.
45. Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012;366:2151-60.
46. Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J 2013;41:1393-400.
47. McLeay S, Vis P, can Heeswijk R, et al. Population pharmacokinetics of bedaquiline (TMC207), a novel antituberculosis drug. Antimicrob Agents Chemother 2014; 58:5315-24.

48. Salinger DH, Nedelman JR, Mendel C, et al. Daily dosing for bedaquiline in patients with tuberculosis. Antimicrob Agents Chemother 2019; 63:e00463-19.
49. Delamanid Investigator Brochure, Otsuka Pharmaceutical Company, Ltd., April 2019.
50. Hafkin J, Frias M, Hesseling A, et al. Pharmacokinetics and safety of delamanid in children ages 6-17 years with MDR TP [poster no. A-960]. In: Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC)/International Congress of Chemotherapy and Infection (ICC); 2015.
51. von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. Lancet Respir Med 2019;7:249-59.
52. Olayanju O, Esmail A, Limberis J, Dheda K. A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug-resistant tuberculosis. Eur Respir J 2020;55:1901181.
53. Clinical Report Synopsis for Protocol 242-08-210. EudraCT No. 2009-014944-13. https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-014944-13/results.
54. Hewison C, Ferlazzo G, Avaliani Z, et al. Six-month response to delamanid treatment in MDR TB patients. Emerg Infect Dis 2017;23:1746-48.
55. Ferlazzo G, Mohr E, Laxmeshwar C, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Inf Dis 2018;18:536-44.
56. Pontali E, Sotgiu G, Tiberi S, et al. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review. Eur Respir J 2018;52:18800934.
57. Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid or both in MDR-TB patients: the DELIBERATE trial. [Abstract 84]. CROI 2019, March 4-7, 2019; Seattle, WA.
58. Hafkin J, Hittel N, Martin A, et al. Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. Eur Respir J 2019; 53:1801154.
59. Cholo MC, Steel HC, Fourie PB, et al. Clofazimine: current status and future prospects. J Antimicrob Chemother 2012;67:290-8.
60. Diacon AH, Dawson R, von Groote-Bidlingmaier F, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. Am J Respir Crit Care Med 2015;191:943-53.
61. Grosset JH, Tyagi S, Almeida DV, et al. Assessment of clofazimine activity in a second-line regimen for tuberculosis in mice. Am J Respir Crit Care Med 2013;188:608-12.
62. Tyagi S, Ammerman NC, Li SY, et al. Clofazimine shortens the duration of the first-line treatment regimen for experimental chemotherapy of tuberculosis. Proc Natl Acad Sci USA 2015;112:869-74.
63. 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.
64. 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.

65. Wang Q, Pang Y, Jing W, Liu Y, et al. Clofazimine for the treatment of pulmonary extensively drug-resistant tuberculosis in China. Antimicrob Agents Chemother 2018;62:e02149-17.
66. Nix DE, Adam RD, Auclair B, et al. Pharmacokinetics and relative bioavailability of clofazimine in relation to food, orange juice and antacid. Tuberculosis (Edinb) 2004;84:365-73.
67. Schaad-Lanyi Z, Dieterle W, Dubois JP, et al. Pharmacokinetics of clofazimine in healthy volunteers. Int J Lepr Other Mycobact Dis 1987;55:9-15.
68. Maartens G, Brill MJE, Pandie M, Svensson EM. Pharmacokinetic interaction between bedaquiline and clofazimine in patients with drug-resistant tuberculosis. Int J Tuberc Lung Dis 2018;22:26-9.
69. McNeeley, DF. Elucidating the role of clofazimine (lamprene®) in the treatment of MDR-TB. Global Multidrug Resistant Tuberculosis Clinical Trials Landscape Meeting, Washington, DC, December 4-5, 2014.
70. Kroger A, Pannikar V, Htoon MT, et al. International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. Trop Med Int Health 2008;13:594-60.
71. Hwang TJ, Dotsenko S, Jafarov A, et al. Safety and availability of clofazimine in the treatment of multidrug and extensively drug-resistant tuberculosis: analysis of published guidance and meta-analysis of cohort studies. BMJ Open 2014;4:e004143.
72. Dannemann BR, Bakare N, De Marez T, et al. Corrected QT interval (QTcF) prolongation in a phase 2 open-label trial of TMC207 plus background regimen as treatment for MDR-TB: effect of coadministration with clofazimine [Abstract A-1259]. In Program and Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 9-13, 2013; Denver, CO.
73. Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med 2014;371:1588-98.
74. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2014;371:1577-87.
75. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med 2014;371:1599-608.
76. Huang YS, Chern HD, Su WJ, et al. Polymorphism of the N-acetyltransferase 2 gene as a susceptibility risk factor for antituberculosis drug-induced hepatitis. Hepatology 2002;35:883-9.
77. Huang YS, Chern HD, Su WJ, et al. Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. Hepatology 2003;37:924-30.
78. Roy PD, Majumder M, Roy B. Genomics of anti-TB drugs-related hepatotoxicity. Pharmacogenomics 2008;9:311-21.
79. Ramachandran G, Swaminathan S. Role of pharmacogenomics in the treatment of tuberculosis: a review. Pharmacogenomics Pers Med 2012;5:89-98.
80. Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. Int J Tuberc Lung Dis 2008;12:994-1002.

81. Yamamoto M, Sobue G, Mukoyama M, Matsuoka Y, Mitsuma T. Demonstration of slow acetylator genotype of N-acetyltransferase in isoniazid neuropathy using an archival hematoxylin and eosin section of a sural nerve biopsy specimen. J Neuro Sci 1996;135:51-4.
82. Wang PY, Xie SY, Hao Q, Zhang C, Jiang BF. NAT2 polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. Int J Tuberc Lung Dis 2012;16:589-95.
83. Goel U, Bajaj S, Gupta O, Dwivedi N, Dubey A. Isoniazid induced neuropathy in slow versus rapid acetylators: an electrophysiological study. J Assoc Physicians India 1992;40:671-2.
84. Kim RB. Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. Eur J Clin Invest 2003;33(Suppl 2):1-5.
85. Chigutsa E, Visser ME, Swart EC, et al. The SLCO1B1 rs4149032 polymorphism is highly prevalent in South Africans and is associated with reduced rifampin concentrations: dosing implications. Antimicrob Agents Chemother 2011;55:4122-7.
86. Fischel-Ghodsian N. Genetic factors in aminoglycoside toxicity. Pharmacogenomics 2005;6:27-36.
87. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des 2007;13:119-26.
88. Guthrie O. Aminoglycoside induced ototoxicity. Toxicology 2008;249:91-6.
89. Guan M-X. Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity. Mitochondrion 2011;11:237-45.
90. Xie J, Talaska AE, Schacht J. New developments in aminoglycoside therapy and ototoxicity. Hear Res 2011;281:28-37.
91. Prezant TR, Agapian JV, Bohlman MC, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. Nat Genet 1993;4:289-94.
92. Pacheu-Grau D, Gómez-Durán A, Montoya J, Ruiz-Pesini E. Influence of mtDNA genetic variation on antibiotic therapy. Pharmacogenomics 2010;11:1185-7.
93. Soriano A, Miró O, Mensa J: Mitochondrial toxicity associated with linezolid. N Engl J Med 2005;353:2305-6.
94. McKee E, Ferguson M, Bentley A, Marks T. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. Antimicrob Agents Chemother 2006;50:2042-9.
95. De Vriese AS, Van Coster R, Smet J, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis 2006;42:1111-17.
96. Garrabou G, Soriano A, López S, et al: Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. Antimicrob Agents Chemother 2007;51:962-7.
97. Carson J, Cerda J, Chae JH, Hirano M, Maggiore P: Severe lactic acidosis associated with linezolid use in a patient with the mitochondrial DNA A2706G polymorphism. Pharmacotherapy 2007;27:771-4.
98. Werk AN, Lefeldt S, Bruckmueller H, et al. Identification and characterization of a defective CYP3A4 genotype in a kidney transplant patient with severely diminished tacrolimus clearance. Clin Pharmacol Ther 2014;95:416-22.
99. Westlind-Johnsson A, Hermann R, Huennemeyer A, et al. Identification and characterization of CYP3A4*20, a novel rare CYP3A4 allele without functional activity. Clin Pharmacol Ther 2006;79:339-49.

100. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther 2003;306:287-300.
101. Kwara A, Lartey M, Sagoe KW, Court MH. Paradoxically elevated efavirenz concentrations in HIV/tuberculosis-coinfected patients with CYP2B6 516TT genotype on rifampin-containing antituberculous therapy. AIDS 2011;25:388-90.
102. Dooley KE, Denti P, Martinson N, et al. pharmacokinetics of efavirenz and treatment of HIV-1 among pregnant women with and without tuberculosis coinfection. J Infect Dis 2015;211:197-205.
103. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Combined effect of CYP2B6 and NAT2 genotype on plasma efavirenz exposure during rifampin-based antituberculosis therapy in the STRIDE study. Clin Infect Dis 2015;60:1860-3.
104. di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. Pharmacogenet Genom 2009;19:300-9.
105. Dorman SE, Savic RM, Goldberg S, et al. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. Am J Respir Crit Care Med 2015;191:333-43.
106. Singla R, Caminero JA, Jaiswal A, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J 2012;39:956-62.
107. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on **April 2, 2020**. Accessed at: **https://www.hhs.gov/ohrp/sites/default/files/fda-covid-guidance-2apr2020.pdf**.

APPENDIX I: A5356 PROHIBITED AND PRECAUTIONARY MEDICATIONS

DIVISION OF AIDS
ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections)
(formerly AIDS Clinical Trials Group)
For Protocol A5356

The prohibited and precautionary medications with linezolid (LZD), bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ) are listed below.

To avoid adverse drug interactions, package inserts of antiretroviral agents should be referenced whenever a concomitant medication is initiated or dose changed to avoid drug interaction adverse events.

I. Prohibited Medications

- Antimycobacterial agents outside of the study regimen, including rifamycins (rifampicin, rifapentine, rifabutin).

- Antiretroviral therapy containing efavirenz or etravirine

- QT prolonging agents
  - Anti-arrhythmic medications (e.g., quinidine, procainamide, disopyramide, encainide, flecainide, sotalol, amiodarone, dofetilide, ibutilide)
  - Certain antimalarials with QT-prolonging potential (e.g., halofantrine, quinine, chloroquine, artesunate/amodiaquine, dihydroartemisinin/piperaquine)
  - Neuroleptics (e.g., phenothiazines, thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole, sultopride, and pimozide)
  - Tricyclic antidepressants: (e.g., amitriptyline, doxepin, desipramine, imipramine, and clomipramine)
  - Some antimicrobials, including:
    - Fluoroquinolones (e.g., moxifloxacin, gatifloxacin, and sparfloxacin)
    - Macrolides (e.g., azithromycin, clarithromycin, erythromycin)
    - Pentamidine
    - Quinolone antimalarials (e.g., chloroquine and quinacrine)
    - Triazole antifungal agents (e.g., fluconazole, itraconazole, posaconazole, voriconazole)
  - Miscellaneous: Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
  - Contact the protocol team with questions about other QT prolonging therapies.

- Strong CYP3A4 inducers, such as carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, and St. John's wort (Reference: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.html)

II. Precautionary Medications

All arms

- Strong CYP3A4 inhibitors, including ritonavir and cobicistat, for greater than 14 days (Reference: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.html)
- Adrenergic agents (such as pseudoephedrine or phenylpropanolamine)
- Serotonergic agents

APPENDIX II: SAMPLE INFORMED CONSENT

Division of AIDS
ACTG (Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections)
(formerly AIDS Clinical Trials Group)
For protocol A5356

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

SHORT TITLE FOR THE STUDY: Linezolid Dosing Strategies in DR-TB

PURPOSE

This is a research study. Your participation in this study is voluntary. You are being approached regarding this research study because you have tuberculosis (TB) that is resistant to some of the drugs generally used to treat it. The purpose of the study is to evaluate the efficacy (how well the medicines work) and tolerability (the level and type of side effects from a drug or treatment) of two different treatment regimens that contain the same four anti-TB medicines: linezolid (LZD), bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ). This study will also measure the level of these medicines in your blood.

NUMBER OF PARTICIPANTS

There will be 132 participants: 66 in each of the two treatment groups.

LENGTH OF STUDY

The study will last for 72 weeks, or about 1 year and 5 months. For the first 26 weeks (about 6 months), you will be taking study-provided medications. After you finish taking study-provided medications, you will have some follow-up visits until week 72.

STUDY TREATMENT

There are four study-provided medications: LZD, BDQ, DLM, and CFZ. Everyone in the study will take these drug once a day for the entire treatment period: BDQ, DLM, and CFZ. The difference between two treatment groups is in how you will take the fourth drug: LZD. If you are in group A, you will take one dose of LZD once a day for the entire treatment period. If you are in group B, you will take a higher dose of LZD once a day for 4 weeks and then continue taking that higher dose of LZD just three times a week for the rest of the treatment period.

REQUIRED ACTIVITIES

Blood and sputum collections

- At most visits, some blood will be collected from a vein in your arm.
- At all visits, sputum (the thick substance that you cough up when you are sick or congested) will be collected from you.

Special procedures

- At several visits, you will have a chest X-ray/scan and ECG.
- At several visits, you will have vision testing and neuropathy tests.

Directly observed therapy (DOT)

- DOT is required at least five times every week while you are taking study treatment. The possible methods to conduct DOT will be according to your site practices. It could include video-DOT, use of community health worker, or other strategies used locally for delivering observed therapy. DOT might be done on 5 days during the week and it could be your self-report on 2 days (e.g., weekend days).

RISKS

Possible risks related to the study-provided drugs LZD, BDQ, DLM, and CFZ are listed later in this informed consent. In brief, the following are possible:

Linezolid

The most common side effects of linezolid are:

- Bad taste in mouth
- Constipation
- Diarrhea
- Dizziness
- Headache
- Nausea or vomiting
- Decreased blood counts
- Vision changes
- Rash
- Abdominal discomfort
- Liver disease
- Fungal infections
- Numbness and tingling in your hands and feet

Bedaquiline

The most common side effects of bedaquiline are:

- Headache
- Dizziness with change in position
- Diarrhea
- Nausea

- Rash
- Sleepiness
- 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
- **Disturbance in the heart's electrical activity (i**ncrease in the QT interval, a measure of the heart's electrical cycle). **See the NOTE below.**
- 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

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
- Changes in your heart rhythm
- Liver disease
- Fever
- Chest pain
- Jaundice (yellowing of the skin or whites of the eyes)

Rare:

- Neuropsychiatric abnormalities (visual hallucinations, insomnia, agitation)
- **Disturbance in the heart's electrical activity (increase in the QT interval, a measure of the heart's electrical cycle). See the NOTE below**

Clofazimine

More common:

- Red-brown skin, urine, sweat, tears, or stool discoloration. This side effect goes away after stopping clofazimine but it may take months to (rarely) years.
- Dry, rough, or scaly skin, which may or may not be itchy
- Diarrhea, nausea or vomiting, or abdominal pain

Rare:

- Colicky or burning abdominal or stomach pain
- Mental depression
- Loss of appetite
- Changes in taste
- Dryness, burning, itching, or irritation of the eyes
- Increased sensitivity of skin to sunlight
- Bloody or black, dark red stools
- **Disturbance in the heart's electrical activity (increase in the QT interval, a measure of the heart's electrical cycle). See the NOTE below**

NOTE: There are three drugs in the study treatment that can cause disturbance in the heart's electrical activity called QT interval prolongation, especially if the drugs are given in combination. 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 a few ECGs (electrocardiograms) to monitor the electrical activity of your heart including QT interval. Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat) or if you feel dizzy or faint.

BENEFITS — You may receive a direct benefit from participating in this study, but no guarantee can be made.

OTHER CHOICES — Enrollment in the study is voluntary. You may choose to not participate in the study. Instead of being in this study, you have the option of treatment with prescription drugs available to you or starting a new treatment or other experimental drugs (if you qualify) under the care of your regular doctor or other health care provider. Please talk to your doctor about these and other choices available to you.

INTRODUCTION

You are being asked to take part in this research study because you have tuberculosis (TB) that is resistant to some of the drugs generally used to treat it. This is known as drug-resistant TB (DR-TB).

This study is sponsored by the U.S. 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?

There is currently no “standard of care” or single standardized treatment regimen recommended for every one with DR-TB. Current DR-TB treatments may not be well tolerated and can often have side effects. There is a need to identify drugs with enough anti-TB activity (treatment against TB) and good safety profiles that can improve outcomes in the treatment of DR-TB.

The main purpose of this study is to evaluate the efficacy and tolerability of two different treatment regimens that contain four anti-TB medicines: linezolid (LZD), bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ). As a secondary aim, the study will also assess the safety of the combination of these drugs.

BDQ and DLM are medicines approved in many countries for the treatment of DR-TB. DLM has been approved in the European Union, Japan, South Korea, Hong Kong, Turkey, India, the Philippines, Turkmenistan, China, Mongolia, and Ukraine for the treatment of MDR-TB for the treatment of MDR-TB, but is not approved by the US FDA. LZD is a medicine approved for the treatment of certain types of bacterial infections, but is not approved to treat TB. CFZ is a drug approved for the treatment of leprosy (another type of non-TB mycobacterial infection) but is not approved to treat TB. However, both of these drugs have been shown to be very active against TB in laboratory and animal studies, clinical trials, and in clinical practice. This study is also evaluating how active each of these medicines is when used in combination with BDQ and DLM. While LZD and CFZ have been shown to have activity in treating TB in animal studies, and LZD in combination with BDQ or DLM has been shown to have activity in treating MDR-TB in humans, the effectiveness of these four medicines in combination for TB treatment are unknown, and whether all four drugs used together can shorten the duration of treatment for MDR-TB is also unknown.

It is important that more information be obtained to evaluate whether LZD, BDQ, DLM, and CFZ can be safely used together. Information generated from this study will help clinicians treating TB to identify safe and effective regimens for people with DR-TB.

The study will have two (2) groups that we call “arms”– Arm A and Arm B. Below are the medicines that you will take during the study depending on which arm you are in.

Everyone in the study will take these drugs once a day for the entire treatment period: BDQ, DLM, and CFZ. The difference between arms is in how you take the fourth drug: LZD.

- If you are in Arm A, you will take one dose of LZD once a day for the entire treatment period.
- If you are in Arm B, you will take a higher dose of LZD once a day for 4 weeks and then continue taking that higher dose of LZD just three times a week for the rest of the treatment period.

Arm A
Weeks 1-26: LZD 600 mg once daily (QD)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Arm B
Weeks 1-4: LZD 1200 mg QD
Weeks 5-26: LZD 1200 mg three times per week (TIW)
Weeks 1-2: BDQ 200 mg QD + DLM 300 mg QD + CFZ 300 mg QD
Weeks 3-8: BDQ 200 mg QD + DLM 300 mg QD + CFZ 100 mg QD
Weeks 9-26 or -38: BDQ 100 mg QD + DLM 300 mg QD + CFZ 100 mg QD

Appendix II Table 1: A5356 Study Treatment Regimens

Arm	Drug and dose	Weeks				
		On-treatment				Follow-up
		1-2	3-4	5-8	9-26 Or 9-38	27-72 Or 39-72
Arm A	LZD 600 mg QD	X	X	X	X	Follow up with no further treatment
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	
Arm B	LZD 1200 mg QD	X	X			
	LZD 1200 mg TIW			X	X	
	BDQ 200 mg QD	X	X	X		
	BDQ 100 mg QD				X	
	DLM 300 mg QD	X	X	X	X	
	CFZ 300 mg QD	X				
	CFZ 100 mg QD		X	X	X	

You may need to receive treatment longer depending on how effective it is for you and whether you miss or are told to skip any doses.

If you have HIV, you must take HIV drugs during the study. If you have not yet started anti-HIV treatment, you will need to start it within the first 30 days of the study, but after you have started your anti-TB treatment. Some of your treatment for HIV may need to be changed while you are taking study medicine.

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

If you agree to take part in this research study, you will be asked to sign this consent form. After you have signed the form, the research staff will determine if you are eligible to join the study. After you enter the study, you will have about 12 visits over 72 weeks (about a year and a half). Some participants may have additional 1 or 2 visits.

Information Collected at Screening

There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, HIV viral load if you have HIV) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

Screening

If you would like to be in this study, after you have read and signed this consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. At this visit:

- You will have a physical exam and answer questions about your medical history.
- You will answer questions about any medications you are taking or have taken in the past.
- You will have a TB evaluation.
- You will be asked to produce sputum samples to determine how much TB bacteria is in your lungs and what drugs can be used to fight your TB infection.
- **If you are able to become pregnant, you will be asked to provide a blood or urine sample for a pregnancy test.**
- You will have approximately 2 tablespoons of blood collected for routine lab tests for safety and to see if you are infected with hepatitis B and/or C virus (viral infections of the liver).
- If your HIV status is unknown or not documented, blood will be drawn to confirm your HIV status. You may have to sign a separate consent form for this test.
- If your HIV tests are positive, some blood collected (approximately 1 tablespoon) from you will be used to measure the amount of HIV in your blood (HIV viral load, also called HIV-1 RNA level) and to measure your CD4+ cell count (CD4+ cells help fight infections).
- You will have a chest X-ray to determine where and how large the TB infection is in your lungs.
- You will have a brief exam to see if you have peripheral neuropathy (numbness and tingling in your hands and feet).
- You will have an electrocardiogram (ECG) to look at the electrical activity of your heart.

If you enter the study

If your screening tests indicate that you are eligible and you decide to join the study, at the study entry visit, you will be randomized (like the flip of a coin) to one of two treatment 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.

If you are living with HIV (the virus that causes AIDS), your doctor will talk with you about the best options for treating your HIV. This study will not provide medications to treat your HIV. 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 change your HIV drug treatment.

You should take all of the study TB drugs with a meal or within 15-30 minutes after a meal.

On the days of your study visits, you must bring your TB medication with you. You may be asked to wait to take the medication until after your blood has been drawn.

Entry

If you are eligible for this study, you will come in for an entry visit. At this visit:

- You will have a clinical assessments including vital signs, weight, ECG, brief physical exam, and a test of your vision.
- If you are able to become pregnant, you will be asked to provide a blood or urine sample for a pregnancy test.
- You will be asked about your health and any changes in your medicines since your last visit.
- You will answer questions about any medications you are taking or have taken in the past.
- You will have approximately 1 tablespoon of blood drawn for routine lab tests for safety and some will be stored for future protocol-required testing.
- Some blood will be collected for a test for thyroid stimulating hormone (TSH).
- You will be asked to produce sputum samples that will be tested to determine how much TB bacteria is in your lungs and what drugs can be used to fight your TB infection; some of your sputum will be stored for future study tests.
- You will be randomized (assigned by chance, as if by the flip of a coin to one of the study's two arms). You will be told what treatment arm you have been placed in.
- You will be given your study-provided drugs.
- The study staff will explain how to take your medications and you will be asked to bring all your study medications with you to every study visit.

Study Visits

After your entry visit, you will come to the clinic at weeks 2, 4, 6, 8, 12, 16, 20, 26, 38, 52, and 72. If any of the study drugs is temporarily stopped or if you take longer to complete the 26 week course, you will come to the clinic for an additional visit at week 30. If your treatment is extended by 12 weeks, you will come to the clinic for an additional visit at week 42. You will also have a study visit if you are suspected of having an unusual inflammatory reaction to TB treatment called IRIS, TB treatment failure or TB recurrence, or if you stop the study medications or discontinue the study early.

It will be important to ensure that study participants receive and take all study TB medicines and complete study treatment as required by the study. This is very important in order to monitor response to treatment. Therefore, directly observed therapy (DOT) will be required at least five times every week while you are taking study treatment. This means that study staff will watch you take study medicines at least five times every week. This can be done by video-DOT or other method suggested by your study staff. TB medication cards, such as those provided by your local TB control programs, could be used if available. You will also be asked to self-report on if you took your medicines and if with food. An example of DOT set up could be that in person DOT is administered on Monday, Wednesday, Friday, video-DOT used on Tuesday and Thursday, and participant self-report on Saturday and Sunday.

During Most Study Visits

- Study staff will perform a targeted physical exam, including a measurement of your weight, your vital signs (temperature, pulse, blood press.
- You will have approximately 1 tablespoon of blood collected for routine lab safety tests, to measure the amount of study medication in your blood, and for future protocol-required testing.
- If you are living with HIV, we will measure the level of HIV in your blood (this is called your viral load) and measure your CD4+ cell counts at weeks 26 and 52. Also when TB IRIS is suspected in order to look at how your TB treatment is working (for example, if the treatment is interrupted or the treatment appears to be failing). If you are not HIV positive but are tested outside of this study and you test positive for HIV after you are enrolled in the study, you will be referred to your local clinic or healthcare provider for management of your HIV. If this happens, we will measure the amount of HIV in your blood and your CD4+ cells counts according to the same schedule.
- You will be asked to produce sputum samples that will be tested to determine how much TB bacteria is in your lungs and what drugs can be used to fight your TB infection. Some of your sputum will be stored for future study use.
- You will be asked questions about how well you take your study medications and the study staff will count your pills. Please note that directly observed therapy will be required at least five times weekly. Your self-report of ingested doses can be used for the remaining two days of the week.
- You will have an ECG performed at weeks 2, 4, 6, 8, 12, 16, 20, 26, and 38 (and 30 and/or 42 as applicable).
- You will have a chest X-ray performed at week 26.
- You will have vision screening performed at weeks 4, 8, 12, 16, 20, 26, and 38 (and at 30 and/or 42 as applicable).
- You will have a brief exam to see if you have peripheral neuropathy (numbness and tingling in your hands and feet).

You will be given the results of the study tests as soon as they are available.

Referral to local clinic or healthcare provider

In the event that any safety evaluation reveals an abnormal result during the study (e.g., abnormal ECG, abnormal vision screening, evidence of worsening peripheral neuropathy) that requires further investigation and treatment, you will be referred to the local clinic or healthcare provider for management.

Pharmacokinetic Sampling

You may be asked to participate in special blood collections called pharmacokinetic (or “PK”) sampling at week 4. The blood samples obtained for PK will be tested to measure the amount or concentration of the TB drugs in your blood at each time period. Only 20 adult participants plus replacements as needed, in each of two study arms will have the intensive PK visits. “PK” sampling helps researchers to learn more about how the amount of study medication changes in your blood over time. During this visit, seven PK blood samples will be taken over a 24 hour

period – before you take medicines (pre-dose), at 1, 2, 4, 8, and 24 hours post-dose. You will be asked about the times of last three doses of the study drugs prior to the week 4 PK visit.

If you do not participate in this intensive PK visit, you will participate in an abbreviated pharmacokinetic sampling at week 4. During this visit, four blood samples will be drawn over a 4-hour period.

If, during the study, your dose of LZD is reduced due to toxicity, you will have an intensive PK sampling visit approximately 2 to 4 weeks after the dose adjustment. The samples will be collected at less than 30 minutes before you take the morning dose of LZD (pre-dose), and then at 1, 2, 4, and 8 hours after the observed LZD dose.

If your LZD dose is reduced due to toxicity but you are not able to participate in the intensive PK, you will have an abbreviated PK sampling visit approximately 2 to 4 weeks after the dose adjustment. The samples will be collected at pre-dose, and 1 and 2 hours post-dose.

For the PK visits, you will have to bring all anti-TB medications to the clinic. You will be given instructions from site staff regarding the morning dose of anti-TB therapy.

Approximately 3 (intensive PK) or 2 (sparse PK) tablespoons of blood will be collected. PK samples will be collected from a tube placed in your arm, if one can be placed and maintained successfully.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your samples will be stored and used for study-required [pharmacokinetic, immunologic (structure and function of the immune system), virologic] testing. Some of these samples will be shipped and stored outside of the country from which they are collected.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described above are required by this study. If you do not agree to the storage or testing that has been described above, you should not join this study.

Please refer to Appendix III for information and consent regarding samples that are collected from you during the study that might be left over after all required study testing is done.

Research With Human Genetic Testing for Pharmacogenetics – OPTIONAL
If you agree, some of your blood will be tested for the human genes that affect how drugs are broken down, interact with other drugs, and potentially lead to side effects in the body. This is called pharmacogenetics. Additionally, if these types of human genetic data are collected using

your samples, it might also be shared on a public database such as dbGaP for use by other researchers.

____ (initials) I understand and I agree to this storage and use of my blood for pharmacogenetic testing.

OR

____ (initials) I understand but I do not agree to this storage or use of my blood for pharmacogenetic testing.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 132 participants will take part in this study – 66 per arm.

HOW LONG WILL I BE IN THIS STUDY?

You will be in the study for 72 weeks, or about 1 year and 5 months.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early if:
- **Y**ou request to be taken off the study
- **Y**our doctor decides the study is no longer in your best interest or that it is unlikely that you will be able to comply with the study requirements
- **T**he study is stopped or cancelled

The study doctor may also need to take you off one or more of the study drugs without your permission if:
- **C**ontinuing the study drugs may be harmful to you
- **Y**ou need a treatment that you may not take while taking the study drugs
- **Y**ou become pregnant or start breast-feeding
- **Y**ou are not able to take the study drugs as required by the study
- **Y**ou are found not to have drug-resistant TB of the lungs

If you have to stop taking the study drugs early or you are taken off the study early, you will have a Premature Treatment or Study Discontinuation visit and have several evaluations. If you have to stop taking study drugs early, you will be encouraged to continue on study through week 72. You will also be referred to the national TB program or local clinic site.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS OR ONCE I LEAVE THE STUDY, HOW WOULD DRUGS BE PROVIDED?

During the study:
If you must permanently stop taking study-provided drugs 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 drugs that you received on the study. If continuing to take these or similar drugs 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-provided 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 study staff at your site.

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.

Linezolid (LZD)
The most common side effects of linezolid are:
- Bad taste in mouth
- Constipation
- Diarrhea
- Dizziness
- Headache
- Nausea or vomiting
- Decreased blood counts
- Vision changes
- Rash
- Abdominal discomfort
- Liver disease
- Fungal infections
- Numbness and tingling in your hands and feet

Since 2000, LZD has been approved for the treatment of bacterial infections caused by susceptible gram-positive bacteria (types of bacteria often found on skin and in the respiratory, gastrointestinal, and urinary systems). It is not approved to treat TB.

Bedaquiline (BDQ)
The most common side effects of bedaquiline are:

- Headache
- Dizziness with change in position
- Diarrhea
- Nausea
- Rash
- Sleepiness
- 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. **Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat) or if you feel dizzy or faint.**
- 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

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

In a clinical study, there were more deaths among people who took bedaquiline for multi-drug resistant TB than among people who did not take the medication. However, after reviewing all of the information now available from several later studies that included BDQ, it is unlikely that the deaths in that study were related to the BDQ.

As of 30 April 2014, BDQ, when taken together with other TB drugs, has been approved to treat difficult adult cases of MDR-/RR-TB in the United States, Europe, and several other countries.

Delamanid (DLM)
The most common side effects of delamanid are:

- Nausea or vomiting
- Abdominal discomfort
- Headache
- Tiredness

- Anxiety or depression
- Rash
- Joint pain
- Decreased blood counts
- Changes in your heart rhythm
- Liver disease
- Fever
- Chest pain
- Jaundice (yellowing of the skin or whites of the eyes)
- **Increase in the QT interval. 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 a few ECGs (electrocardiograms) to monitor the electrical activity of your heart including QT interval. Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat) or if you feel dizzy or faint.**

Rare:

- Neuropsychiatric abnormalities (visual hallucinations, insomnia, agitation)

As of April 2019, DLM, when taken together with other TB drugs, has been approved to treat MDR-TB in the European Union, Japan, South Korea, Hong Kong, Turkey, India, the Philippines, Turkmenistan, China, Mongolia, and Ukraine, and is recommended for use in MDR-TB patients by the WHO, although it is not currently recommended for use in children or pregnant or breastfeeding women due to limited safety and efficacy data.

<u>Clofazimine (CFZ)</u>

More common:

- Red-brown skin, urine, sweat, tears, or stool discoloration. This side effect goes away after stopping clofazimine but it may take months to (rarely) years.
- Dry, rough, or scaly skin, which may or may not be itchy.
- Diarrhea, nausea or vomiting, or abdominal pain.
- **Increase in the QT interval. 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 a few ECGs (electrocardiograms) to monitor the electrical activity of your heart including QT interval. Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat) or if you feel dizzy or faint.**

Rare:

- Colicky or burning abdominal or stomach pain
- Mental depression
- Loss of appetite
- Changes in taste
- Dryness, burning, itching, or irritation of the eyes

- Increased sensitivity of skin to sunlight
- Bloody or black, dark red stools
- Disturbance in heart electrical activity (prolonging the QTcF interval). While on the study, your heart rhythm will be monitored with an ECG test at multiple visits. If a disturbance in electrical activity is found, you will be monitored more closely with once weekly ECG testing. The severity of the disturbance in electrical activity will be evaluated with specific criteria. Depending on the severity, clofazimine and other study medications may be discontinued, and in extreme cases you may even be hospitalized for monitoring until your QTcF interval improves. In this case, you would be referred to the National Tuberculosis Program for TB treatment according to local standard of care.

As of December 1986, CFZ has been approved by the U.S. FDA for treatment of leprosy, another type of non-TB mycobacterial infection. It is not approved for treatment of TB.

Risks of Electrocardiogram (ECG)
For your safety, you will have blood tests and an electrocardiogram (ECG) performed before you are allowed to participate in the study. The ECG measures the electrical activity of your heart and allows the study staff to see if your heart rhythm is normal. You will have regular ECGs during the trial to watch for any important heart rhythm changes. The QT interval is a heart rhythm measurement and if you are found to have a significant change in this interval while on study, study-provided drugs will be stopped immediately.

You may experience mild irritation, slight redness, and itching on your skin where the electrodes from the electrocardiogram machine are placed. You may be hospitalized for monitoring. Although cases of lengthened QT interval have happened with delamanid in clinical trials of participants treated for TB with delamanid, to date no participants in the delamanid trials experienced harm from it; however, lengthened QT intervals caused by other medications or illnesses have been associated with abnormal heart rhythms and sudden death.

Risks of Combination Antiretroviral Drugs Used to Treat HIV Infection
The risks of combination antiretroviral drugs used to treat HIV infection apply only to participants who are living with HIV. Some anti-HIV drugs might interact with BDQ leading to either a decrease or increase in BDQ levels in the blood or in one of your anti-HIV medications. These drug interactions could affect the activity of BDQ in treating your TB infection or the activity of your anti-HIV medicines in treating your HIV. These drug interactions might also increase the risk of developing side effects related to BDQ or your anti-HIV medicines. If you are taking one of the anti-HIV drugs (or other medicines) that might interact with BDQ or any other study medicines, the study doctors will make a recommendation to your doctor to change your anti-HIV medicines. Also, in some people with advanced HIV, symptoms from other infections or certain diseases may occur weeks to months after starting combination anti-HIV treatment. This is called immune reconstitution inflammatory syndrome (IRIS). 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.

Risks of Combination Anti-TB Drugs Used to Treat TB
In some people with TB, TB symptoms might get worse weeks or months after starting anti-TB treatment. This is called MTB immune reconstitution inflammatory syndrome (MTB IRIS). Some of these symptoms may be life threatening. If you start having new symptoms, or notice that current symptoms are getting worse after starting your anti-TB therapy, tell your healthcare provider right away.

There are three drugs in the study treatment that can also increase QT interval, especially if the drugs are given in combination. A prolonged QT interval may increase the risk of heart rhythm disturbances, which in rare cases, may be fatal. Tell your healthcare provider right away if you have a change in your heartbeat (a fast or irregular heartbeat) or if you feel dizzy or faint.

Risks of Non-Study Medications
There is a risk of 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, vitamins, and herbal supplements you are taking before you start the study and 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 Developing Increased Drug Resistance
There is a chance that you might develop resistance to some of the drugs being used in your treatment. This means that these drugs might not work as well against your TB. We will know if you are resistant to some non-study TB drugs at the very start of the study treatment. If you develop resistance to study-provided drugs during the study, these drugs may not be strong enough to kill your TB. This risk is rare when all four drugs are being taken together, but it is important for you to be aware that increased drug resistance could occur.

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 Chest X-ray or Chest CT
The amount of high-energy radiation used in a chest x-ray is relatively small and does not pose any significant risk to you.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your drug-resistant TB status (or if you have HIV your HIV status) secret from people close to you. This may lead to unwelcome discussions about or reactions to your drug-resistant TB or for those who have HIV your HIV status. Please talk with the study staff if you are worried about this.

ARE THERE RISKS RELATED TO PREGNANCY?

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in women taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

LZD, DLM, and possibly CFZ may be unsafe for unborn babies. For bedaquiline, while animal reproduction studies showed no adverse effects on fetuses, there are no human data.

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 linezolid and/or delamanid and for 30 days after stopping the study drug(s). You must use at least two of the following methods of birth control (discuss with the study staff):

- Male or female condoms
- Diaphragm or cervical cap (with a cream or gel that kills sperm, if available)
- Intrauterine device (IUD) or intrauterine system
- Hormone-based birth control (for example: oral contraceptives, Depo-Provera, Nuva-Ring, implants)

If you are not able to become pregnant, you are not required to use contraceptives. You are not of reproductive potential if you have undergone menopause (at least 1 year with no menstrual periods [amenorrheic]), hysterectomy, bilateral oophorectomy, or bilateral tubal ligation.

If you become pregnant while taking part in this study, your study-provided drugs will be stopped and you will be referred to your national or local TB clinic/provider for treatment of DR-TB according to local standard of care and to a prenatal care program. If you agree, you will continue to attend study visits and your pregnancy outcome will be recorded. If you are taking antiretroviral therapy for treatment of HIV, your pregnancy will be reported to the Antiretroviral Pregnancy Registry. This report will not use your name or other information that could be used to identify you.

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 drug-resistant tuberculosis.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Enrollment in the study is voluntary. You may choose to not participate in the study.

Instead of being in this study you have the choice of:
- Treatment with prescription drugs available to you
- Treatment with other experimental drugs, if you qualify

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 U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations and policies of your country and research site.

A description of this clinical trial will be available on http://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. Costs may include but not be limited to transportation costs, time away from work or home.

WILL I RECEIVE ANY PAYMENT?

[This section will include information on any planned reimbursement or payment to the participants. The site will complete this based on their guidelines.]

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 and be referred for further treatment, if necessary. The U.S. National Institutes of Health (NIH) does not have a mechanism to provide direct compensation for research-related injury, whether or not clinical trials insurance (CTI) is available.

[Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry clinical trials insurance (CTI), this must be indicated in the informed consent.]

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.*
- *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 NIH.*

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. Your site will share a summary of the results when they are ready to be presented. Your study staff can answer any questions you may have.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:

- **N**ame of the investigator or other study staff
- **T**elephone number of above

For questions about your rights as a research participant, contact:

- **N**ame or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- **T**elephone 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) (As appropriate)	Legal Representative's Signature and Date
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
Witness's Name (print) (As appropriate)	Witness's Signature and Date

APPENDIX III: SAMPLE CONSENT FORM FOR USE OF SAMPLES AND INFORMATION IN OTHER STUDIES

DIVISION OF AIDS
For protocol A5356

A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

SHORT TITLE FOR THE STUDY: Linezolid Dosing Strategies in DR-TB

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples”. The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository in the United States.

There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to insert limits if your regulatory authority imposes them.]*

When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan*. [Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

You will not be paid for your samples. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you.

You may withdraw your consent for research on your extra samples at any time and the samples will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

Research without Human Genetic Testing

If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved TB-related or HIV-related research that does not include human genetic testing (testing of material passed from parents to child that determines the makeup of the body and mind).

____ (initials) I understand and I agree to this storage and possible use of my samples.

OR

____ (initials) I understand but I do not agree to this storage and possible use of my samples.

APPENDIX IV: SUMMARY OF STUDY VISITS AND EVALUATIONS

DIVISION OF AIDS

For protocol A5356
A Phase II, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis

I. Summary of Study Schedule

The study staff can answer any questions you have about individual study visits, and 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.

Evaluation or Procedure	Screening	Entry	On Study Treatment Visits (at least 6 months)[3]	Post Study Treatment Visits (until study end)[4]	Extra Visits	Early Treatment or Study Discontinuation[7]
Consent & Contact Information	X					
HIV Status	X					
Medical History	X					
Medication History	X					
Clinical Assessments	X	X	X	X	X	X
Sputum Collection	X	X	X	X	possible	X
Blood Collection	X	X	X	X	X	X
Pregnancy Test	**X**	X	As clinically indicated			
Chest X-ray	X		X	X	possible	X
ECG	X	X		X		X
Peripheral Neuropathy Assessment	X		X	X	possible	X
Vision Screening		X		X	possible	X
Adherence Assessment / DOT			X	**As clinically indicated**	possible	X

II. Explanation of Visits

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. This will be approximately 14 days before study start.

Entry Visit: If you are able to join the study, you will enter the study and receive your treatment assignment.

Visits During Treatment: You will have visits at week 2, 4, 6, 8, 12, 16, 20, and 26. For any reason, if you will have 30 weeks to complete 26 weeks of treatment, you will have one more visit at week 30.

Post Study Treatment / Follow-up Visits: After completing 26 weeks of on-study treatment part, you will have post study treatment visits at weeks 38, 52, and 72. You may have an additional visit at week 42 as needed.

Extra Visits: You could be asked to come in for a visit for any of the following reasons:
- Suspected MTB IRIS
- Following Dose Reduction of LZD Due to Toxicity
- Suspected TB Treatment Failure or TB Recurrence: If the study drugs fail to treat your TB infection or if you have a recurrent TB infection.

Early Treatment or Study Discontinuation: If you discontinue study drug early, you will come in for an Early Treatment Discontinuation Visit, and you will be encouraged to continue on study and receive all evaluations through week 72. If you leave the study early, you will be asked to come in for an early study discontinuation. You will leave the study early if, after you enter the study, tests show that you do not have TB, or if your TB infection is not resistant to anti-TB drugs.

III. 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 blood 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 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 Status
If there is no record of your HIV status, a HIV test will be done. If a HIV test has to be done, you may have to sign a separate consent form before this is done. You will be told the result of the HIV test as soon as it is available.

Clinical Assessments, Medical and Medication History
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.

Sputum Collection
You will be asked to provide sputum samples at screening, entry, at all study visits, and, if you are suspected of TB treatment failure or TB recurrence, or if you stop the study medications or discontinue the study early. 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.

Blood Collection
Blood may be collected at most visits. Blood collected from you will be used for various tests during the study, including:

Hematology, chemistry, and liver function tests:
These are routine blood tests for safety. You will be asked not to eat or drink for a period of time before you have blood collected for these tests.

HIV viral load:
If you are living with HIV, this is a test that shows how much HIV is in your blood.

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

Pharmacokinetic (PK) sampling:
Special blood sampling called pharmacokinetic (or "PK") sampling is performed at various time points before and after study medications are taken to measure the amount or concentration of the study drugs in your blood. "PK" sampling helps researchers to learn more about how the amount of study medication changes in your blood over time.

TSH:
This is a test to measure the amount of thyroid stimulating hormone in your blood stream. It is used as a test to detect whether study medications are affecting your thyroid gland function.

Pharmacogenetic analyses:
If you agree, you will have one blood sample collected and stored to look at how your genes (material passed from parents to child that determines the makeup of the body and mind) affect your response to the study drugs.

Pregnancy Test: If you are a female who is able to become pregnant, you will be asked to give a small urine or blood sample for a pregnancy test.

Chest X-ray: You will have a chest X-ray at screening and at week 26, at any extra visit, and at early treatment or study discontinuation.

ECG: You will have an ECG to look at the electrical activity of your heart.

Peripheral Neuropathy Assessment: You will have a brief neuropathy check, for example, if you have any numbness, tingling, burning pain, sensitivity to touch.

Vision Screening: You will have a checkup of your eyes to look for signs and symptoms of optic neuritis, a condition where your optic nerve becomes inflamed, and to look for eye pain or other vision problems.

Directly Observed Therapy: Study staff will watch you take your study medication five or seven times per week *[Site to insert site-specific information about directly observed therapy]*.