A5356

Primary Statistical Analysis Plan

Version 5.0

11 April 2025

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

ClinicalTrials.gov Identifier: NCT05007821

Protocol Version 3.0

Created by:

Michelle A. Kendall

Statistical and Data Analysis Center
Harvard T.H. Chan School of Public Health

Table of Contents

Version History

Version	Changes Made	Date Finalized
1.0	Original Version	16 Nov 2021
2.0	The SAP was reviewed and revised after the protocol was amended to Version 2.0 (dated 28 April 2023): revised analysis sets and second secondary tolerability outcome measure as per the amended protocol; removed imputing 182 days for all visits falling within the week-26 visit window; clarified secondary analyses; added secondary objective analysis information that was inadvertently omitted; changed SAE table to EAE table; revised the level of detail in Adverse Events reports from HLT to PT; and removed "Tuberculous infections" from the Grade 1 or Higher Adverse Events reports and placed them in their own table.	25 Jul 2023
3.0	**Throughout:** Added back the numbering of the main sections **Section 5.1**: The efficacy analysis set was clarified; the SMC requested how baseline cultures were defined **Section 9.3**: Defined baseline cultures as screening/entry/week 2	15 Feb 2024
4.0	The SAP was reviewed after the protocol was amended to Version 3.0 (dated 16 July 2024); no revisions were required. **Sections 1.0**, **4.0**, **5.0**, and **7.0** were revised to remove the analysis of the interim efficacy objective.	17 Sept 2024
5.0	**Section 2.3:** Added all of the exploratory objectives and bolded the ones that are addressed in this SAP. **Section 4.2:** Revised LZD Dose Reduction Table to align with Protocol Version 3.0. **Section 4.3:** Added exploratory outcome measures. **Section 5.1:** Added Efficacy-Rapid-Test Analysis Set for a new supplementary analysis. **Section 6.1:** Added sensitivity and supplementary analyses for the First Primary Estimand. **Section 6.2:** Added two supplementary analyses for the Second Primary Estimand. **Section 7:** Expanded Objective 1.3.2 to analyze BDQ, DLM, and CFZ; and added two supplementary PK objectives for analyzing DLM and CFZ PK parameters data **New Section 8:** Added to address which exploratory objectives will be done at which time and corrected the analysis set for Objective 1.4.5.	11 Apr 2025

	Section 9: Clarified the statistical analysis timepoints in the table and, throughout, refined the table contents in response to study team review (in particular, expanded the AE summaries) **Section 10.1:** Added Section 10.1.4 to describe the BDQ and CFZ intensive PK analyses that were added to Objective 1.3.2.	

1 Introduction

1.1 Purpose

This Primary Statistical Analysis Plan (SAP) describes the primary and key secondary estimands and other secondary outcome measures that will address specific study objectives of the A5356 study. The Primary SAP includes general analytic approaches for all primary estimands, key secondary estimands, and other outcome measures in the primary manuscript(s) or submitted to ClinicalTrials.gov (regardless of the reporting timeline). The Primary SAP facilitates discussion of the statistical analysis components among the lead study investigators and statisticians, helping them agree on the statistical analyses to be performed and presented in the primary analysis report.

The separate Analysis Implementation Plan (AIP) provides detailed outlines of tables, figures, and coding descriptions.

A separate SAP will provide outlines of analyses for other objectives and outcome measures not included in the Primary SAP.

1.2 Version History

The SAP was reviewed in anticipation of the primary analysis of outcome measures through Week 26.

Section 2.3: Added all of the study objectives and bolded the ones that are addressed in this SAP.

Section 4.2: Revised LZD Dose Reduction Table to align with Protocol Version 3.0.

Section 4.3: Added exploratory outcome measures.

Sections 5.1 and 6.1: Added the Efficacy-Rapid-Test Analysis Set for another supplementary analysis of the First Primary Estimand. This new supplementary analysis will compare time to rapid test conversion between treatment arms in participants who were rapid test MTB-positive at baseline.

Section 6.1: Added another sensitivity analysis in which missing liquid culture results will be replaced by solid culture results.

Section 6.2: Added two supplementary analyses for the Second Primary Estimand. The first is time to first Grade 3 or higher AE by week 26 and the second is time to first Grade 3 or higher AE by 2 weeks after permanent discontinuation of study treatment.

Section 7: Changed to address secondary objectives only. Added two supplementary PK objectives to determine BDQ and CFZ PK parameters (objectives 1.3.6A and 1.3.6B) and corrected the analysis set for Objective 1.4.5 (MTB-IRIS should be analyzed within the Safety Analysis Set).

New Section 8: Added to address which exploratory objectives will be done at which time and corrected the analysis set for Objective 1.4.5.

Section 9: Clarified the statistical analysis timepoints in the table by changing “Through week 26” to “Outcome measures through week 26” and changing “After week 26” to “Outcome measures at weeks 38 and 72”. Throughout Section 8, refined table contents in response to study team review.

Section 10.1: Added Section 10.1.4 to describe the BDQ and CFZ intensive PK analyses, which follows the same approach as the LZD and DLM intensive PK analyses that were added to Objective 1.3.2.

2 Study Overview

2.1 Overview of Study Design

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 drug-resistant TB (DR-TB) comparing two dosing strategies of linezolid (LZD) combined with bedaquiline (BDQ), delamanid (DLM), and clofazimine (CFZ). The trial will randomize 132 participants aged 18 years and older, regardless of HIV status, who are recently diagnosed with pulmonary rifampicin resistant (RR-), multidrug resistant (MDR-), pre-extensively resistant (XDR-), or XDR-TB.

In this parallel group design, randomization will be 1:1 and balanced by site.

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 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 will be followed for TB outcomes and safety to 72 weeks.

2.2 Hypothesis

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.

2.3 Study Objectives

All objectives in the study protocol are provided below.

This Primary SAP addresses the bolded primary, secondary, and exploratory objectives below. The remaining study objectives will be addressed in subsequent statistical analysis plans.

Analysis of the study objectives below will be analyzed under a superiority framework.

2.3.1 Primary Objectives

1. **To compare time to sputum culture conversion in liquid media between treatment arms [Objective 1.2.1]**
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 [Objective 1.2.2]**

2.3.2 Secondary Objectives

1. **To compare proportion with sputum culture conversion in liquid media at 8, 16, 26, and 38 weeks between treatment arms [Objective 1.3.1]**
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 [Objective 1.3.2]**
3. **To compare the occurrence of treatment-related AEs between treatment arms [Objective 1.3.3]**
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 [Objective 1.3.4]**
5. **To determine LZD pharmacokinetic (PK) parameters for each LZD dosing strategy [Objective 1.3.5]**
6. **To determine DLM PK parameters within each treatment arm [Objective 1.3.6]**
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) [Objective 1.3.7]**

2.3.3 Exploratory Objectives

1. To investigate efficacy and safety between A5356 and contemporaneous DR-TB clinical trials [Objective 1.4.1]
2. To determine baseline prognostic risk factors for unfavorable TB treatment outcome [Objective1.4.2]
3. To investigate unfavorable TB treatment outcome and treatment-related AEs by baseline prognostic risk factors between treatment arms [Objective1.4.3]
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.
5. **To characterize the occurrence and signs and symptoms of MTB immune reconstitution inflammatory syndrome (MTB-IRIS) events [Objective 1.4.5]**
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 [Objective 1.4.6]
7. To describe exposure-outcome relationships between DLM PK parameters achieved and antimicrobial efficacy and DLM-related AEs [Objective 1.4.6]
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 [Objective 1.4.8]
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) [Objective 1.4.9]

2.4 Overview of Sample Size Considerations

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

The total sample size is 132 participants. The sample size calculations were based on a two-sided log rank test, with the alpha level set at 10% and 90% power, 104 weeks (24 months) to accrue, and 72 weeks (18 months) of follow-up. 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.

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%, if the observed proportion is 25% in 59 participants, then the 95% confidence interval would be sufficiently precise at a width of 0.216.

Accounting for the possibility of unevaluable participants without DR-TB or were otherwise deemed clinically ineligible for the study and interim analyses, sample size per arm was boosted by 10%. Thus, the total sample size is 66 participants per arm: 2 x 66 = 132 participants. See **Protocol Section 10.4** for additional details.

The final sample size was 138 participants to account for eligible participants who were unevaluable for the primary efficacy objective due to not having culture-confirmed TB.

2.5 Overview of Formal Interim Monitoring

The study will undergo interim review at least annually by the ACTG-appointed TB TSG Study Monitoring Committee (SMC). The first interim review will occur approximately six months after the enrollment of the first study participant or after 30 participants have enrolled into the study, whichever occurs first.

The 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 unacceptable proportions of participants with the following (analyzed separately).

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

Sputum culture results from week 16 is an important outcome measure since the protocol requires participants with an MTB-positive culture at week 16 to extend their treatment by an additional 12 weeks. If too many participants require extended TB treatment, then efficacy may be an issue.

To monitor results for the efficacy outcome measure, 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.

To monitor results for the tolerability outcome measure, 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 Representatives will determine whether the combined efficacy, tolerability, and safety data warrant discontinuation of the arm or the entire study. See **Protocol Section 10.5** for additional details.

3 Final Analysis Reports

There will be three analysis reports describing the analyses of the primary objective, secondary objectives, and exploratory objective 1.4.5. Exploratory objectives 1.4.1-1.4.4 and 1.4.6-1.4.9 as listed in **Section 2.3.3** will be analyzed later. The analyses will be described in separate statistical analysis plans.

1. Week 26 Primary Analysis Report: This report will include analyses of the primary objectives, secondary objectives, and exploratory objective 1.4.5 with outcome measures collected through week 26. This report will be finalized after results of the week 26 cultures for the last participant (primary completion date or PCD) have been entered into the study database and all queries have been resolved. This report will form the basis of the initial ClinicalTrials.gov submission, which will take place within one year after the PCD.

2. Week 72 Primary Analysis Report: This report will include analyses of the secondary objectives and exploratory objective 1.4.5 with outcome measures collected after week 26 and through week 72. This report will be finalized once the last participant has completed the week 72 study visit (study completion date), all queries have been resolved, and the study database closure/data lock has been completed. This report will form the basis of the second ClinicalTrials.gov submission, which will take place within one year after the study completion date.

3. Intensive Pharmacokinetic Final Analysis Report: This report will summarize the analysis of the PK secondary objectives related to the intensive PK sampling at the week 4 and LZD dose reduction visits. The intensive PK specimens will be batch-shipped after the last participant has completed his/her treatment regimen (could be as late as week 42). This report will be finalized once the PK parameters have been loaded into the study database and all queries have been resolved.
Note: This analysis report will be provided in multiple parts since the LZD and DLM intensive PK analyses are needed for the initial ClinicalTrials.gov submission and the timing of the other analyses (BDQ, CFZ, and LZD dose reduction) is uncertain

4 Outcome Measures

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

4.1 Primary Outcome Measures

These outcome measures will be included in the Week 26 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.

Efficacy Outcome Measures

The primary efficacy outcome measure is time from randomization date to collection date of the sputum corresponding to the first MTB-negative culture in liquid media (i.e., sputum culture conversion) up through week 26. Sputum culture conversion is defined as at least two consecutive MTB-negative liquid sputum cultures obtained at least 7 days apart with no subsequent positive cultures. Inability to produce sputum with

or without induction is considered an 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 liquid 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. If both liquid cultures are contaminated, indeterminate, and/or missing for reasons other than inability to produce sputum with or without induction, then the culture result is considered missing. Participants with missing cultures as defined above and cannot have their outcome measure determined based on available culture results through week 26 will be excluded from the analysis. There will be sensitivity analyses to assess how missing data was handled.

Primary Tolerability Outcome Measure

The primary tolerability outcome measure is the proportion of participants with permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death due to any cause by week 26.

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 **Protocol Section 8.0**, due to participant non-compliance with at least one anti-TB drug or study visits, or due to participant request.

4.2 Secondary Outcome Measures

Unless otherwise noted, these outcome measures will be included in the Week 26 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.

Secondary Efficacy Outcome Measures

The first secondary efficacy outcome measures are proportions of participants with sputum culture conversion in liquid media at week 8, week 16, week 26, and week 38.

- These outcome measures will assess protocol objective 1.3.1.
- The definition of sputum culture conversion is as given in **Section 4.1**.
- The outcome measures collected at week 8, week 16, and week 26 will be included in the Week 26 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.
- The outcome measure collected at week 38 will be included in the Week 72 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after the study completion date.

The second secondary efficacy outcome measures are proportions of participants with unfavorable TB treatment outcome at week 26, week 38 (for those who extend TB treatment due to an MTB-positive culture at week 16), and week 72.

- These outcome measures will assess protocol objective 1.3.4.
- Unfavorable TB treatment outcome (absence of cure) is defined as meeting one or more of the following as laid out in **Protocol Section 6.3.18**.
    - Participant with confirmed microbiologic TB treatment failure defined as the presence of an 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.

- 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 positive sputum MTB culture at their last study visit, whether confirmed by a second sputum sample or not, unless determined to have been re-infected with a new strain of *Mycobacterium tuberculosis*
- 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

- The outcome measure collected at week 26 will be included in the Week 26 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.
- The outcome measures collected at week 38 and week 72 will be included in the Week 72 Primary Analysis Report and submitted to ClinicalTrials.gov within one year after the study completion date.

Secondary Tolerability Outcome Measures

The first secondary tolerability outcome measure is the proportion of participants with permanent discontinuation of LZD due to AEs, intolerance, or death by week 26. This outcome measure will assess protocol objective 1.3.2. The definition of intolerance is as given in **Section 4.1**.

The second secondary tolerability outcome measure is the proportion of participants with temporary discontinuation of LZD for any reason by week 26. This outcome measure will assess protocol objective 1.3.2.

The third secondary tolerability outcome measure is the proportion of participants with dose reduction of LZD by week 26. This outcome measure will assess protocol objective 1.3.2.

LZD Dose Reduction Table from Protocol Section 8.0:

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

Secondary Safety Outcome Measure

The secondary safety outcome measure is the proportion of participants with treatment-related AEs as determined by the site by week 26. This outcome measure will assess protocol objective 1.3.3.

Secondary Pharmacokinetic Outcome Measure

The first secondary pharmacokinetic outcome measure is LZD PK parameters in those participants completing the week 4 intensive PK sampling visit.

- This outcome measure will assess protocol objective 1.3.5.
- This outcome measure will be included in the Week 4 Pharmacokinetic Final Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.

The second secondary pharmacokinetic outcome measure is DLM PK parameters in those participants completing the week 4 intensive PK sampling visit.

- This outcome measure will assess protocol objective 1.3.6.
- This outcome measure will be included in the Week 4 Pharmacokinetic Final Analysis Report and submitted to ClinicalTrials.gov within one year after PCD.

Secondary Adherence Outcome Measure

The secondary adherence outcome measure is proportion of doses taken up through week 26. This outcome measure will assess protocol objective 1.3.7.

4.3 Exploratory Outcome Measures

4.3.1 Week 26 and Week 72 Primary Analysis Reports

- Exploratory Objective 1.4.5
    - The outcome measure is MTB-IRIS diagnosis and associated signs and symptoms in HIV/TB co-infected participants.
    - This outcome measure will be included in the Week 26 Primary Analysis Report and the Week 72 Primary Analysis Report but will not be submitted to ClinicalTrials.gov.

4.3.2 Subsequent Final Analysis Reports

- Exploratory Objective 1.4.1: culture conversion by week 26 and occurrence of permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death by week 26 (i.e., the primary outcome measures), with the equivalent data from contemporaneous DR-TB clinical trials
- Exploratory Objective 1.4.2: unfavorable TB treatment outcome by week 72
- Exploratory Objective 1.4.3: unfavorable TB treatment outcome by week 72 and treatment-related AEs by week 26
- Exploratory Objective 1.4.4: occurrence of resistance to LZD, BDQ, DLM, and CFZ by week 26 (by week 38 for those who extend treatment by 12 weeks) and by week 72 (batch tested after study completion)
- Exploratory Objectives 1.4.6-1.4.8: PK parameters, culture conversion, TB cure, and treatment-related AEs by week 26
- Exploratory Objective 1.4.9: occurrence of polymorphisms in human genes and PK parameters, culture conversion, TB cure, and treatment-related AEs by week 26

5 General Considerations

5.1 Analysis Sets

Efficacy: All randomized participants who had at least one MTB-positive sputum culture at baseline (based on cultures from Screening, Entry, and Week 2 as per SMC request) except those who did not have pulmonary DR-TB or were otherwise clinically ineligible for the study (e.g., those with DST pending at study entry who later showed resistance to one or more study drugs)

Efficacy-Extended-Treatment: Participants in the Efficacy analysis set who were required to extend study treatment by 12 weeks

Efficacy-Rapid-Test: All randomized participants who had at least one MTB-positive rapid test result at baseline (based on Xpert, Hain, and other rapid test results from Screening, Entry, and Week 2 as per SMC request) except those who did not have pulmonary DR-TB or were otherwise clinically ineligible for the study (e.g., those with DST pending at study entry who later showed resistance to one or more study drugs)

Safety: All randomized participants who took at least one dose of study drug

PK-Wk4: Participants who were deemed eligible for the week 4 intensive PK analysis

PK-LZD: Participants who were deemed eligible for the LZD dose reduction due to adverse events intensive PK analysis

5.2 Day 0 and Visit Windows

Time on study is based on the date of randomization (Day 0).

The window for study visits before week 26 is ±7 days as defined by the protocol. For example, the visit window for the week 26 study visit is [175, 189] days.

The window for the week 72 study visit is [476, 532] days, which expands the visit window to ±28 days to allow for early and delayed end of follow-up visits. For time-to-event analyses through 72 weeks of follow-up, events and censoring falling within this visit window will be imputed at exactly 72 weeks = 504 days.

5.3 Summarizing Variables

No statistical comparisons of baseline characteristics between randomized treatment arms are planned.

- Discrete variables will be summarized by frequencies and percentages.
- Continuous variables will be summarized by at least n, median, first and third quartiles, and number missing.
- Time-to-event variables will be summarized using Kaplan-Meier methods. Censoring details vary by analysis; see **Section 6** and **Section 7** for details.

5.4 Analysis Adjustments

- No adjustments for multiple comparisons are planned

5.5 Strategies for Handling Intercurrent Events

These definitions are taken from **International Council for Harmonisation (ICH) E9 (R1) Addendum: Statistical Principles for Clinical Trials, Section A.3.2**.

Hypothetical strategy: A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined. If a hypothetical strategy is proposed, it should be made clear what hypothetical scenario is envisaged.

Treatment policy strategy: The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the

intercurrent event occurs. This strategy cannot be implemented for intercurrent events that are terminal events (e.g., death), since values for the variable after the intercurrent event do not exist.

While on treatment strategy: Response to treatment prior to the occurrence of the intercurrent event is of interest.

6 Primary and Secondary Estimands and Estimation

6.1 Primary Estimands

6.1.1 First Primary Estimand

Primary Objective 1.2.1: To compare time to sputum culture conversion in liquid media between treatment arms	
Estimand description	Hazard ratio of sputum culture conversion among adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB who were prescribed LZD 600 mg daily for 26 weeks or LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks
Treatment	LZD 600 mg daily for 26 weeks versus LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks
Target population	Analysis set
Adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB	Efficacy
Variable	Outcome measure
Time from TB treatment initiation to sputum culture conversion up through 26 weeks of treatment Sputum culture conversion is defined as at least two consecutive MTB-negative liquid sputum cultures obtained at least 7 days apart with no subsequent positive liquid sputum cultures	Time from randomization date to collection date of the sputum corresponding to the first MTB-negative liquid culture through week 26 Inability to produce sputum with or without induction is considered an MTB-negative culture Culture results are defined: 1. MTB positive at a visit if at least one of the two liquid cultures is MTB positive 2. MTB negative at a visit if both liquid cultures are MTB negative or if one liquid culture from the visit is MTB negative and the other is missing or contaminated Participants who do not culture convert will be censored at their last non-MTB-negative liquid culture
Handling of intercurrent events	Handling of missing data

The following intercurrent events are relevant to the estimand: 1. Failure to start TB drugs *All observations will be used to determine the variable (treatment policy strategy)* *2.* Premature discontinuation of all TB drugs for any reason except death *All observations will be used to determine the variable (treatment policy strategy)* 3. Death due to trauma *Observations will be censored at the last liquid culture (while on treatment strategy)* 4. Death due to all causes except trauma and without prior culture conversion through week 26 *Observations will be censored at week 26; this recognizes that they had the worst possible outcome through 26 weeks (hypothetical strategy; i.e., had the individual not died, they would have remained culture positive through 26 weeks)*	If the first MTB-negative culture result is at week 26, then sputum culture conversion will be met If both liquid cultures are contaminated, indeterminate, and/or missing at a visit, then the culture result is considered missing at the visit Participants with missing culture data at every visit will be excluded from the analysis Participants who do not culture convert by week 26 will be censored at the sputum collection date for the last non-missing liquid culture result
Population-level summary measure	**Analysis approach**
Hazard ratio of sputum culture conversion through 26 weeks	Hazard ratio with two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test Kaplan-Meier curves of time to sputum culture conversion will be created. Within-arm Kaplan-Meier estimates of probability of sputum culture conversion through week 26 will be calculated with two-sided 95% confidence intervals using standard errors based on Greenwood's formula

Subgroup Analysis

As required by NIH and ACTG, there will also be an analysis of this estimand by sex and site-specific race (will use country if site-specific race/ethnicity is not available) with treatment interactions tested using a Cox proportional hazards regression analysis.

Sensitivity Analyses

There will be three sensitivity analyses to assess the effect of missing liquid cultures. In the first, participants with missing liquid cultures at every visit will be considered not culture converted at week 26. In the second, they will be considered culture converted at week 26. In the third, visits with missing liquid culture results will be replaced with any non-missing solid culture results before culture conversion status is determined.

A fourth sensitivity analysis will assess the effect of considering contaminated and indeterminate cultures as missing. These cultures will be considered MTB positive.

A fifth sensitivity analysis will exclude participants who fail to initiate study treatment.

Supplementary Analyses

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.

AFB smear and cavitary size are the strongest predictors for culture conversion and favorable TB treatment outcome. If there is evidence of significant differences in baseline AFB smear positivity and/or baseline aggregated cavitary size between treatment arms, a Cox proportional hazards regression analysis adjusting for one or both of these variables will be undertaken.

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.

Sputum culture conversion based on both solid and liquid cultures will also be analyzed using the same approaches for handling intercurrent events and missing data and the same analysis approach as outlined above. In this supplementary analysis, a participant will be considered MTB-culture positive at a visit if at least one solid and/or liquid culture result is MTB-positive.

Since some participants did not have an MTB-positive culture at baseline (i.e., at Screening, Entry, or Week 2), liquid culture results will be replaced by Xpert, Hain, or other rapid test results at every visit. This supplementary analysis will compare time to rapid test conversion by treatment arm in the Efficacy-Rapid-Test analyses set, using similar approaches for handling intercurrent events and missing data and the same analysis approach as outlined above.

6.1.2 Second Primary Estimand

Primary Objective 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	
Estimand description	Probabilities of permanently discontinuing at least one anti-TB drug due to AEs, intolerance, or death through 26 weeks of TB treatment among adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB taking LZD 600 mg daily for 26 weeks or LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ
Treatment	LZD 600 mg daily for 26 weeks versus LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks

Target population	Analysis set
Adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB	Safety
Variable	**Outcome measure**
Permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death through 26 weeks of TB treatment	Permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death by week 26 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 **Protocol Section 8.0**, due to participant non-compliance with at least one anti-TB drug or study visits, or due to participant request
Handling of intercurrent events	**Handling of missing data**
The following intercurrent event is relevant to the estimand:	Participants who complete 26 weeks of study treatment will be censored at week 26

1. Premature discontinuation of all TB drugs for reasons other than AEs, intolerance, or death *Observations will be censored at treatment discontinuation (while on treatment strategy)*	
Population-level summary measure	Analysis approach
Probabilities of permanently discontinuing at least one anti-TB drug due to AEs, intolerance, or death through 26 weeks after TB treatment initiation	Within-arm Kaplan-Meier estimates of probability of permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death through week 26 will be calculated with two-sided 95% confidence intervals using standard errors based on Greenwood's formula

Supplementary Analysis

Differences between treatment arms will be tested 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 the same approaches for handling intercurrent events and handling missing data as above. A hazard ratio with a two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to sputum culture conversion will also be created.

Time to permanent treatment discontinuation of at least one anti-TB drug due to AEs, intolerance, or death by sex and site-specific race (will use country if site-specific race/ethnicity is not available), with treatment interactions, will be examined using a Cox proportional hazards regression analysis.

6.2 Secondary Estimands

6.2.1 First Secondary Estimand

Secondary Objective 1.3.3: To compare the occurrence of treatment-related AEs between treatment arms	
Estimand description	Difference in probabilities of experiencing treatment-related AEs through 26 weeks of TB treatment among adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB taking LZD 600 mg daily for 26 weeks or LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ
Treatment	LZD 600 mg daily for 26 weeks versus LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks
Target population	Analysis set
Adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB	Tolerability
Variable	Outcome measure
Treatment-related AEs through 26 weeks of TB treatment	Treatment-related AEs by week 26
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Premature discontinuation of all TB drugs for reasons other than treatment-related AEs *Observations will be censored at treatment discontinuation (while on treatment strategy)*	Participants who do not report a treatment-related AE will be censored at week 26

2. Non-treatment-related death *Observations will be censored at last clinic visit (hypothetical strategy; i.e., had the individual not died, they would have not experienced treatment-related AEs through 26 weeks) Note: Treatment-related deaths are included in the outcome measure*	
Population-level summary measure	Analysis approach
Difference in probabilities of experiencing treatment-related AEs through 26 weeks of TB treatment	Within-arm Kaplan-Meier estimates of probability of experiencing a treatment-related AE through week 26 will be calculated with two-sided 95% confidence intervals using standard errors based on Greenwood's formula. Treatment differences will be tested using a *Z* test

Supplementary Analyses

An analysis of time to first treatment-related AE by week 26 will be undertaken using the approaches for handling intercurrent events and missing data as above. A hazard ratio with a two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to sputum culture conversion will also be created.

An analysis of time to first Grade 3 or higher AE (or only for hemoglobin, time to first 25% decline in hemoglobin from baseline) by week 26 will be undertaken using the approaches for handling intercurrent events and missing data as above. A hazard ratio with a two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to sputum culture conversion will also be created.

An analysis of time to first Grade 3 or higher AE (or only for hemoglobin, time to first 25% decline in hemoglobin from baseline) by 2 weeks after permanent discontinuation of study treatment will be undertaken using the approaches for handling intercurrent events and missing data as above. A hazard ratio with a two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to sputum culture conversion will also be created.

6.2.2 Second Secondary Estimand

Secondary Objective 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	
Estimand description	Difference in probabilities of unfavorable TB treatment outcome at 26, 38, and 72 weeks among adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB who were prescribed LZD 600 mg daily for 26 weeks or LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks
Treatment	LZD 600 mg daily for 26 weeks versus LZD 1200 mg daily for 4 weeks then 3x per week thereafter through 26 weeks, both with a backbone of BDQ+DLM+CFZ for 26 weeks
Target population	Analysis sets
Adults with pulmonary RR-, MDR-, pre-XDR-, or XDR-TB	Efficacy Efficacy-Extended-Treatment
Variables	Outcome measures
Unfavorable TB treatment outcome at 26, 38, and 72 weeks after TB treatment initiation	Unfavorable TB treatment outcome at weeks 26, 38, and 72 (Efficacy analysis set) Unfavorable TB treatment outcome at week 38 (Efficacy-Extended-Treatment analysis set)

	Unfavorable TB treatment outcome is defined as meeting one or more of the following as detailed in **Section 4.2**: 1. Participant with confirmed microbiologic TB treatment failure 2. Participants who fail to complete study treatment or require extension of study treatment beyond the study-prescribed treatment duration due to clinically inadequate response 3. Participants who had a positive sputum MTB culture at their last study visit 4. Participants who die from any cause during study treatment, except from violent or accidental cause 5. Participants failing to complete study treatment and not assessable at the end of the follow-up period
Handling of intercurrent events	Handling of missing data
The following intercurrent events are relevant to the estimand: 1. Failure to start TB drugs *All observations will be used to determine the variable (treatment policy strategy)* 2. Premature discontinuation of all TB drugs for any reason *All observations will be used to determine the variable (treatment policy strategy)*	Participants without an unfavorable TB treatment outcome at week 26, 38, or 72 will be censored at the respective week Participants with no TB treatment status determinations by week 26, 38, or 72 will be excluded from the respective analysis
Population-level summary measures	Analysis approach
Differences in probabilities of unfavorable TB treatment outcome at 26, 38, and 72 weeks of TB treatment	Within-arm Kaplan-Meier estimates of probability of unfavorable TB treatment outcome through weeks 26, 38, and 72 will be calculated with two-sided 95% confidence intervals using standard errors based on Greenwood's formula. Treatment differences will be tested using a Z test

Sensitivity Analyses

There will be two sensitivity analyses to assess the effect of missing TB treatment status determinations. In the first, participants with missing TB treatment status determinations will be considered as having an unfavorable TB treatment status. In the second, they will be considered as not having an unfavorable TB treatment status.

Supplementary Analyses

An analysis of time to unfavorable TB treatment outcome will be undertaken using the approaches for handling intercurrent events and missing data as above. A hazard ratio with a two-sided 95% Wald confidence interval will be calculated. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to sputum culture conversion will also be created.

Unresolved cavities are a strong predictor for relapse. If there is evidence of a significant difference in unresolved cavities at week 26 between treatment arms, analyses testing for the independence of unresolved cavitary lesions at week 26 and unfavorable TB treatment outcome at weeks 26, 38, and 72 will be undertaken using Chi-square tests of independence.

An additional supplementary analysis will exclude participants who fail to initiate study treatment.

7 Analysis Plan for Other Secondary Objectives

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

- Analysis sets: Efficacy and Efficacy-Extended-Treatment
- Outcome measures: Sputum culture conversion in liquid media by week 8, week 16, week 26, and week 38
- Handling of intercurrent events and handling of missing data will follow the approach as outlined in the first primary estimand
- Population-level summary measures: Differences in probabilities of culture conversion through weeks 8, 16, 26, and 38
- Analysis approach:
    - Within-arm Kaplan-Meier estimates of probability through weeks 8, 16, 26, and 38 will be calculated with two-sided 95% confidence intervals using standard errors based on Greenwood's formula
    - Treatment differences will be tested using Z tests
- Supplementary analyses:
    1. Proportions of participants with sputum culture conversion through weeks 2, 4, 6, 12, 20, 30, 42, 52, and 72 will be summarized and compared using an approach similar to that used above
    2. Sputum culture conversion will also be analyzed based on solid and liquid cultures

Objective 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

This objective was expanded to also examine BDQ, DLM, and CFZ. The analyses outlined below for LZD (except the dose reduction analysis) will be repeated for each of BDQ, DLM, and CFZ.

- Analysis set: Safety
- Outcome measures:
    1. Permanent discontinuation of LZD due to AEs, intolerance, or death by week 26
    2. Temporary discontinuation of LZD for any reason by week 26
    3. Dose reduction of LZD by week 26
- Handling of intercurrent events and handling of missing data will follow the approach as outlined in the second primary estimand
- Population-level summary measures:
    1. Difference in probabilities of permanent discontinuation of LZD due to AEs, intolerance, or death through 26 weeks after TB treatment initiation
    2. Difference in probabilities of temporary discontinuation of LZD for any reason through 26 weeks after TB treatment initiation

3. Difference in probabilities of dose reduction of LZD through 26 weeks after TB treatment initiation

- Analysis approach will follow the approach as outlined in objective 1.3.1
- Supplementary analyses:
  1. Time to permanent discontinuation of LZD due to AEs, intolerance, or death will be analyzed using a hazard ratio with a two-sided 95% Wald confidence interval. Treatment differences will be tested using a log rank test. Kaplan-Meier curves of time to permanent discontinuation of LZD due to AEs, intolerance, or death will also be created
  2. Time to temporary discontinuation of LZD due to AEs, intolerance, or death will be analyzed using the same approach as given in Supplementary Analysis #1
  3. Time to dose reduction of LZD will be analyzed using the same approach as given in Supplementary Analysis #1

Objective 1.3.5: To determine LZD pharmacokinetic (PK) parameters for each LZD dosing strategy
Objective 1.3.6: To determine DLM PK parameters within each treatment arm

- Analysis set: PK-Wk4
- Outcome measures: Minimum concentration (C_{min}), maximum concentration (C_{max}), time of maximum concentration (T_{max}), area under the concentration-time curve (AUC), apparent oral clearance (CL/F), and (if available) elimination half-life ($T_{1/2}$) and volume of distribution (Vd)
  - LZD
  - DLM and its metabolite
- Population-level summary measures: n, median, first and third quartiles, and minimum and maximum values
- Analysis approach: Summary of the PK parameters
- Supplementary analyses: Treatment differences will be tested using Wilcoxon rank sum tests

Supplementary Objectives to objective 1.3.6:

- Objective 1.3.6A: To determine BDQ PK parameters within each treatment arm
- Objective 1.3.6B: To determine CFZ PK parameters within each treatment arm

Analysis of supplementary objectives 1.3.6A-1.3.6B will follow the approach for objectives 1.3.5 and 1.3.6.

Objective 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)

- Analysis set: Tolerability
- Outcome measure: Proportion of DOT doses taken through week 26
- Handling of intercurrent events:
  - Premature discontinuation of all TB drugs *All observations will be used to determine the variable (treatment policy strategy)*
- Handling of missing data: Days on study from end of treatment to week 26 will be missed doses
- Population-level summary measure: Difference in proportions of participants who took >90% of expected DOT doses (days during temporary holds will be excluded [i.e., doses not expected])
- Analysis approach: Treatment differences will be tested using Fisher's Exact Tests
- Supplementary analysis: Participants who required study treatment beyond 26 weeks will be analyzed with time due to protocol-required temporary treatment holds removed. Treatment differences will be tested using Fisher's Exact tests

8 Analysis Plan for Exploratory Objectives

8.1 Week 26 and Week 72 Primary Analysis Reports

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

- Analysis set: Safety
- Outcome measures: MTB-IRIS diagnosis and associated signs and symptoms
- Analysis approach: Listing of outcome measures

8.2 Subsequent Final Analysis Reports

The analyses of Exploratory Objectives 1.4.1-1.4.4 and 1.4.6-1.4.9 will be addressed in subsequent SAPs.

9 Week 26 and Week 72 Primary Analysis Report Contents

General contents of the two primary analysis reports are detailed in the table below. Specific contents are detailed in the subsections that follow.

	Week 26 Primary Analysis Report	**Week 72 Primary Analysis Report**
Flow Diagram	Included	Excluded
Study Entry/Accrual	Included	Excluded
Baseline Characteristics	Included	Excluded
Study Retention	Through week 26	Through week 72
Study Treatment Status	Through week 26	Through week 72
Study Treatment Adherence	Through week 26	Through week 72
Pregnancies	Through week 26	Through week 72
MTB-IRIS	Through week 26	Through week 72
Adverse Events	Through week 26	Through week 72
Mortality	Through week 26	Through week 72
TB Outcomes	Through week 26	Through week 72
Statistical Analyses	Outcome measures through week 26	Outcome measures at weeks 38 and 72

The contents below will be summarized by randomized treatment arm.

9.1 Flow Diagram

To illustrate flow of all participants from screening (if available) to randomization and into the efficacy and safety analysis set populations, including reasons individuals were excluded

9.2 Study Entry/Accrual

- Accrual by site
- Figure: Accrual by month

9.3 Baseline Characteristics

- Age (continuous and <30 years versus ≥30), sex at birth, gender, country, and (if available) site-specific race

- BMI (continuous and <17 kg/m^2 versus ≥17)
- HIV-1 status
- For participants with HIV,
  - CD4+ count (continuous and <250 cells/mm^3 versus ≥250)
  - HIV-1 RNA (≤lower limit of quantification [LLOQ] versus >LLOQ)
  - For participants with HIV-1 RNA >LLOQ, log_{10} HIV-1 RNA copy number
  - ARV regimen (at study entry or within 30 days after study entry)
  - Time on ARVs in relation to study entry
- Type of TB (RR-, MDR-, pre-XDR-, or XDR-TB)
- TB drug resistance profile by type of TB
- AFB smear grade (highest grade of the two smear results)
- Sputum culture results (based on screening, entry, and week 2 per SMC request):
  - Liquid: summary result based on all cultures, with shortest time to detection based on all positive cultures
  - Solid: summary result based on all cultures with largest MTBC colony count based on all positive cultures
  - Overall: summary result based on all cultures
- Chest x-ray findings:
  - Presence of cavitary lesions and, in participants with cavitary lesions, estimated aggregate cavity size (continuous and <4 cm versus ≥4)
  - Extent of TB disease (i.e., limited to one lobe or region, unilateral, bilateral, or diffuse)
- History of prior TB diagnoses (yes versus no) and, if yes, number of prior TB diagnoses
- Medical history of peripheral neuropathy, optic neuropathy, cardiac disorders/diseases, psychiatric conditions, diabetes, alcoholism, drug addictions (each summarized as yes versus no)
- Number of concomitant medications ongoing at study entry

9.4 Study Retention

- Reasons off study
- Time to last clinic visit:
  - Overall
  - Within participants who completed the study
  - Within participants who prematurely discontinued the study

9.5 Study Treatment

9.5.1 Study Treatment Status

- Participants who did not start randomized treatment, with reasons
- Participants who temporarily discontinued study treatment (defined as temporarily discontinued at least one study drug)
  - Total number of temporary discontinuations
  - Number of participants who had at least one temporary discontinuation
  - Number of temporary discontinuations per participant
  - Summary of lengths of temporary discontinuations
  - Figure: Time to first temporary discontinuation
  - Reasons for temporary discontinuations
- Participants who temporarily discontinued LZD
  Note: The following will be repeated for each of the other study drugs: BDQ, DLM, and CFZ

  - Total number of temporary discontinuations of LZD
  - Number of participants who had at least one temporary discontinuation of LZD
  - Number of temporary discontinuations of LZD per participant
  - Summary of lengths of temporary discontinuations of LZD
  - Figure: Time to first temporary discontinuation of LZD
  - Reasons for temporary discontinuations of LZD
- Participants who had dose reductions of LZD
  - Total number of LZD dose reductions
  - Number of participants who had at least one LZD dose reduction
  - Number of LZD dose reductions per participant
  - Figure: Time to first LZD dose reduction
  - Reasons for LZD dose reduction
- Participants who were required to extend study treatment by 12 weeks
- Reasons off study treatment
- Time to study treatment discontinuation:
  - Overall
  - Within participants who completed study treatment
  - Within participants who prematurely discontinued study treatment
  - Within participants who were required to extend study treatment by 12 weeks

9.5.2 Study Treatment Adherence

- TB and ARV adherence assessment questionnaires summary at each study week
- Proportion of expected DOT doses taken based on estimated number of DOT doses (continuous and dichotomized at >90% and >95%) at each study week
- Figure: Proportion of DOT doses taken at each study week, overall and by whether participants required extended study treatment beyond 26 weeks
  Note: Temporary holds and discontinuations of study treatment will be excluded from the expected doses.
- **Secondary Adherence Analysis [Objective 1.3.7]:** Summary of analysis comparing treatment arms for proportions of participants who took >90% of expected DOT doses through week 26 (see **Section 7**)

9.6 Safety

9.6.1 Pregnancies

- Participants who become pregnant while on study
- Additional data summarized includes treatment arm, weeks from study entry to estimated date of conception, weeks from estimated date of conception to last visit, treatment status at estimated date of conception, weeks from study entry to treatment discontinuation, and pregnancy outcome

9.6.2 MTB-IRIS

- Participants with MTB-IRIS
- Additional data summarized includes treatment arm, weeks from study entry to date of diagnosis, treatment status at diagnosis, and weeks from study entry to study treatment discontinuation
- **Exploratory Analysis [Objective 1.4.5]:** The analysis will consist of listing signs and symptoms reported in participants with MTB-IRIS (see **Section 7**)

9.6.3 Adverse Events

Note: Need to take into account the possibility of double-reporting (e.g., liver function test AEs or drug-induced liver injury diagnoses; hemoglobin AEs or anemia diagnoses; lactate AEs or lactic acidosis diagnoses; neutrophil AEs or neutropenia diagnoses; platelet AEs or thrombocytopenia diagnoses; creatinine clearance AEs or estimated glomerular filtration rate (eGFR) AEs; and paraesthesia and hypoesthesia AEs or peripheral neuropathy diagnoses)

- All Grade 1 or higher reportable AEs by MedDRA Preferred Term (PT) and toxicity grade, grouped by System Organ Class (SOC)
  Note: Exclude "Tuberculous infections" (includes TB-IRIS), Creatinine/Creatinine clearance AEs graded based only on change from baseline)
- All Grade 1 or higher reportable Tuberculous infections AEs by MedDRA PT and toxicity grade, grouped by SOC
- All AEs that led to a change in study treatment regardless of grade by MedDRA PT and toxicity grade, grouped by SOC
- For treatment-related AEs, summary table providing:
  - Related to which study drugs
  - AE status (not resolved, resolved, etc.)
  - AE duration
  - Study treatment modification (e.g., drug withdrawn, drug rechallenge successful, drug rechallenge unsuccessful, etc.)
  - AE recurrence status
- EAEs by MedDRA PT and toxicity grade, grouped by SOC
- Peripheral neuropathy screening findings by week, through week 26
- ECG results and variants for Grade 2 or higher QTcF interval prolongation
- Optic neuritis symptoms in participants diagnosed with optic neuritis
- Creatinine change from baseline summary (to replicate what was done in A5362 CLO-FAST)
- Listing of all creatinine and creatinine clearance results for participants with creatinine clearance AEs
- Figures: Line plots of values over time (from screening to end of study treatment) by participant, one panel per treatment arm
  Note: (1) Add lines indicating Grade 1, Grade 2, Grade 3, and Grade 4; and (2) Lab values graded in relation to ULN need to be presented as value/ULN
  - Hemoglobin
  - Absolute neutrophil count
  - Platelet count
  - ALT
  - Total bilirubin
  - Lactate
  - Creatinine clearance
  - QTcF interval
- Figures: Time to first occurrence of the following targeted AEs
  Note: Present as four subgroups as determined by treatment arm and whether the participant had the AE at study entry
  - Grade 1 or higher optic neuritis AE
  - Grade 2 or higher peripheral neuropathy AE

  Note: Create a second figure that presents four subgroups as determined by treatment arm and whether the participant had a LZD dose reduction due to anemia
  - Grade 2 or higher hemoglobin AE
  - Grade 2 or higher absolute neutrophil count AE

- Grade 2 or higher platelet count AE
- Grade 2 or higher ALT AE
- Grade 2 or higher total bilirubin AE
- Grade 2 or higher lactate AE
- Grade 1 or higher creatinine clearance or eGFR AE
- Grade 2 or higher QTcF interval prolongation AE
- Grade 1 or higher neuropsychiatric AE (MedDRA Psychiatric SOC)
- Grade 1 or higher treatment-limiting AEs

9.6.4 Mortality

- Deaths, including primary cause diagnosis and category
- Additional data summarized includes treatment arm, weeks from study entry to date of death, treatment status at death, and weeks from study entry to date study treatment discontinued

9.7 TB Outcomes

- AFB smears at each study week
- Sputum culture results at each post-baseline study week
  - Liquid: summary results based on two cultures with shortest time to detection based on all positive cultures
  - Solid: summary result based on two cultures with largest MTBC colony count based on all positive cultures
  - Overall: summary result based on four cultures
- Phenotypic and genotypic drug susceptibility testing (DST) results at each study week
- Unresolved cavitary lesions at week 26 within participants with cavitary lesions at baseline
- TB treatment outcome at each study week

9.8 Statistical Analyses

9.8.1 Efficacy

- Number of participants with intercurrent events and timing (one table per outcome measure)
- **Primary Efficacy Analysis [Objective 1.2.1]:** The analysis will examine time to sputum liquid culture conversion (see **Section 6.1.1**)
- **Secondary Efficacy Analysis [Objective 1.3.1]:** The analysis will examine proportions of participants with sputum liquid culture conversion at weeks 8, 16, 26, and 38 (see **Section 7**)
- **Secondary Efficacy Analysis [Objective 1.3.4]:** The analysis will examine proportions of participants with unfavorable TB treatment outcome at weeks 26, 38, and 72 (see **Section 6.2.2**)

9.8.2 Tolerability

- Number of participants with intercurrent events and summary of the timing (one table per outcome measure)
- **Primary Tolerability Analysis [Objective 1.2.2]:** The analysis will summarize proportions of participants with permanent discontinuation of at least one anti-TB drug due to AEs, intolerance, or death by week 26 within each treatment arm (see **Section 6.1.2**)
- **Secondary Tolerability Analysis [Objective 1.3.2]:** The analysis will examine proportions of participants with permanent discontinuation of LZD due to AEs, intolerance, or death by week 26 within each treatment arm (see **Section 7**)

Note: This analysis will be repeated for each of the other study drugs: BDQ, DLM, and CFZ

- **Secondary Tolerability Analysis [Objective 1.3.2]:** The analysis will examine proportions of participants with temporary discontinuation of LZD for any reason (see **Section 7**)
  Note: This analysis will be repeated for each of the other study drugs: BDQ, DLM, and CFZ
- **Secondary Tolerability Analysis [Objective 1.3.2]:** The analysis will examine proportions of participants who had LZD dose reductions (see **Section 7**)

9.8.3 Safety

- Number of participants with intercurrent events and timing
- **Secondary Safety Analysis [Objective 1.3.3]:** The analysis will examine proportions of participants with treatment-related AEs (see **Section 6.2.1**)

10 Intensive Pharmacokinetic Final Analysis Report Contents

The contents below will be summarized by randomized treatment arm.

10.1 Week 4 Intensive PK

10.1.1 Flow Diagram

To illustrate flow of all participants from randomization into the PK-Wk4 analysis populations (i.e., intensive PK sampling versus abbreviated PK sampling), including reasons individuals were excluded

10.1.2 Baseline Characteristics

Two sets of tables will be created:

1. All randomized participants summarized by Week 4 PK analysis status (i.e., in PK substudy versus not)
2. All participants in the Week 4 PK analysis by intensive PK versus abbreviated PK sampling

- Age, sex at birth, gender, country, and (if available) site-specific race
- BMI
- HIV-1 status and, for participants with HIV, ARV regimen at study entry or within 30 days after study entry
- Type of TB (RR-, MDR-, pre-XDR-, or XDR-TB)
- AFB smear grade (highest grade of the two smear results)
- Chest x-ray findings: presence of cavitary lesions and, in participants with cavitary lesions, estimated aggregate cavity size
- Concomitant medications (all or partial list to be determined by pharmacologist)

10.1.3 LZD, DLM, and DLM Metabolite Intensive PK

- **Secondary PK Analysis [Objective 1.3.5]:**
  - Figure: within-participant concentration-time curves
  - LZD PK parameters by intensive versus abbreviated PK sampling (see **Section** 7)
- **Secondary PK Analysis [Objective 1.3.6]:**
  - Figures: within-participant concentration-time curves
  - DLM and DLM metabolite PK parameters by intensive versus abbreviated PK sampling (see **Section 7**)

10.1.4 BDQ and CFZ Intensive PK

- **Supplementary Secondary PK Analysis [Objective 1.3.6A]:**
  - Figure: within-participant concentration-time curves
  - BDQ PK parameters by intensive versus abbreviated PK sampling (see **Section** 7)
- **Supplementary Secondary PK Analysis [Objective 1.3.6B]:**
  - Figures: within-participant concentration-time curves
  - CFZ PK parameters by intensive versus abbreviated PK sampling (see **Section 7**)

10.2 LZD Dose Reduction due to Toxicity PK Parameters

Objective: To address a pharmacology objective in **Protocol Section 11.0** and to summarize pharmacokinetic exposure when there is a treatment limiting adverse event related to LZD with a subsequent dose reduction

10.2.1 Flow Diagram

To illustrate flow of all participants from randomization into the PK-LZD analysis populations (i.e., intensive PK sampling versus abbreviated PK sampling), including reasons individuals were excluded

10.2.2 Baseline Characteristics

Two sets of tables will be created:

1. All randomized participants summarized by LZD dose reduction PK analysis status (i.e., included versus excluded)
2. All participants in the LZD dose reduction PK analysis by intensive PK versus abbreviated PK sampling

- Age, sex at birth, gender, country, and (if available) site-specific race
- BMI
- HIV-1 status and, for participants with HIV, ARV regimen at study entry or within 30 days after study entry
- Type of TB (RR-, MDR-, pre-XDR-, or XDR-TB)
- AFB smear grade (highest grade of the two smear results)
- Chest x-ray findings: presence of cavitary lesions and, in participants with cavitary lesions, estimated aggregate cavity size
- Concomitant medications (all or partial list to be determined by pharmacologist)

10.2.3 LZD PK Parameters

- Figure: within-participant concentration-time curves
- LZD PK parameters by intensive versus abbreviated PK sampling, with treatment differences tested using Wilcoxon rank sum tests