Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

OPC-167832

CLINICAL PROTOCOL

A Multicenter, Phase 2b/c, Open-label, Randomized, Dose-finding Trial to Evaluate the Safety and Efficacy of a 4-month Regimen of OPC-167832 in Combination with Delamanid and Bedaquiline in Participants with Drug-susceptible Pulmonary Tuberculosis in Comparison with Standard Treatment

Protocol No. 323-201-00006
IND No. 129303

CONFIDENTIAL — PROPRIETARY INFORMATION

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Immediately Reportable Event	Clindev Pty Ltd Fax: CCI [redacted] Email: CCI [redacted]
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1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Products: OPC-167832, bedaquiline (BDQ), and delamanid (DLM)

Protocol No.: 323-201-00006

IND No.: 129303

Protocol Title: A Multicenter, Phase 2b/c, Open-label, Randomized, Dose-finding Trial to Evaluate the Safety and Efficacy of a 4-month Regimen of OPC-167832 in Combination with Delamanid and Bedaquiline in Participants with Drug-susceptible Pulmonary Tuberculosis in Comparison with Standard Treatment

Clinical Phase: Phase 2b/c, Therapeutic use

Treatment/Indication: Drug-susceptible pulmonary tuberculosis (DS-TB)

Objectives and Endpoints:

Objectives	Endpoints
Primary: • To assess the safety and efficacy of OPC-167832 combined with DLM and BDQ in participants with DS-TB administered for 4 months compared to rifampin, isoniazid, ethambutol, pyrazinamide (RHEZ) administered for 6 months	Safety: • Adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, electrocardiograms (ECGs) • The proportion of participants with a grade 3 or higher AE • The rate of all-cause treatment discontinuation Efficacy: • The proportion of participants achieving sputum culture conversion ([SCC] in Mycobacteria Growth Indicator Tube® [MGIT]) by the end of the treatment period

Objectives	Endpoints
Secondary: • To evaluate efficacy in sputum MGIT culture and lipoarabinomannan (LAM) for OPC-167832 combined with DLM and BDQ administered for 4 months as compared to RHEZ • To evaluate the development of resistance to anti-tuberculosis (TB) drugs in all treatment arms • To inform dose selection of OPC-167832 combined with DLM and BDQ	Efficacy: • The proportion of participants who achieve SCC in MGIT by 8 weeks of treatment • Time to detection of MGIT cultures • The proportion of participants who convert sputum LAM to negative by 8 weeks of treatment and by end of treatment • Proportion of participants who develop drug resistance • Time to SCC of OPC-167832, DLM, and BDQ, as well as RHEZ
Exploratory Biomarker Analysis: • To evaluate various novel biomarkers for association with microbiological and clinical response	Efficacy: • Longitudinally assess positron emission tomography/computerized axial tomography (PET/CT) imaging response over the course of treatment • Longitudinally evaluate the ribosomal ribonucleic acid synthesis ratio (RS ratio) decline in sputum • Longitudinally assess whole blood transcriptomic signatures previously associated with TB cure from serum
Exploratory Efficacy Analysis: • To evaluate the efficacy of experimental arms in comparison to RHEZ through the end of the posttreatment follow-up period	Efficacy: • The proportion of participants with favorable outcome at 12 months postrandomization • The proportion of participants with relapse at 12 months postrandomization

Trial Design:

Trial 323-201-00006 is a multicenter, phase 2b/c, open-label, randomized, dose-finding trial in participants with DS-TB. The microbiology laboratory will be blinded to treatment assignments.

Following a screening period of up to 14 days, eligible participants will be randomized on Day −1 or predose Day 1 in a ratio of 1:2:2:1 to one of the following treatment arms:

- Arm 1: DLM (300 mg once daily [QD]) + BDQ (400 mg QD x 2 weeks, then 200 mg thrice-weekly [TIW]) + OPC-167832 (10 mg QD) for 17 weeks
- Arm 2: DLM (300 mg QD) + BDQ (400 mg QD x 2 weeks, then 200 mg TIW) + OPC-167832 (30 mg QD) for 17 weeks
- Arm 3: DLM (300 mg once daily [QD]) + BDQ (400 mg QD x 2 weeks, then 200 mg TIW) + OPC-167832 (90 mg QD) for 17 weeks
- Arm 4: RHEZ for 8 weeks followed by 18 weeks of rifampin and isoniazid (for a total of 26 weeks)

Randomization will be stratified by HIV status (yes or no) and presence of bilateral cavitation on screening chest x-ray (yes or no). After the end of the treatment period, participants will be followed until 12 months postrandomization.

Trial Population:

The trial population will consist of participants who are ≥ 18 years to ≤ 65 years at screening with body weight of ≥ 35.0 kg and who have newly diagnosed pulmonary DS-TB. Approximately 120 participants (including no more than 15% with HIV-coinfection) will be enrolled at approximately 8 sites in South Africa.

Key Inclusion/Exclusion Criteria:

Key inclusion criteria are noted above, under Trial Population.

Key exclusion criteria are as follows:

- Participants are known or suspected of having resistance to rifampin, isoniazid, ethambutol, pyrazinamide, DLM, or BDQ either confirmed by the laboratory, or based on epidemiological history, at screening.
- Evidence of clinically significant metabolic (for example, including ongoing or current hypokalemia [ie, potassium < 3.5 mEq/dL at screening]), gastrointestinal, neurological, psychiatric, endocrine, or liver (eg, hepatitis B and C) disease; malignancy; or other abnormalities (other than the indication being studied).
- History of, or current, clinically relevant cardiovascular disorder such as heart failure, coronary heart disease, uncontrolled hypertension, arrhythmia, or symptom strongly suggestive of such a problem (for example, syncope or palpitations), tachyarrhythmia or status after myocardial infarction.
- Known bleeding disorders or family history of bleeding disorders.
- Any diseases or conditions in which the use of DLM, BDQ, OPC-167832, rifampin, isoniazid, pyrazinamide, or ethambutol is contraindicated.

- Clinical evidence of severe extrapulmonary TB (eg, miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis).
- Evidence of pulmonary silicosis, lung fibrosis, or other lung condition considered as severe by the investigator (other than TB). In particular, any underlying condition that could interfere with the assessment of x-ray images, sputum collection, or interpretation of sputum findings, or otherwise compromise the subject's participation in the trial.
- Any renal impairment characterized by creatinine clearance/estimated glomerular filtration rate of < 60 mL/min/1.73 m^2, hepatic impairment characterized by alanine transaminase or aspartate transaminase > 2.0 × upper limit of normal of the clinical laboratory reference range or bilirubin > 2.0 × upper limit of normal of the clinical laboratory reference range, at screening.
- Screening glucose (nonfasting) ≥ 200 mg/dL or glycosylated hemoglobin ≥ 7.0%.
- QT interval corrected by Fridericia's method > 450 msec in male participants (> 470 msec in female participants), atrioventricular block II or III, bi-fasicular block, at screening or current or history of clinically significant ventricular arrhythmias. Other ECG abnormalities, if considered clinically significant by the investigator.
- Participants receiving any of the prohibited medications (see Section 6.5.1) within the specified periods or who would be likely to require prohibited concomitant therapy during the trial.
- Current history of significant drug and/or alcohol abuse that is likely to result in poor adherence to trial requirements or that would pose a risk to the participant's well-being during the course of the trial.
- Participants who test positive for cocaine or other drugs of abuse (excluding known prescription stimulants and other prescribed medications and marijuana) at screening are excluded. Detectable levels of alcohol, marijuana, barbiturates, or opiates in the drug screen are not exclusionary if, in the investigator's documented opinion, the participant does not meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for moderate to severe substance use disorder and the positive test does not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results, and participation is agreed to by the medical monitor prior to treatment.
- History of having taken an investigational drug within 30 days preceding trial entry.
- Participants with significant medical comorbidities that in the opinion of the investigator, should not participate in the trial.
- Participants with Karnofsky score < 60 will be excluded from the trial.
- Participants with HIV co-infection not on a stable anti-retroviral regime consisting of a combination of tenofovir, emtricitabine/ lamivudine, plus dolutegravir (ie, > 3 months), or who have a detectable viral load, or who have a CD4 count < 250 cells/mm^3 will be excluded from the trial.

Trial Site(s):

This trial will be conducted at approximately 8 sites in South Africa.

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

All investigational medicinal product (IMP) (ie, OPC-167832, DLM, or BDQ) must be administered after the completion of a meal.

Bedaquiline should be administered as follows: 400 mg QD for the first 2 weeks of treatment and 200 mg TIW thereafter with at least 48 hours between doses for the remainder of the trial (ie, a total of 17 weeks [Arm 1 or Arm 2 or Arm 3] of treatment).

Participants randomized to treatment Arm 4 will receive RHEZ orally QD for 8 weeks followed by 18 weeks of rifampin and isoniazid per the local standard of care.

Trial treatments (IMP or RHEZ) will be administered using the locally accepted adherence monitoring techniques which could include directly observed therapy (DOT), Wisepill, video DOTs, or other adherence monitoring techniques. In addition, all doses of IMP or RHEZ given during trial visits will be observed via the hand-and-mouth procedure. All trial treatments will be administered with approximately 240 mL of still (noncarbonated) water.

Trial Assessments:

Assessments for Efficacy: Sputum for MGIT culture, LAM concentration, drug susceptibility testing, and *Mycobacterium tuberculosis* strain typing (as necessary); sputum for RS ratio; assessment of clinical signs and symptoms of TB; PET/CT scan; chest radiograph; and whole blood biomarkers.

Assessments for Safety: AE reporting; clinical laboratory tests (serum chemistry, hematology, urinalysis, and coagulation); physical examination; vital signs; ECGs; and concomitant medications.

Screening (excluding safety assessments mentioned above)/Other: demographics, medical history, prior medications; height and weight; visual assessment; sputum for confirmation of DS-TB; viral hepatitis serology (hepatitis B surface antigen [HBsAg] and hepatitis C virus [HCV]) and HIV screening (and CD4 count and HIV viral load for those with a known history of HIV); urine pregnancy testing; urine or blood alcohol, and urine drug screen; severe acute respiratory syndrome coronavirus (SARS-CoV-2) testing.

CCI [redacted]

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will be contracted by Otsuka to review safety, efficacy, data during the conduct of the trial. The DMC will convene and operate based on an established charter. The DMC will be permitted to seek additional independent expertise, as needed. The primary responsibility of the DMC will be to monitor safety and to advise the sponsor of the clinical project regarding whether or not the safety concerns merit stopping the trial. Towards this objective the DMC will meet on a predetermined schedule to review safety and available efficacy .

Statistical Methods: Primary: Safety endpoints will be summarized using descriptive statistics (number, median, mean, standard deviation, minimum, maximum) for continuous values, and by frequency and percentage for discrete variables. Percentage and frequency of adverse events and clinical laboratory test results by grades will be analyzed.

The modified intent-to-treat (mITT) analysis set includes all randomized participants who take at least 1 dose of IMP or RHEZ, have at least 1 postbaseline culture result, and demonstrate positive culture results by 1 week and susceptibility to rifampin and isoniazid (from the screening specimen).

The primary efficacy endpoint of the trial is the proportion of participants who have SCC and no subsequent positive culture at the end of treatment. Sputum culture conversion occurs when a participant has the first of 2 visits of at least 1 week apart with sputum cultures negative and without a positive sputum culture result in between.

The 3 DLM + BDQ + OPC-167832 arms will be pooled, and noninferiority with RHEZ will be established if the lower limit of 80% confidence interval (CI) for the difference of proportion of participants with SCC between the pooled DLM + BDQ + OPC-167832 group is larger than -0.12. The Miettinen and Nurminen CI of common risk difference stratified by HIV status and cavitation status prior to randomization will be used. If there is a stratum of very small size, strata may be collapsed. The statistical analysis plan (SAP) will describe the details.

The 80% CI of the proportion difference between each dose level of DLM + BDQ + OPC-167832 arm and RHEZ will be provided.

In exploratory analysis, the difference between proportion of participants with favorable outcome between each DLM + BDQ + OPC-167832 group and RHEZ group will be studied.

Definition of favorable and **unfavorable** outcome:

A participant is considered to have a **favorable** outcome if, during the postrandomization evaluation period, the participant is alive, completed the postrandomization evaluation, and otherwise did not meet the definition of an unfavorable outcome.

A participant is considered to have an **unfavorable** outcome if one of the following occurs:

1) Clinical progression of pulmonary disease during treatment or the need for an unanticipated surgical intervention for TB (eg, lobectomy)
2) Any growth of *M tuberculosis* from an extrapulmonary site during the post-treatment period (Note: Excludes reinfection with a new strain of *M tuberculosis*).
3) Signs and symptoms of active tuberculosis during the follow-up period (ie, after the end of treatment), including radiographic worsening compared to baseline findings, resulting in re-initiation of anti-mycobacterial therapy (Note: excludes a re-initiation that is subsequently found to be due to a misdiagnosis and/or alternative diagnosis)
4) Death during treatment or follow-up
5) A sputum culture with growth of *M tuberculosis* at certain time points as follows:
    - Failure to achieve SCC by the end of the treatment period that results in a change in anti-mycobacterial therapy.
    - Microbiologic relapse during the follow-up period (ie, after the end of treatment) (Note: Excludes reinfection and requires more than 1 positive sputum culture with a new strain of *M tuberculosis*).

CCI [redacted].

Trial Duration:

Each participant in this trial is expected to participate in the following periods of the trial (approximate durations listed):

- Eligibility screening period (up 14 days)
- Treatment period (Arm 1, Arm 2, and Arm 3: 17 weeks; or Arm 4: 26 weeks)
- Post-treatment follow-up period (12 months postrandomization)

Overall, the per-patient trial duration from signing of the first informed consent form to the final participant assessment is expected to be approximately 12 months.

1.2 Schema

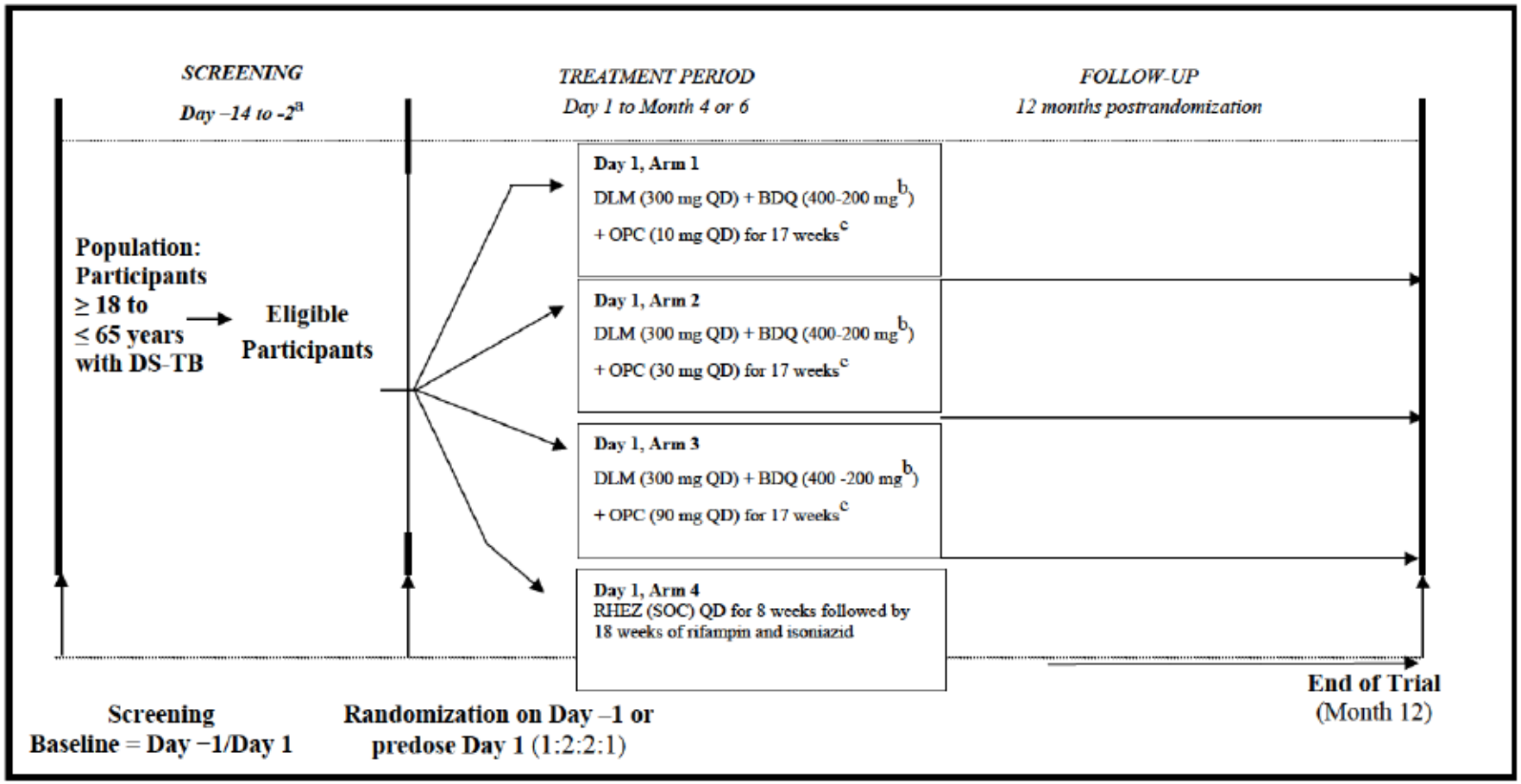


Figure 1.2-1 Trial Design Schematic

SOC = standard-of-care.

[a]Screening can occur for up to 14 days but should be completed in as few days as possible.

[b]BDQ dose 400 mg QD x 2 weeks, then 200 mg TIW.

[c]Rescue treatment consisting of the standard of care treatment, ie, RHEZ, will be provided to participants in Arm 1, or Arm 2, or Arm 3 in the following circumstances: 1) If a participant is sputum culture positive for *M tuberculosis* at the end of treatment; 2) If a participant has a microbiologic relapse subsequent to the end of treatment; or, 3) If, in the opinion of the investigator, a participant is clinically deteriorating, based on any combination of signs, symptoms, or chest radiograph data. Participants in Arm 4 will be managed according to local guidelines if not responding to therapy.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments - All Participants

Period	Pre-treatment Period		Treatment Period																		Follow-up Period								
	SCR	BSL																											
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	ET	Notes
	Day		Week (± 2 days)																				Week (± 7 days)						
Day/ Week	−14 to −2	−1	1	1	2	3	4	5	6	7	8	10	12	13	15	17	19	21	23	26	28	30	34	39	43	47	52	N/A	
Informed consent	X																												Section 10.1.2
Demography	X																												Section 5.1
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.5
Medical history	X																												Section 5.2
TB treatment history	X																												Section 5.2
Inclusion/ exclusion criteria	X	X																											Section 5.2
Chest radiograph[a]	X															X[a]				X[a]							X	X	Section 8.1.2
Randomization		X																											Section 4.1
Physical examination	X	X[b]			X b		X b		X b		X b	X b	X b	X[b]	X[b]	X[b]		X[b]		X[b]		X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X b	Section 8.7.2
Karnofsky score	X																												Section 5.2.2
Vital signs[c]	X	X			X		X		X		X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	Section 8.7.3
Visual assessment[d]	X															X				X									Section 8.7.2

Table 1.3-1 Schedule of Assessments - All Participants

Period	Pre-treatment Period		Treatment Period																		Follow-up Period									
	SCR	BSL																												
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	ET	Notes
	Day		Week (± 2 days)																		Week (± 7 days)									
Day/ Week	−14 to −2	−1	1	1	2	3	4	5	6	7	8	10	12	13	15	17	19	21	23	26	28	30	34	39	43	47	52	N/A	
PET/CT scan[e]		X[e]					X[e]									X[e]				X[e]									Section 8.7.6
Standard 12-lead ECG[f]	X	X			X		X		X		X	X	X	X	X	X		X		X		X	X	X	X	X	X	X	Section 8.7.4
Signs and symptoms of TB	X	X			X		X		X		X			X		X		X		X		X	X	X	X	X	X	X	Section 8.1.2
Hematology, serum chemistry, and urinalysis	X	X			X		X		X		X			X		X		X		X						X	X	Section 8.7.1 and 10.2
HbA1c[g]	X																												Section 10.2
Coagulation	X																												Section 8.7.1
Urine drug screen	X																												Section 8.7.1
Urine pregnancy test FOCBP	X																										X	X	Section 10.3
HIV[h], HBsAg, anti-HCV	X																												Section 8.7.1
Testing for SARS-CoV-2	X																												Section 5.2.2
Sputum for eligibility	X																												Section 8.1.1.1

Table 1.3-1 Schedule of Assessments - All Participants

Period	Pre-treatment Period		Treatment Period																		Follow-up Period								
	SCR	BSL																											
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	ET	Notes
	Day		Week (± 2 days)																		Week (± 7 days)								
Day/ Week	−14 to −2	−1	1	1	2	3	4	5	6	7	8	10	12	13	15	17	19	21	23	26	28	30	34	39	43	47	52	N/A	
Sputum MGIT culture/ sputum LAM		X	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Acid fast bacilli smear microscopy		X																											
Susceptibility testing[j]		X	X[j]	X[j]												X	X[j]	X[j]	X[j]	X									Section 8.1.1.2
Sputum for RS ratio[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
M tuberculosis strain genotyping[l]		X	X	X												X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.1.1
Paxgene tube for transcriptomics	X	X			X		X		X		X			X		X		X		X							X	X	Section 8.5
IMP administration[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								Section 6
Compliance check of IMP[m]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X								Section 6.4
CCI																													
HIV viral load, CD4 count[o]	X																			X							X	X	Section 10.2

Table 1.3-1 Schedule of Assessments - All Participants

Period	Pre-treatment Period		Treatment Period																		Follow-up Period								
	SCR	BSL																											
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	ET	Notes
	Day		Week (± 2 days)																		Week (± 7 days)								
Day/ Week	−14 to −2	−1	1	1	2	3	4	5	6	7	8	10	12	13	15	17	19	21	23	26	28	30	34	39	43	47	52	N/A	
AEs and IREs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.8

BSL= Baseline; ET = early termination; FOCBP = female of childbearing potential; HbA1c = glycosylated haemoglobin; IRE = immediately reportable event; SCR=Screening.

[a] An end of treatment chest radiograph will be taken at Week 17 (for participants in Arm 1, Arm 2, and Arm 3) or Week 26 (for participants in Arm 4) and at Month 12.

[b] A full physical examination will be conducted at screening and Week 52. A targeted physical examination is a review that focuses on participant driven issues eg, the investigator enquires if the participant has any complaints, pains or disturbances and this would lead to further evaluation of the problematic area. At a minimum, an assessment of general appearance and a chest examination should be performed. Note, visual assessments to be completed during screening will consist of Snellen and Ishihara testing and will be repeated during the trial if the investigator suspects abnormalities.

[c] At screening, blood pressure and heart rate will be taken with the participant in the supine (performed first) and sitting position after remaining for > 3 minutes in each position and temperature and respiratory rate will be taken with the participant in the supine position. At all other time points, vital signs will be obtained after the participant has been at rest in the supine position for at least 1 minute. Height will only be captured at screening. Weight, as well as BMI will also be captured at screening and other applicable time-points.

[d] Visual assessments will occur at screening, Week 17 (for participants in Arm 1, Arm 2, and Arm 3), or Week 26 (for participants in Arm 4). Note, visual assessments to be completed during screening will consist of Snellen and Ishihara testing and will be repeated during the trial if the investigator suspects abnormalities.

[e] Only for participants consenting to this trial procedure. The PET/CT scan will be done fasting within 1 week prior to starting treatment and within 1 week after the first dose, Week 4 (± 7 days), and at the end of treatment visit (± 7 days) for each group (ie, Week 17 for Arm 1, Arm 2, and Arm 3, and Week 26 for Arm 4).

[f] One standard 12-lead ECG will be performed during screening, plus 3 ECGs at baseline (Day −1) spaced 5 to 10 minutes apart after the dose of IMP [redacted]. Triplicate ECGs will be performed at subsequent visits during the treatment and follow up periods.

[g]In diabetics, HbA1c should be repeated every 3 months.

[h]If not already known to be HIV-infected. This HIV test can be repeated if clinically indicated.

[i]The Day 1 sputum will be collected prior to the first dose of IMP. Please note that for sputum culture results, Day 1 result will be used as the baseline, If the subject does not have a positive result on Day 1, his/her Day -1/Week 1 result will be used as the baseline.

[j]Drug susceptibility testing for anti-tuberculosis drugs will be performed on Day –1 (or Day 1 or Week 1 if Day –1 is not positive for MTB or useable for testing) and on the end of treatment visit, if positive for *M tuberculosis* (Week 17 for Arm 1, Arm 2, and Arm 3, and Week 26 for Arm 4). If Week 17 is negative for MTB, DST will be performed on the first positive culture between Week 19 and Week 26.

[k]If the participant is willing and able to spontaneously produce a subsequent specimen during the visit, specimen number 3 will be collected directly into ribonucleic acid preservation media and frozen for batch measuring of the RS ratio. If this sputum cannot be collected, this will not be considered a protocol deviation.

[l]*M tuberculosis* genotyping will be performed on a baseline culture (Day –1 and/or Day 1, or Week 1 if necessary) and the first of any subsequent positive culture during the posttreatment follow-up period to determine if the participant has relapsed or has new infection of *M tuberculosis*. In addition, the sponsor may request genotyping as needed.

[m]Participants in Arm 1, Arm 2, and Arm 3 will receive DLM and OPC-167832 QD for 17 weeks combined with BDQ QD for 2 weeks, then BDQ TIW. Participants in Arm 4 will receive RHEZ QD for 8 weeks followed by rifampin and isoniazid for 18 weeks per the local standard of care.

CCI [redacted]

[o]For HIV positive participants who are included, HIV testing does not need to be repeated at screening if the HIV positive status has been documented prior to screening (within the last year) and the documentation can be kept with the trial documentation for the required duration. For participants who are HIV positive, blood samples are to be drawn for CD4 and viral load assessment at the local laboratory.

2 Introduction

Tuberculosis (TB) remains a major global health problem and is a leading cause of death from an infectious disease worldwide.[1] Progress has been made in the research and development of new anti-tuberculosis drugs to help overcome the current TB treatment situation. In recent years, bedaquiline (BDQ) (Sirturo™) and the sponsor's delamanid (DLM) (Deltyba™) have been used as part of a combination therapy in adults with pulmonary multidrug-resistant tuberculosis (MDR-TB). These 2 new drugs offer the opportunity to form the backbone for a novel oral anti-TB drug regimen that can shorten the treatment for both drug-susceptible tuberculosis (DS-TB) and MDR-TB.[1,2,3] Thus, there is an urgent need for the development of new potent anti-TB agents with low toxicity that are effective against drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis* and can be combined with BDQ and DLM.[4]

Otsuka Pharmaceutical Co, Ltd (Otsuka) initiated a program to screen for new anti-TB agents that can be used in combination with DLM. As a result of research efforts, Otsuka discovered OPC-167832, a novel 3, 4 dihydrocarbostyril derivative. OPC-167832 is an inhibitor of decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1), an essential enzyme for *M tuberculosis* cell wall biosynthesis. The minimum inhibitory concentrations (MIC) of OPC-167832 for *M tuberculosis* on clinically isolated strains, including MDR-/extensively drug-resistant-TB, ranged from 0.00024 to 0.002 µg/mL. It has bactericidal activity against both growing and intracellular bacilli. The frequency of spontaneous resistance of OPC-167832 was 2.60×10^{-9} to 1.52×10^{-7} for *M tuberculosis* H37Rv at 16 × MIC.

Please refer to the OPC-167832 Investigator's Brochure (IB) for more detailed information.[5]

2.1 Trial Rationale

In vitro and in vivo studies have shown that OPC-167832 has potent bactericidal activity.[5] Further, OPC-167832 in combination with DLM or BDQ may have additive effects on bactericidal activity. No antagonistic activity has been shown with OPC-167832 and DLM or OPC-167832 and BDQ. Because of OPC-167832's high bactericidal activity, and novel mechanism of action (different from all other TB drugs currently available for human use), it is likely a good candidate to be included in a regimen to possibly improve efficacy and prevent resistance development to concomitant TB drugs.[5]

Single oral doses up to 480 mg OPC-167832 were well tolerated in healthy participants; there were no serious or severe adverse events (AEs) and no participants were discontinued from the trial due to a treatment emergent AE. One participant did decide to withdraw consent after occurrence of the nonserious and mild AEs of arthralgia, pain in extremity, and ecchymosis.

The safety, tolerability, pharmacokinetics (PK), and efficacy of OPC-167832 are being evaluated in adult participants with uncomplicated, smear-positive, pulmonary DS-TB, in an ongoing, multiple-dose trial. Stage 1, which was testing multiple ascending doses of OPC-167832 has been completed. Clinically meaningful early bactericidal activity as measured by change from baseline at 14 days in Log10 colony-forming unit (CFU) was seen across all doses of OPC-167832 tested. OPC-167832 demonstrated an average decline of 0.101, 0.138, 0.151, and 0.149 Log10 CFU/mL per day in sputum specimens obtained from participants administered with 3 mg, 10 mg, 30 mg, and 90 mg per day, respectively, versus 0.200 Log10 CFU/mL per day for the rifampin, isoniazid, ethambutol, and pyrazinamide (RHEZ) arm. There was a single serious adverse event (SAE) of haemoptysis that led to discontinuation of investigational medicinal product (IMP) (3 mg dose); however, this SAE was not considered to be related to the IMP.

The proposed treatment regimen in this trial has not yet been evaluated in a clinical trial but is supported by the clinical and nonclinical data on DLM, BDQ, and OPC-167832. In a mouse chronic TB model, the 3-drug combination of OPC-167832, DLM, and BDQ significantly killed *M tuberculosis* faster than the standard care of treatment regimen of RHEZ[4] and is more efficacious in a hollow fiber system of tuberculosis (HFS-TB). In the HFS-TB, the 3-drug combination sterilized the system much faster than the standard treatment regimen and suggested a potential 3 to 4 months treatment regimen.

This trial will evaluate the safety, tolerability, CCI [redacted] and efficacy of 2 doses of OPC-167832 combined with DLM and BDQ in participants who are ≥ 18 to ≤ 65 years old with pulmonary DS-TB. Standard-of-care treatment with RHEZ will be included for comparison.[6,7]

2.2 Background

Delamanid and BDQ are 2 of the most recently developed anti-TB drugs that have been extensively studied in patients with MDR-TB, and have received regulatory approval and World Health Organization endorsement to be used as part of an optimal background regimen for patients with MDR-TB. Delamanid is a nitro-dihydro-imidazooxazole derivative that inhibits the synthesis of mycolic acid, an important component of the *M tuberculosis* cell wall. Bedaquiline is a diarylquinoline derivative that inhibits

M tuberculosis adenosine triphosphate synthase. Both DLM and BDQ have been studied together as part of a National Institutes of Health-sponsored combination drug-drug interaction/safety trial (NCT02583048).

OPC-167832 is a newly discovered 3,4-dihydrocarbostyril derivative that is an inhibitor of DprE1, an essential enzyme for *M tuberculosis* to synthesize lipoarabinomannan (LAM) and arabinogalactan (key components of the *M tuberculosis* cell wall). OPC-167832 is currently under clinical development: a single ascending dose trial in healthy participants (Trial 323-201-00001) has been completed, and a multiple, ascending-dose and early bactericidal activity trial in participants with DS-TB has completed Stage 1 and is ongoing (Trial 323-201-00003).

These 3 drugs have distinct mechanisms of actions against *M tuberculosis* that are also distinct from other approved TB drugs (one notable exception is pretomanid, which has a similar mechanism of action and likely near complete cross-resistance to DLM).

2.3 Known and Potential Risks and Benefits

2.3.1 OPC-167832

CCI [redacted]

CCI [redacted]. The no observed adverse effect level (NOAEL) was estimated to be CCI mg/kg/day for males and CCI mg/kg/day for females. At the NOAEL, the maximum (peak) plasma concentration (C_{max}) and area under the concentration-time curve from zero to 24 hours (AUC_{24h}) of OPC-167832 in Week 4 (on Day 28) were respectively CCI µg/mL and CCI µg·h/mL in males and CCI µg/mL and CCI µg·h/mL in females. CCI [redacted].

CCI [redacted]

CCI

. CCI

.

CCI

.[5]

Single oral doses up to 480 mg OPC-167832 were well tolerated during Trial 323-201-00001; CCI

.[5] In the single ascending dose trial of OPC-167832 (Trial 323-201-00001), where single oral doses up to 480 mg were administered to healthy participants, CCI

.

The safety, tolerability, PK, and efficacy of OPC-167832 are being evaluated in adult participants with uncomplicated, smear-positive, DS-TB, in an ongoing, multiple-dose trial (Trial 323-201-00003). Stage 1, which was testing multiple ascending doses of OPC-167832 has been completed. Clinically meaningful early bactericidal activity as measured by change from baseline at 14 days in Log10 CFU was seen across all doses of OPC-167832 tested. There was a single SAE of haemoptysis that led to discontinuation of IMP (3 mg dose); however, this SAE was not considered to be related to the IMP.

Trial sites will receive updated versions of the IB, when available, and trial sites should refer to the most current version as needed.

2.3.2 Delamanid

The first marketing approval for DELTYBA® (DLM) was granted on 28 Apr 2014 in Europe (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden), and United Kingdom, followed by approvals in Japan (04 Jul 2014), South Korea (29 Oct 2014), Hong Kong (29 Mar 2016), Turkey (31 May 2017), India (24 Aug 2017), the Philippines (08 Sep 2017), China (12 Mar 2018), Mongolia (05 Dec 2018), Ukraine (30 Jan 2019), South Africa (25 Mar 2019), Indonesia (05 Apr 2019), Peru (01 Jun 2019), Kazakhstan (08 Aug 2019), Turkmenistan (22 Sep 2019), Russia (08 May 2020), and Azerbaijan (26 Jan 2021). In all completed and ongoing clinical trials of DLM, as of 31 Jan 2019, including healthy participants and participants with TB (uncomplicated DS-TB, MDR-TB, and MDR TB refractory to treatment), 1419 participants received at least 1 dose of DLM.

In the 14 completed trials in healthy participants, the treatment-emergent adverse events (TEAEs) that led to the discontinuation of the IMP (ie, DLM) in more than 1 participant in the Any DLM group were rash generalised (12 participants), haematochezia (3 participants), and headache (3 participants). There were 2 serious TEAEs, delirium and ischaemic colitis, both occurring in Trial 242-07-209. No deaths were reported in any of the completed trials in healthy participants.

In the 2 completed trials of participants with uncomplicated DS-TB treated with DLM, there were no deaths, and no participants discontinued IMP due to TEAEs. There were 5 serious TEAEs (3 events of prolonged electrocardiogram (ECG) QT interval and 2 events of increased transaminases), all occurring in Trial 242-06-101.

In the 4 completed trials of participants with MDR-TB, the only TEAE that led to the discontinuation of IMP in more than 1 participant in the DLM + optimized background regimen (OBR) group was prolonged ECG QT interval (7 participants in the DLM + OBR group and 2 participants in the placebo + OBR group). The serious TEAEs that occurred in at least 1% of participants in the DLM + OBR group and at a higher incidence than in the placebo + OBR group were prolonged ECG QT interval (3.4% DLM + OBR, 1.2% placebo + OBR), TB (2.1% DLM + OBR, 0.9% placebo + OBR), and hypokalaemia (1.6% DLM + OBR, 0.9% placebo + OBR).

Additional information regarding the safety and the potential risks and benefits of DLM is provided in the IB.[3]

2.3.3 Bedaquiline

Bedaquiline (SIRTURO®) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adult and pediatric patients (≥ 5 years and weighing ≥ 15 kg) with pulmonary MDR-TB. For the known and potential risks of SIRTURO, please see the package insert for SIRTURO (BDQ) tablets.[2]

2.3.4 Rifampin, Isoniazid, Ethambutol, and Pyrazinamide

.The local standard treatment regimen for drug susceptible TB consists of 6 months of rifampin plus isoniazid, supplemented by ethambutol and pyrazinamide during the first 2 months (RHZE).Rifampin is a semi-synthetic, broad-spectrum bactericidal antibiotic. Isoniazid is a synthetic, antitubercular agent which is bacteriostatic against semi-dormant bacilli and bactericidal against actively dividing mycobacteria. Pyrazinamide may be bactericidal or bacteriostatic, depending on its concentration and the susceptibility of the organism. Ethambutol is a synthetic, bacteriostatic antitubercular agent. All agents are readily absorbed following oral administration, with wide distribution to most tissues and fluids including cerebrospinal fluid. For a complete list of known and potential risks of RHEZ.[6,7]

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: • To assess the safety and efficacy of OPC-167832 combined with DLM and BDQ in participants with DS-TB administered for 4 months compared to RHEZ administered for 6 months	Safety: • AEs, clinical laboratory tests, vital signs, physical examinations, ECGs • The proportion of participants with a grade 3 or higher AE • The rate of all-cause treatment discontinuation Efficacy: • The proportion of participants achieving sputum culture conversion (SCC) in Mycobacteria Growth Indicator Tube® (MGIT) by the end of the treatment period

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Secondary: • To evaluate efficacy in sputum MGIT culture and LAM for OPC-167832 combined with DLM and BDQ administered for 4 months as compared to RHEZ • To evaluate the development of resistance to anti-TB drugs in all treatment arms • To inform dose selection of OPC-167832 combined with DLM and BDQ	Efficacy: • The proportion of participants who achieve SCC in MGIT by 8 weeks of treatment • Time to detection of MGIT cultures • The proportion of participants who convert sputum LAM to negative by 8 weeks of treatment and by end of treatment • Proportion of participants who develop drug resistance • Time to SCC of OPC-167832, DLM, and BDQ, as well as RHEZ
Exploratory Biomarker Analysis: • To evaluate various novel biomarkers for association with microbiological and clinical response	Efficacy: • Longitudinally assess positron emission tomography/computerized axial tomography (PET/CT) imaging response over the course of treatment • Longitudinally evaluate the ribosomal ribonucleic acid synthesis ratio (RS ratio) decline in sputum • Longitudinally assess whole blood transcriptomic signatures previously associated with TB cure from serum
Exploratory Efficacy Analysis: • To evaluate the efficacy of experimental arms in comparison to RHEZ through the end of the posttreatment follow-up period	Efficacy: • The proportion of participants with favorable outcome at 12 months postrandomization • The proportion of participants with relapse at 12 months postrandomization

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

Trial 323-201-00006 is a multicenter, phase 2b/c, open-label, randomized, dose-finding trial in participants with DS-TB. The microbiology laboratory will be blinded to treatment assignments.

Following a screening period of up to 14 days, eligible participants will be randomized on Day −1 or predose Day 1 in a ratio of 1:2:2:1 to one of the following treatment arms:

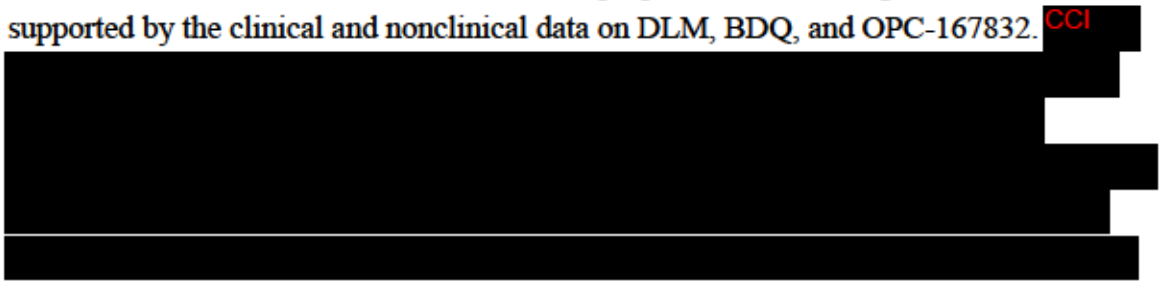
- Arm 1: DLM (300 mg once daily [QD]) + BDQ (400 mg QD x 2 weeks, then 200 mg thrice-weekly [TIW]) + OPC-167832 (10 mg QD) for 17 weeks
- Arm 2: DLM (300 mg QD) + BDQ (400 mg QD x 2 weeks, then 200 mg TIW) + OPC-167832 (30 mg QD) for 17 weeks
- Arm 3: DLM (300 mg QD) + BDQ (400 mg QD x 2 weeks, then 200 mg TIW) + OPC-167832 (90 mg QD) for 17 weeks
- Arm 4: RHEZ for 8 weeks followed by 18 weeks of rifampin and isoniazid (for a total of 26 weeks)

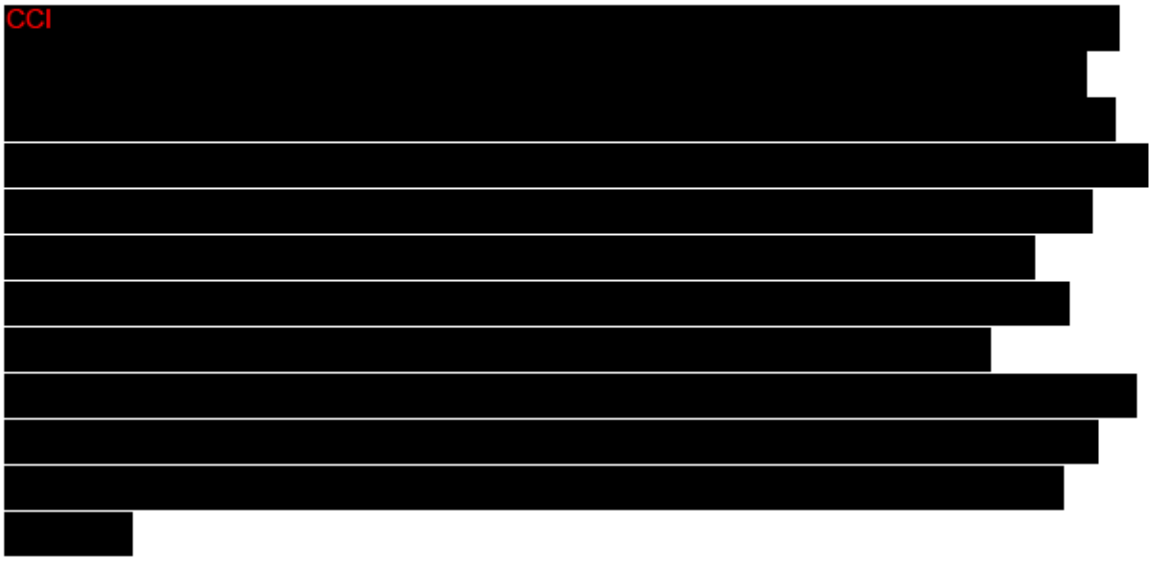
Randomization will be stratified by HIV status (yes or no) and presence of bilateral cavitation on screening chest x-ray (yes or no). At the end of the treatment period, participants will be followed until 12 months postrandomization.

4.2 Scientific Rationale for Trial Design

Treatment of TB requires multiple drugs with different mechanisms of action and the ability to kill *M tuberculosis* bacilli within heterogeneous TB lesions (ie, different pathophysiologic environments) in order to ensure rapid sterilization of lesions, a durable relapse-free cure, and prevent the development of resistance. Development of novel TB treatment regimens that are comprised of potent new TB drugs that can shorten the treatment duration to 4-months or less will simplify TB treatment, enhance compliance, and potentially improve treatment outcomes.

This trial will be conducted to evaluate a new proposed treatment regimen that is supported by the clinical and nonclinical data on DLM, BDQ, and OPC-167832. CCI





This trial will evaluate the safety, tolerability, CCI and efficacy of OPC-167832 combined with DLM and BDQ in participants with DS-TB. Standard-of-care treatment with RHEZ will be included for comparison.

4.3 Dosing Rationale

A key goal of the trial is to determine if the combination of DLM, OPC-167832, and BDQ is efficacious, safe and can potentially shorten the treatment duration in patients with DS-TB. In order to maximize the chances of success in achieving this goal, doses were chosen such that they can provide the highest possible exposures of the drugs without compromising patient safety. Since OPC-167832 has only been evaluated in the 14-day early bactericidal activity (EBA) trial in participants with TB, and long-term efficacy and safety are not available, 3 doses of this compound will be evaluated in this trial. Both doses are selected to achieve near maximal efficacy based on the pharmacokinetics/pharmacodynamics (PK/PD) analyses of the EBA trial. Delamanid QD dosing regimen in combination with QD dosing of OPC-167832 and BDQ is being proposed in this trial due to the need to facilitate patient adherence.

Delamanid exposure-response modeling using DLM steady state area under the concentration-time curve (AUC) and change from baseline in CFU found cumulative fraction of response (CFR) of 96 to 98% and 89 to 96% following the approved DLM dose of 100 mg twice daily (BID) (from Trial 242-07-204) and the 200 mg QD dose regimen (from Trial 242-09-213), respectively. Following dosing of DLM 300 mg QD (from Trials 242-06-201 and 242-08-211), DLM AUC were about 20 to 25% higher than those obtained following 200 mg QD and hence correspondingly, the CFR also would be higher than that of the 200 mg QD dose. From a safety perspective, the exposures following 300 mg QD were lower than that following the approved 100 mg BID dosing,

indicating that the 300 mg QD dose would likely have less of an effect on a key safety issue, QT interval prolongation, compared to the approved 100 mg BID dose. Hence the dose of 300 mg QD DLM has been selected for the trial.

In the current multiple ascending dose (MAD)/EBA trial of OPC-167832 (Trial 323-201-00003), doses of 3 mg, 10 mg, 30 mg, and 90 mg have been studied. An exposure-response analysis of OPC-167832 of data obtained to date from the MAD/EBA trial indicated that the effect of 10 mg, 30 mg and 90 mg doses on CFU reduction were similar while the effect from the 3 mg dose is slightly less (ie, CFU count). All 4 doses were efficacious and well tolerated with no significant safety concerns. Because the efficacy and safety of long-term use in combinations with other TB drugs of OPC-167832 are unknown, in order to maximize exposures, and at the same time have a reasonable safety margin, the 10 mg, 30 mg, and 90 mg doses of OPC-167832 were chosen for the trial.

4.4 End of Trial Definition

The end of trial date is defined as the last date of contact or the date of final contact attempt from the post-treatment follow-up electronic case report form (eCRF) page for the last participant completing or withdrawing from the trial.

4.5 Definition of Completed Participants

The treatment period is defined as the time period during which participants are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the participant actually took all doses of the IMP. For the purpose of this trial, treatment completers will be randomized participants who take IMP through either Week 17 (for Arm 1, Arm2, and Arm 3) or Week 26 (for Arm 4) and complete at least some of the end-of-treatment assessments. Trial completers will be randomized participants who remain on the study till the 12 months post-randomization visit.

Completer categories are as follows: (1) Treatment completer and trial completer (2) Treatment non-completer and trial completer (3) Treatment completer, trial non-completer and (4) Treatment non-completer and trial non-completer.

Further details can be found in Section 10.6.

5 Trial Population

The trial population will consist of participants who are ≥ 18 years to ≤ 65 years at screening and who have newly diagnosed pulmonary DS-TB. Approximately 120 participants (including no more than 15% with HIV-coinfection) will be enrolled at approximately 8 sites in South Africa.

5.1 Participant Selection and Numbering

All participants will be given a unique participant identifier (identification [ID]; site number [3 digits] + participant number ['S' + 5 digits] upon providing consent). The site number will be designated by the sponsor. Participant's numbers will be assigned sequentially across the trial from S00001.

Demographic information (collection date, date of birth, sex, childbearing potential, race, ethnicity, country) and medical history will be recorded in the eCRF at the screening visit.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Participants are required to meet the following inclusion criteria when assessed:

1) Able to provide written, informed consent prior to initiation of any trial-related procedures or treatments, and able, in the opinion of the investigator, to comply with all the requirements of the trial.
2) Male or female participants between 18 and 65 years of age (inclusive) at the screening visit.
3) Body weight $\geq$ 35.0 kg at the screening visit.
4) Newly diagnosed, rifampin and isoniazid susceptible (on the screening sample) pulmonary TB.
5) Able to spontaneously produce sputum.
6) Females of childbearing potential (FOCBP) must agree to use 2 different approved methods of birth control or remain abstinent throughout the participation in the trial and for 12 weeks after the last dose of IMP or dose of RHEZ.
7) Male participants must agree to use 2 different approved methods of birth control or remain abstinent throughout the participation in the trial and for 12 weeks after the last dose of IMP or RHEZ.

5.2.2 Exclusion Criteria

Participants will be excluded if they meet any of the following exclusion criteria when assessed:

1) Participants are known or suspected of having resistance to rifampin, isoniazid, ethambutol, pyrazinamide, DLM, or BDQ either confirmed by the laboratory, or based on epidemiological history, at screening.

2) Evidence of clinically significant metabolic (for example, including ongoing or current hypokalemia [ie, potassium <3.5 mEq/dL at screening]), gastrointestinal, neurological, psychiatric, endocrine or liver (eg, hepatitis B and C) disease; malignancy; or other abnormalities (other than the indication being studied).
3) History of, or current, clinically relevant cardiovascular disorder such as heart failure, coronary heart disease, uncontrolled hypertension, arrhythmia or symptom strongly suggestive of such a problem (for example, syncope or palpitations), tachyarrhythmia or status after myocardial infarction.
4) Known bleeding disorders or family history of bleeding disorders.
5) Any diseases or conditions in which the use of DLM, BDQ, OPC-167832, rifampin, isoniazid, pyrazinamide, or ethambutol is contraindicated.
6) Any prior treatment for *M tuberculosis* within the past 2 years.
7) Any treatment with a drug active against *M tuberculosis* (eg, quinolones) within the 3 months prior to screening.
8) Clinical evidence of severe extrapulmonary TB (eg, miliary TB, abdominal TB, urogenital TB, osteoarthritic TB, TB meningitis).
9) Evidence of pulmonary silicosis, lung fibrosis, or other lung condition considered as severe by the investigator (other than TB). In particular, any underlying condition that could interfere with the assessment of x-ray images, sputum collection, or interpretation of sputum findings, or otherwise compromise the subject's participation in the trial.
10) Any renal impairment characterized by creatinine clearance/estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m^2, or hepatic impairment characterized by alanine transaminase or aspartate transaminase > 2.0 × upper limit of normal of the clinical laboratory reference range or bilirubin > 2.0 × upper limit of normal of the clinical laboratory reference range, at screening.
11) Screening glucose (nonfasting) ≥ 200 mg/dL or glycosylated hemoglobin (HbA1c) ≥ 7.0%.
12) QTcF > 450 msec in male participants (> 470 msec in female participants), atrioventricular block II or III, bi-fasicular block, at screening or current or history of clinically significant ventricular arrhythmias. Other ECG abnormalities, if considered clinically significant by the investigator.
13) Participants receiving any of the prohibited medications (see Section 6.5.1) within the specified periods or who would be likely to require prohibited concomitant therapy during the trial.
14) Female participants who are breast-feeding or who have a positive pregnancy test result prior to receiving the first dose of IMP or RHEZ on Day 1.
15) Current history of significant drug and/or alcohol abuse that is likely to result in poor adherence to trial requirements or that would pose a risk to the participant's well-being during the course of the trial.
16) History of current hepatitis or carriers of hepatitis B surface antigen (HBsAg) and/or anti hepatitis C virus (HCV).

17) Participants who test positive for cocaine or other drugs of abuse (excluding known prescription stimulants and other prescribed medications and marijuana) at screening are excluded. Detectable levels of alcohol, marijuana, barbiturates, or opiates in the drug screen are not exclusionary if, in the investigator's documented opinion, the participant does not meet Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for moderate to severe substance use disorder and the positive test does not signal a clinical condition that would impact the safety of the participant or interpretation of the trial results, and participation is agreed to by the medical monitor prior to treatment.
18) History of having taken an investigational drug within 30 days preceding trial entry.
19) A history of difficulty in donating blood.
20) Donation of blood or plasma within 30 days prior to dosing.
21) History of serious mental disorders that, in the opinion of the investigator, would exclude the participant from participating in this trial.
22) Any known prior exposure to OPC-167832, DLM, or BDQ.
23) Participants with significant medical comorbidities that in the opinion of the investigator, should not participate in the trial.
24) Participants with Karnofsky score < 60 will be excluded from the trial.
25) Participants testing positive for active severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection at screening.
26) Participants with HIV co-infection not on a stable anti-retroviral regimen consisting of tenofovir, emtricitabine/ lamivudine, dolutegravir (ie > 3 months), or who have a detectable viral load, or who have a CD4 count < 250 cells/mm^3 will be excluded from the trial.

A definition of childbearing potential can be found in Section 10.3.

Participants must agree to restrictions to lifestyle and medications described in Section 5.3 and Section 6.5.1, respectively.

5.3 Lifestyle Considerations

Not applicable.

5.3.1 Meals and Dietary Restrictions

Consumption of grapefruit, grapefruit products, Seville oranges, or Seville orange products within 72 hours prior to the first dose of IMP (ie, DLM, OPC-167832, or BDQ) or RHEZ and during the trial is prohibited.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants will be encouraged to refrain from drinking alcoholic beverages or using illicit drugs during participation in the trial.

5.4 Screen Failures

Participants who sign an informed consent form (ICF) but who are not started on treatment are permitted to be rescreened. In the event that the participant is rescreened for trial participation, and the rescreening was not completed within the original screening window, a new ICF must be signed. Participants excluded for positive drug/alcohol screen are not eligible to be rescreened for participation in the trial. However, participants excluded for other reasons may be rescreened at any time if the exclusion characteristic has changed. In the event that the participant is rescreened a new ICF must be signed, a new screening number assigned, and all screening procedures repeated.

A screen failure is a participant from whom informed consent is obtained and is documented in writing (ie, participant signs an ICF), but who is not randomized or assigned trial treatment. All AEs must be reported after participant informed consent has been obtained, including screening failures due to AEs, irrespectively of IMP administration.

If the participant meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of informed consent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Screen failure date
- Reason for screen failure

6 Trial Treatments

6.1 Trial Treatments Administered

Treatment Arms 1, 2, and 3:

All IMP (ie, OPC-167832, DLM, or BDQ) must be administered after the completion of a meal.

Bedaquiline should be administered as follows: 400 mg QD for the first 2 weeks of treatment and 200 mg TIW thereafter with at least 48 hours between doses for the remainder of the trial (ie, a total of 17 weeks [Arm 1 or Arm 2 or Arm 3] of treatment).

IMP will be administered using the locally accepted adherence monitoring techniques which could include directly observed therapy (DOT), Wisepill, video DOTs, or other adherence monitoring techniques. In addition, all doses of IMP given during trial visits

will be observed via the hand-and-mouth procedure. IMP will be administered with approximately 240 mL of still (noncarbonated) water.

Treatment Arm 4:

Participants randomized to treatment Arm 4 will receive RHEZ orally QD for 8 weeks followed by 18 weeks of rifampin and isoniazid per the local standard of care.

RHEZ will be administered using the locally accepted adherence monitoring techniques which could include DOT, Wisepill, video DOTs, or other adherence monitoring techniques. In addition, all doses of RHEZ given during trial visits will be observed via the hand-and-mouth procedure. RHEZ will be administered with approximately 240 mL of still (noncarbonated) water. The RHEZ will be taken 1 hour prior to or 2 hours after a meal.

For information regarding the dose regimen and treatment period(s), including any follow-up period(s) for each treatment group/arm of the trial, see Section 4.1.

6.1.1 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

The IMPs to be administered during this trial include OPC-167832, DLM, and BDQ.

The reference product to be administered is RHEZ and rifampin/isoniazid.

For full details on IMP management, please refer to the OPC-167832 and DLM IBs and BDQ prescribing information.

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided by the sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). The IMP will be supplied as packages. OPC-167832 or DLM may not be repackaged by the trial site.

OPC-167832 and DLM will be provided to the investigator(s) and the persons designated by the investigator(s) or institutions by the sponsor or designated agent.

OPC-167832 and DLM will be supplied as follows:

- OPC-167832 will be supplied as 10 mg or 30 mg immediate-release tablets
- DLM will be supplied as 50 mg film-coated tablets

Each bottle or carton of OPC-167832 or DLM provided by the sponsor will be labeled to clearly disclose the compound identity, protocol number, the sponsor's name and address, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities.

Both BDQ and RHEZ will be sourced in country.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees. Neither the investigator(s) nor any designees may provide IMP or RHEZ to any participant not participating in this protocol.

The IMP and RHEZ will be stored according to the storage conditions indicated on the clinical labels.

The clinical trial site staff will maintain a temperature log in the drug storage area recording the temperature at least once each working day.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP and RHEZ received, dispensed, administered, and returned.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMPs, and partially-used IMPs must be destroyed at the trial site(s).

The assigned trial monitor will facilitate the destruction of used IMP containers, unused IMPs, and partially-used IMPs. The trial site(s) may utilize qualified third-party vendors for IMP destruction. A certificate of destruction should be filed within the IMP accountability.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, clinical trial participant, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, or performance of a medical device or medicinal product after it is released for distribution.

Examples include, but are not limited to, communications involving:

- Failure of a product to meet any of its specifications.

- Packaging defects (eg, damaged, dirty, crushed, missing product or component, incorrect or missing labeling).
- Product defects (eg, odor, chipped, broken, damaged, crushed, embossing illegible, under-filled bottle, over-filled bottle, empty bottle, no safety seal).
- Loss or theft of product.

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the sponsor IMP (ie, DLM or OPC-167832) from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including participant dosing. The investigator or designee must notify the sponsor (or sponsor's designee) by email within 24 hours of becoming aware of the PQC according to the procedure outlined below.

- Send PQC reporting information to the Otsuka Pharmaceutical Development & Commercialization, Inc. IMP complaints mailbox email: IMP-PQC@otsuka-us.com.

Also indicate whether or not the complaint sample is available for return.

Identification of a PQC by the participant should be reported to the site investigator, who should then follow the reporting mechanism above.

The investigator should report PQCs in accordance with respective manufacturing authorization holders for nonOtsuka products (per package label).

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter ID (eg, investigator, site, etc)
- Reporter contact information (eg, address, phone number, email address)
- Subject number
- Clinical site number
- ID of material (product/compound name, lot/batch number, shipment number, expiry date)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

If the complaint sample is available but not at the clinical site, please instruct the participant to bring the complaint sample to their next site visit.

It must be documented in the site accountability record that the complaint sample has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor. The investigator should report PQCs in accordance with the respective manufacturing authorization holders for nonOtsuka products (per package label).

6.3 Measures to Minimize/Avoid Bias

This is an open-label trial; however, the microbiology laboratory will be blinded to treatment assignments. The Miettinen and Nurminen confidence interval (CI) of common risk difference stratified by HIV status and cavitation status prior to randomization will be used to reduce bias in participant allocation to treatment groups.[8]

6.4 Participant Compliance

The time and dose of IMP and RHEZ administration during the trial will be recorded on the eCRF. Information regarding any inappropriately administered doses will also be documented on the eCRF. A Medication Event Reminder Monitor System will also be used to measure compliance.

6.5 Concomitant Medications or Therapies

The investigator will record all medications (including prescription medications, vaccines, over-the-counter medications, herbal remedies, etc) and therapies taken by the participant from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which participants are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the participant for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date and end date.

6.5.1 Prohibited Medications or Therapies

Quinolones should not be used within 3 months prior to the screening visit and during the screening period. The only antiretroviral therapy allowed for this trial is tenofovir, emtricitabine/ lamivudine, dolutegravir. Furthermore, participants must be on a stable antiretroviral regimen for at least 3 months prior to screening.

The selected cytochrome P450 (CYP)3A4 inhibitors and inducers presented in Table 6.5.1-1 and Table 6.5.1-2, respectively should not be used from Day −2 until the end of treatment.

Table 6.5.1-1 List of Selected Cytochrome P450 3A4 Inhibitors Prohibited During the Trial

Potent CYP3A4 Inhibitors:	
Viekira PAK2	Itraconazole
Tipranavir	Mibefradil
Ritonavir	Clarithromycin
Cobicistat	Nelfinavir
Ketoconazole	Nefazodone
Troleandomycin	Idelalisib
Telaprevir	Boceprevir
Posaconazole	Voriconazole
Telithromycin	
Grapefruit juice	
Conivaptan	
Moderate CYP3A4 Inhibitors:	
Erythromycin	Faldaprevir
Fluconazole	Imatinib
Atazanavir	Verapamil
Diltiazem	Netupitant
Darunavir	Nilotinib
Dronedarone	Tofisopam
Crizotinib	Cyclosporine
Atazanavir	Ciprofloxacin
Aprepitant	Isavuconazole
Casopitant	Cimetidine
Amprenavir	

Note: Please communicate with the sponsor's medical monitor if the participant needs to receive any medication (other than IMP or RHEZ) that is not on this list.

Table 6.5.1-2 List of Selected Cytochrome P450 3A4 Inducers Prohibited During the Trial	
Potent CYP3A4 Inducers:	
Carbamazepine	Enzalutamide
Mitotane	Phenytoin
St. John's wort	
Moderate CYP3A4 Inducers:	
Bosentan	Efavirenz
Etravirine	Modafinil

Note: Please communicate with the sponsor's medical monitor if the participant needs to receive any medication (other than IMP or RHEZ) that is not on this list.

6.5.2 Permitted Medications or Therapies

Not applicable.

6.5.3 Rescue Medications

Rescue treatment consisting of the standard of care treatment, ie, RHEZ, will be provided in the following circumstances:

1) If a participant is sputum culture positive for *M tuberculosis* at the end of treatment,
2) If a participant has a microbiologic relapse subsequent to the end of treatment, or
3) If, in the opinion of the investigator, a participant is clinically deteriorating, based on any combination of signs, symptoms, or chest radiograph data.

Note: Standardized rescue treatment consisting of RHEZ is to be used for Arm 1, Arm 2, and Arm 3 not responding to therapy. However, participants in Arm 4 will receive individualized care according to local guidelines. All participants who require rescue treatment will be considered treatment failures for the purposes of the trial.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, Independent Ethics Committee (IECs)/Institutional Review Boards (IRBs), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IEC if judged to be necessary for medical, safety, regulatory, ethical or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP). The investigator will notify the sponsor promptly if the trial is terminated by the investigator or the IEC at the site.

7.3 Individual Participant Discontinuation

After the first dose of IMP or RHEZ on Day 1, a participant may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a participant or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other reasons, as determined by the investigator. However, each investigator must comprehensively review the circumstance and offer the participant options for continued treatment to the degree possible as described in Section 7.3.5.

A participant who discontinues treatment will have an end of treatment visit, which should be scheduled as soon as possible after the participant's last dose of IMP to conduct the assessments defined in Table 1.3-1.

After the end of treatment visit, off-treatment completers may remain in the trial to complete some or all of the remaining visit assessments as defined in Table 1.3-1.

Participants whose consents are completely withdrawn will be discontinued from the trial as trial non-completers.

If during the trial the sponsor finds any unacceptable safety concerns on the safety of a high dose DLM + BDQ + OPC-167832 group, the enrollment of new participants in the high dose group can be discontinued or reduced and allocated to the remaining sample size for other dose level(s).

7.3.1 Treatment Interruption

Not applicable.

7.3.2 Treatment Discontinuation

After treatment assignment, a participant may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a participant or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator. However, each investigator

must comprehensively review the circumstances and offer the participant options for continued treatment to the degree possible as described in Section 7.3.5.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

A participant may discontinue IMP for the reasons listed below:

- Adverse event
  - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard
  - Continuing IMP places the participant at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
    - SAE
    - Other potentially IMP-related safety concerns or AEs
- Death
- Disease relapse
- Failure to meet randomization criteria
- Lack of efficacy
- Lost to follow-up
- Noncompliance with IMP
- Physician decision
- Pregnancy (see Section 10.3)
- Progressive disease
- Protocol deviation
- Protocol violation
- Protocol-specific withdrawal criterion met
- Randomized by mistake
- Randomized by mistake with trial treatment
- Site terminated by sponsor
- Trial terminated by sponsor
- Withdrawal by participant

If the participant discontinues IMP due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.2 must be followed.

7.3.4 Withdrawal of Consent

Each participant has the right to withdraw their consent from further participation in the trial at any time without prejudice. Participants can withdraw consent for use of data which has not previously been anonymously transferred into trial data sets collected as part of the trial and can only withdraw consent for future participation. The investigator can also discontinue a participant's participation in the trial at any time if medically necessary. Unless the participant provides their written withdrawal of consent or there is other written documentation by the investigator confirming the participant's verbal intent to completely withdraw from the trial, participants should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a participant's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by participant and trial site staff).
- Contact of the participant by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the participant's medical condition, even if only by telephone, mail, or email (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a participant's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the participant and the integrity of the trial. A participant may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.2). A participant may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should follow the procedures outlined in Section 7.3.3 to determine if the participant can continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only participants who withdraw their permission for

all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

CCI [redacted].

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators will be instructed to meet and discuss (without undue coercion) with the participant their options of continuing in the trial, preferably on therapy. The investigator should ensure understanding and documentation of the reasons for the participant's desire to withdraw consent. Refer to Section 6.5.3 regarding rescue medications.

7.4 Definition of Participants Lost to Follow-up

Participants who cannot be contacted on or before the trial visits at Weeks 17 (for Arm 1, Arm 2, and Arm 3) and Week 26 (for Arm 4) during the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up". Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the participant, medical records, successful telephone contact with the participant, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the participant by telephone and in the event the site is unable to reach the participant by telephone, the site will attempt to contact the participant via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the participant was classified as "lost to follow-up", "Were you able to contact the participant?", "Date of contact/Date of final contact attempt" and "Contact method" will be recorded in the eCRF.

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Table 1.3-1.

8.1 Efficacy Assessments

8.1.1 Sputum Sampling and Microbiology Laboratory Assessments

Refer to Section 10.5 (Appendix 5) for a detailed collection schedule of sputum samples for each treatment arm.

8.1.1.1 Sputum for Eligibility Assessments

A sputum sample will be collected spontaneously (ie, not induced) by the site staff during the screening period (Day −14 to Day −2) to confirm the presence of *M tuberculosis* that is susceptible to isoniazid and rifampin. The specimen will be tested by a molecular assay that can rapidly detect drug resistance to these 2 drugs.

8.1.1.2 Sputum for Efficacy Assessments

Sputum samples will be collected as per Table 1.3-1 for processing.

Up to 3 sputum samples will be tested at each scheduled visit except for Day −1 and Day 1 (on these days, site staff will collect 1 sputum sample for culture, and 1 sputum for ribosomal ribonucleic acid synthesis ratio [RS ratio] on each day). The Day 1 sputum will be collected prior to the first dose of IMP. For subsequent visits, specimen number 1 will be collected by the participant early in the morning, preferably prior to the morning meal. On Day −1 only, sputum specimen 1 will be tested for acid-fast bacilli smear microscopy to assess baseline bacterial burden, in addition to the assays below.

Specimen number 2 will be collected at the site by the trial site staff. Sputum specimens 1 and 2 from all study visits will be processed using the Mycobacteria Growth Indicator Tube® (MGIT) liquid culture system. Culture growth will be confirmed as *M tuberculosis* complex using a rapid commercial test (immunochromatographic or molecular). An immunoassay to measure sputum LAM concentration will also be performed at each visit. Lowenstein-Jensen cultures may be performed on sputum as necessary.

If a participant (in Arms, 1, 2, and 3) is unable (RHEZ) to spontaneously expectorate sputum number 2 during site collection, an attempt will be made to induce sputum production by aerosol inhalation. Trial sites will use their local procedure for sputum induction. If neither sputum number 1 nor sputum number 2 is collected on the visit date, participants should return to the site to attempt to produce a sample(s) once over the next 72 hours, if necessary. Sputum samples will be defined as unobtainable if no sputum can be obtained during this 72-hour period after an attempt at sputum induction.

If the participant is able to spontaneously produce a subsequent specimen during the visit, specimen number 3 will be collected directly into ribonucleic acid preservation media

and frozen for batch measuring of the RS ratio. If this sputum cannot be collected, this will not be considered a protocol deviation.

Refer to the trial operations manual for further guidance on proper collection of sputum specimens at each scheduled visit.

Susceptibility testing (DST) for anti-TB medications will be performed on positive *M tuberculosis* isolates from Day –1 cultures. If Day –1 culture is not positive for *M tuberculosis*, testing will be performed on Day 1 or Week 1 cultures. Susceptibility testing will also be performed on the end of treatment sputum specimen, if positive for *M tuberculosis* (Week 17 for Arms 1, 2, and 3, or Week 26 for Arm 4), as well as on positive cultures from participants suspected of relapse. Susceptibility testing may also be performed at other timepoints at the request of the principal investigator or the sponsor.

To determine if the participant has relapsed or has a new infection of *M tuberculosis*, genotyping will be performed on the baseline culture (Day –1 and/or Day 1, or Week 1, if necessary) and the first of any subsequent positive culture during the post treatment follow-up period. In addition, the sponsor may request genotyping as needed.

Positive *M tuberculosis* isolates will be stored long-term for confirmatory testing and potential additional characterization of the bacteria, as necessary.

8.1.2 Signs and Symptoms of Tuberculosis

An aggregate of clinical signs and symptoms of pulmonary TB will be assessed at screening and throughout the trial. Signs and symptoms will be assessed by the investigator (cough, hemoptysis, dyspnea, chest pain, loss of appetite, feeling feverish, and night sweats); from vital signs and physical examination (weight, body mass index, body temperature, respiratory rate and heart rate); from clinical laboratory tests (hemoglobin, hematocrit, c-reactive protein, and serum albumin); and from chest radiograph. A chest radiograph must be taken during the screening period, and an official interpretation must be available, and the assessment of its compatibility with pulmonary TB must be made, prior to randomization. An end of treatment chest radiograph will be taken at Week 17 (for participants in Arms 1, 2, and 3) or Week 26 (for participants in Arm 4) and at Month 12.

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8.3 Pharmacodynamic Assessments

8.3.1 Pharmacodynamic Laboratory Tests

Sputum culture using MGIT: culture conversion and time-to-detection.

8.4 Pharmacogenomic Assessments

8.4.1 Pharmacogenomic Samples

Not applicable.

8.5 Exploratory Biomarker Assessments

Exploratory biomarkers include positron emission tomography/computerized axial tomography (PET/CT) imaging, RS ratio, and transcriptomic signatures from whole blood. The type of PET/CT in this trial is positron emission tomography with 2-[^{18}F]-fluoro-2-deoxy-D-glucose.

Whole blood samples to longitudinally assess transcriptomic signatures previously associated with TB cure will be collected using Paxgene ribonucleic acid tubes at the time points described in the schedule of assessments (Table 1.3-1). Genomic ribonucleic acid will be extracted from a whole blood sample and stored until shipped to the designated laboratory for analysis. Additional information will be provided in the Laboratory Manual.

Results from exploratory biomarker assessments will be reported separately from the main clinical study report.

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8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2. Refer to Section 8.8.5 for potential serious hepatotoxicity. The Division of AIDS (DAIDS) table criteria will be used for identifying laboratory values of potential clinical relevance.[9] The total volume of blood to be collected during the trial will be documented in the ICF form.

8.7.2 Physical Examination

Either a complete or targeted physical examination will be performed at the time points described in the schedule of assessments (Table 1.3-1). Visual assessments to be completed during screening will consist of Snellen and Ishihara testing and will be repeated during the trial if the investigator suspects abnormalities.

8.7.3 Vital Signs

Vital signs include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (rpm), body temperature (C), height (cm) (only at screening), weight, and body mass index (BMI). Vital signs will be obtained prior to CCI [redacted] and ECGs at the nominal time points, where applicable. At screening, blood pressure and heart rate will be taken with the participant in the supine (performed first) and sitting position after remaining for ≥ 3 minutes in each position and temperature and respiratory rate will be taken with the participant in the supine position. At all other time points, vital signs will be obtained after the participant has been at rest in the supine position for at least 1 minute.

Vital signs will be collected at the trial visits described in the schedule of assessments (Table 1.3-1). Participants should be monitored for potentially clinically significant vital signs values. The DAIDS table criteria will be used for identifying vital signs of potential clinical relevance.[9]

8.7.4 Electrocardiogram

One standard 12-lead ECG will be performed during screening, plus 3 ECGs at baseline (Day −1) spaced 5 to 10 minutes apart, and 3 ECGs at all subsequent visits during the treatment and follow up periods. Where multiple ECGs are required in a visit, the participant should be recumbent for 10 minutes prior, if possible, and ECGs should be collected 5 to 10 minutes apart after the dose of IMP [redacted].

Electrocardiograms will be performed at the trial visits described in the schedule of assessments (Table 1.3-1). Participants should be monitored for potentially clinically significant ECG results. The DAIDS table criteria will be used for identifying ECGs of potential clinical relevance.[9]

8.7.5 Suicidality Monitoring

Not applicable.

8.7.6 Other Safety Variables

A PET/CT scan will be performed on participants that consent to this assessment at the trial visits described in the schedule of assessments (Table 1.3-1). If the PET/CT scan is unavailable, the participant is permitted to continue in the trial.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a clinical trial participant administered an IMP or trial treatment and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the IMP or trial treatment and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

TEAEs are defined as AEs with an onset date on or after the start of treatment. In more detail, TEAEs are all AEs which started after the start of IMP treatment; or if the event was continuous from baseline and was worsening, serious, IMP related, or resulted in death, discontinuation, interruption, or reduction of IMP.

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Adverse Events of Special Interest (AESIs): A noteworthy event for the particular product/IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as immediately reportable event (IREs). No AESIs have been identified for the IMP to be administered during this trial. There are no AESIs in this trial.

Immediately Reportable Event (IRE):

- Any SAE.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.5).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Clinical Trial Pregnancy and Breastfeeding Form(s) to the sponsor. This includes pregnancy of the participant or the partner of the participant. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a female participant and there is an abnormality or complication.

Clinical Laboratory Test Value Changes: It is the investigator's responsibility to review the results of laboratory tests for each individual participant as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (participant is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity: Adverse events will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild:	Discomfort noticed, but no disruption to daily activity.
2 = Moderate:	Discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	Inability to work or perform normal daily activity.

Note: In addition, all AEs will be graded on a 5-point scale according to the "DAIDS Table for Grading the Severity of Adult and Pediatric AEs".[9]

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

8.8.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess participants for the occurrence of AEs. To avoid bias in eliciting AEs, participants should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the participant must be recorded on the source documents and eCRF provided by the sponsor. Adverse event collection will begin after a participant signs the ICF and will continue until the follow up visit 12 months postrandomization. All AEs must be reported after participant informed consent has been obtained, including screening failures due to AEs, irrespective of IMP administration.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the sponsor must be notified immediately by telephone, fax, or email of any IREs according to the procedure outlined below, in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

The adverse event, start date, end date, seriousness, severity, relationship to trial treatment (IMP causality), action taken with trial treatment, and outcome will be recorded on the source documents and in the eCRF.

8.8.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after he/she or site personnel become aware of any IRE (SAE, AE related to occupational exposure, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or email to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Subject confidentiality must be protected and contact information such as name, address, phone number or any other protected health information as determined by applicable local regulation must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.8.7.2.

8.8.4 Adverse Events of Special Interest

Not applicable.

8.8.5 Potential Serious Hepatotoxicity

For a participant who experiences an elevation in AST or ALT that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and also report as an AE in the eCRF.

8.8.6 Procedure for Breaking the Blind

Except for the microbiology laboratory being blinded to the treatment assignment of each participant, this trial does not use blinding procedures.

8.8.7 Follow-up of Adverse Events

8.8.7.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time during the trial must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.8.7.2 Follow-up of Immediately Reportable Events

This trial requires that participants be actively monitored for IREs up to 12 months after randomization, or the last scheduled visit.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such on the AE eCRF page and the IRE form. If updated information (eg, resolved status) on IRE status becomes available after a participant's last scheduled contact (up to last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded on the AE eCRF page and the IRE form, according to the appropriate reporting procedures described in Section 8.8.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the participant and will provide prompt updates on the participant's status to the sponsor. The investigator will follow IREs until the events are:

- Resolved,
- Recovered/Resolved with sequelae
- The participant is lost to follow-up, or
- Has died.

Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for participants that become pregnant or for pregnant partners of male participants.

8.8.7.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator which occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3.This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the participant is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdose, please refer to the IB for DLM or OPC-167832, or the package insert for BDQ and RHEZ.

8.10 Participant Assessment Recording

Not applicable.

8.11 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

It is planned to enroll enough participants so there will be 20 participants in DLM + BDQ + 10 mg OPC-167832, 40 participants each in DLM + BDQ + 30 mg OPC-167832, and DLM + BDQ + 90 mg OPC-167832, and 20 participants in RHEZ group. This is a pilot trial and exploratory in nature. Thus 80% CIs between proportion differences will be calculated to compare with noninferiority margin. Assuming that the sputum culture conversion (SCC) rate for the primary endpoint is 93% for the RHEZ group, and assuming the SCC rate of the investigational arms is identical to the RHEZ group, with a noninferiority margin of 12%, sample size of 120 participants (100 for pooled DLM + BDQ + OPC-167832 and 20 for RHEZ) will have about 84% power to reject the null hypothesis with a one-sided alpha level of 0.1, ie, the lower limit of the two-sided 80% CI of the difference in proportions of sputum conversion between the pooled investigational arms and RHEZ is larger than -0.12. The Miettinen and Nurminen method to construct 80% CI was used in the sample size calculation.[8] Assuming 11% randomized participants will not demonstrate at least 1 positive culture result by Week 1 and susceptibility to rifampin and isoniazid, approximately 135 participants will be

randomized in 1:2:2:1 ratio to obtain 120 participants in the modified intent-to-treat (mITT) analysis set.

9.2 Datasets for Analysis

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The safety analysis set includes all participants who receive any dose of IMP or RHEZ. Safety analysis will be conducted based on the safety analysis set.

The mITT analysis set includes all randomized participants who take at least 1 dose of IMP or RHEZ, have at least 1 postbaseline culture result, and demonstrate positive culture results by Week 1 and susceptibility to rifampin and isoniazid (from the screening specimen).

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

Missing data caused by participant discontinuation will be handled by a composite variable strategy according to International Council for Harmonisation (ICH) E9 (R1) Addendum.[10] Participants who discontinue early from the trial during the treatment period without an SCC outcome will be considered as no SCC.

9.4 Statistical Analyses

9.4.1 Efficacy Analyses

9.4.1.1 Primary Efficacy Endpoint Analysis

The primary efficacy endpoint of the trial is the proportion of participants who have SCC and no subsequent positive culture by the end of treatment. Sputum culture conversion occurs when a participant has the first of 2 visits of at least 1 week apart with sputum cultures negative and without a positive sputum culture result in between.

The 3 DLM + BDQ + OPC-167832 arms will be pooled, and noninferiority with RHEZ will be established if the lower limit of 80% CI for the difference of proportion of participants with SCC between the pooled DLM + BDQ + OPC-167832 group is larger than -0.12. The Miettinen and Nurminen CI of common risk difference stratified by HIV status and cavitation status prior to randomization will be used.[8] If there is a stratum of very small size, strata may be collapsed. The SAP will describe the details. The 80% CI of the proportion difference between each dose level of DLM + BDQ + OPC-167832 arm and RHEZ will be provided. In addition, Cochran-Armitage test will be used to detect trend in proportion of SCC with increasing OPC-167832 dose.

9.4.1.2 Secondary Efficacy Endpoint Analysis

The secondary efficacy endpoints of this protocol are:

- The proportion of participants in each arm who achieve SCC in MGIT by 8 weeks of treatment.
- Time to detection of MGIT cultures.
- The proportion of participants in each arm who convert sputum LAM to negative by 8 weeks of treatment and by end of treatment.
- Proportion of participants who develop drug resistance.
- Time to SCC.

For a proportion endpoint, the same analysis methodology specified for the primary endpoint will be used. A 12% noninferiority margin will be used if the goal is to establish noninferiority.

The Kaplan-Meier curve of time to SCC will be provided for each group and relationship between time to SCC and PK parameters will be studied.

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Control of Experiment-wise Type 1 Error is not applicable to this trial.

9.4.1.3 Exploratory Biomarker Endpoint Analysis

Exploratory biomarker endpoints are:

- Longitudinally assess PET/CT imaging response over the course of treatment.
- Longitudinally evaluate the RS ratio decline in sputum.
- Longitudinally assess whole blood transcriptomic signatures previously associated with TB cure from serum.

Results from exploratory biomarker assessments will be reported separately from the main clinical study report.

9.4.2 Safety Analysis

Safety endpoints will be summarized using descriptive statistics (number, median, mean, standard deviation, minimum, maximum) for continuous values, and by frequency and percentage for discrete variables. Percentage and frequency of AEs and clinical laboratory test results by grades will be analyzed.

9.4.2.1 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. The incidence of the following events will be summarized by treatment group:

- TEAEs
- TEAEs by severity
- TEAEs potentially causally related to the IMP or trial medication
- TEAEs with an outcome of death or trial medication
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP or trial medication

In addition, TEAEs by DAIDS grades will be summarized.

9.4.2.2 Clinical Laboratory Data

For clinical laboratory tests data, baseline is defined as the last nonmissing value obtained at a scheduled visit on or before Day −1. If the Day −1 measurement is missing, the baseline value will be the last nonmissing measurement from the screening visit (the previous scheduled visit). Clinical laboratory test parameters and mean changes from baseline will be summarized by treatment. The incidence of potentially clinically significant changes and abnormalities in clinical laboratory test parameters will be summarized. Clinical laboratory test data will be presented in listings.

9.4.2.3 Physical Examination and Vital Signs Data

Physical examination data will be presented in listings.

Vital sign parameters and mean changes from baseline will be summarized by treatment arm. The incidence of potentially clinically significant changes and abnormalities in vital sign parameters will be summarized. Vital sign data will be presented in listings.

9.4.2.4 Electrocardiogram Data

Electrocardiogram measurements and mean changes from baseline will be summarized by treatment. The baseline ECG is defined as Day −1. If the measurement from Day −1 is missing, the screening ECG is taken as baseline. The incidence of potentially clinically significant changes and abnormalities in ECG evaluations will be summarized. Electrocardiogram data will be presented in listings.

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Summaries of demographics, TB medical history, TB disease severity, and sputum specimen results at baseline will be provided. Continuous variables will be summarized with mean, standard deviation, minimum, median, and maximum.

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[redacted]

9.4.3.3 Pharmacodynamic Analysis

Not applicable.

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[redacted]

9.4.3.5 Pharmacogenomic Analysis

Transcriptomic signatures previously associated with TB cure from serum will be longitudinally assessed. Details will be included in the approved SAP.

9.4.3.6 Exploratory Efficacy Endpoint Analysis

Exploratory efficacy endpoints are:

- The proportion of participants with relapse at 12 months postrandomization
- The proportion of participants with favorable outcome in each experimental arm as compared to the RHEZ standard treatment arm at 6 months post end of treatment and at 12 months postrandomization.

Detailed analysis methods for these exploratory efficacy endpoints will be provided in the SAP.

As an exploratory efficacy analysis, the proportion of participants with favorable outcome at 6-month post end of treatment and at 1-year postrandomization will be

compared between each and pooled DLM + BDQ + OPC-167832 group(s) and RHEZ group using differences and its 80% CI.

As an exploratory analysis, the proportion of participants with relapse at 1-year postrandomization will be compared between each and pooled DLM + BDQ + OPC-167832 group(s) and RHEZ group using differences and its 80% CI.

Definition of favorable and unfavorable outcome:

A participant is considered to have a **favorable** outcome if, during the postrandomization evaluation period, the participant is alive, completed the postrandomization evaluation period, and otherwise did not meet the definition of an unfavorable outcome.

A participant is considered to have an **unfavorable** outcome if one of the following occurs:

1) Clinical progression of pulmonary disease during treatment or the need for an unanticipated surgical intervention for TB (eg, lobectomy).
2) Any growth of *M tuberculosis* from an extrapulmonary site during the post-treatment period (Note: Excludes reinfection with a new strain of *M tuberculosis*).
3) Signs and symptoms of active tuberculosis during the follow-up period (ie, after the end of treatment), including radiographic worsening compared to baseline findings, resulting in re-initiation of anti-mycobacterial therapy (Note: Excludes a re-initiation that is subsequently found to be due to a misdiagnosis and/or alternative diagnosis).
4) Death during treatment or follow-up.
5) A sputum culture with growth of *M tuberculosis* at certain time points as follows:
    - Failure to achieve SCC at the end of the treatment period that result in a change in anti-mycobacterial therapy.
    - Microbiologic relapse during the follow-up period (ie, after the end of treatment) (Note: Excludes reinfection and requires more than 1 positive sputum culture with a new strain of M tuberculosis).

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9.5.1 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be contracted by Otsuka to review safety and efficacy data during the conduct of the trial. The DMC will convene and operate based on an established charter. The DMC will be permitted to seek additional independent expertise, as needed. The primary responsibility of the DMC will be to monitor safety and to advise the sponsor of the clinical project regarding whether or not the safety concerns merit stopping the trial. Towards this objective the DMC will meet on a predetermined schedule to review safety and available efficacy data.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, applicable ICH GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB or IEC according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB/IEC will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting participant privacy. To this end, a participant ID will be used to identify each participant.

Financial aspects, participant insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

10.1.2 Informed Consent

Informed consent will be freely obtained from all participants (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB/IEC that approves this protocol.

Each ICF will comply with the ICH (International Council for Harmonisation) GCP Guidelines, and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB/IEC.

Investigators may discuss trial availability and the possibility for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential participants are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the participant by the investigator (or a qualified designee), and it

has been documented that the participant has had the opportunity to ask questions and have those questions answered, the IRB/IEC-approved paper ICF will be signed and dated by both the participant and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB/IEC. The participant will receive a copy of the signed ICF; the original shall be kept on file by the investigator. Participants may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the participants, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male participants who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the non-participant partner and fetus.

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10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, participant bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Participants will be identified only by unique participant ID in the eCRF. If further participant ID is required, participants' full names may be made known to a regulatory agency or other authorized officials if necessary, sub participant ject to local regulations.

10.1.4 Quality Control and Quality Assurance

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, email, and written communications. In addition, all investigators and trial

site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via email. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the participant's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, logs, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, participant confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each participant's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator's decision to enroll the participant into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the participant's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General participant status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and IMP compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record.

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 Code of Federal Regulations Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on eCRF, such as data received from central laboratories and central ECG readers, will be reconciled using key data fields by the sponsor or the clinical research organization with the eCRF data to ensure consistency.

10.1.6.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

Regulatory requirements for the archival of records for this trial necessitate that participating investigators maintain detailed clinical data for the longest of the following 3 periods:

- A period of at least 2 years after the date on which approval to market the drug is obtained (or if IMP development is discontinued, the date regulatory authorities were notified of discontinuation); OR
- A period of at least 3 years after the sponsor notifies the investigator that the final report has been filed with regulatory authorities.
- Longer, region-specific storage requirements, if applicable.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is participant to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial participants who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial participants consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology: Hemoglobin Hematocrit Mean corpuscular hemoglobin concentration Mean corpuscular volume Red blood cell (RBC) count White blood cell (WBC) count (absolute and differential) Platelets Coagulation (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR]) CD4 count Urinalysis: Specimen appearance Color Occult blood Glucose Microscopic analysis, if indicated, WBC/RBC counts per high powered field pH Protein Specific gravity Additional Tests: Urine pregnancy for FOCBP Serology (hepatitis B surface antigen [HbsAg], hepatitis C antibodies [anti-HCV], HIV), SARS-CoV-2 polymerase chain reaction test or antigen test (where appropriate) HIV-viral load HbA1c	Serum Chemistry: Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bilirubin Blood urea nitrogen Calcium Cholesterol Creatinine/eGFR Gamma glutamyl transferase Glucose Lactate dehydrogenase Magnesium Potassium Protein Sodium Triglycerides Serum albumin C-reactive protein Drug Screen (all items in urine except where noted) Alcohol (urine or blood test) Amphetamines Barbiturates Benzodiazepines Cannabinoids Cocaine Methadone Opiates Phencyclidine

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential (FOCBP) are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months). Females of nonchildbearing potential do not meet definition of FOCBP.

For males and FOCBP, or their partners, who are sexually active, there must be a documented agreement that the participant and their partner will take effective measures (ie, 2 different approved methods of birth control or abstinence) to prevent pregnancy during the course of the trial and for 12 weeks after the last dose of IMP or RHEZ. Unless the participant is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months; or males who have had a bilateral orchiectomy) and for 12 weeks after the last dose of IMP of RHEZ, 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, birth control implant, birth control depot injection, birth control patch, condom, sponge, or occlusive cap (vaginal diaphragm or cervical/vault cap). Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. The contraceptive method will be documented in the eCRF or source document. Male participants must also agree not to donate sperm from trial screening through 12 weeks after the last dose of IMP or RHEZ.

Before enrolling males and females in this clinical trial, investigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Participants must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin will be performed at screening on all FOCBP and female participants ≥ 12 years of age, if menstruation has

started. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male participants must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a participant is suspected to be pregnant before she receives IMP or RHEZ, the IMP or RHEZ administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the participant must not receive the IMP or RHEZ and must not be enrolled in the trial. If pregnancy is suspected while the participant is taking IMP or RHEZ, the IMP or RHEZ must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety) but the participant will not be automatically withdrawn from the trial. Pregnant participants will be encouraged to remain in the trial and continue with all visit procedures as scheduled other than dispensation of IMP unless contraindicated by pregnancy.

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP or RHEZ exposure during the trial and for at least 12 weeks after the last dose of IMP or RHEZ, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Clinical Trial Breastfeeding and Pregnancy form in addition to the IRE form to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Clinical Trial Breastfeeding and Pregnancy Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth. Local regulatory requirements must be followed for follow-up and reporting on pregnancy cases and/or infants.

10.4 Appendix 4: List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Anti-HCV	Hepatitis C antibodies
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{24h}	Area under the concentration-time curve from zero to 24 hours
BDQ	Bedaquiline
BID	Twice daily
BMI	Body mass index
CFR	Cumulative fraction of response
CFU	Colony-forming unit
CI	Confidence interval
C_{max}	Maximum (peak) plasma concentration
CYP	Cytochrome P450
DAIDS	Division of AIDS
DprE1	Decaprenylphosphoryl-β-D-ribose 2'-oxidase
DLM	Delamanid
DMC	Data Monitoring Committee
DOT	Directly observed therapy
DS-TB	Drug-susceptible tuberculosis
EBA	Early bactericidal activity
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ET	Early termination
CCI	[redacted]
FOCBP	Female of childbearing potential
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HFS-TB	Hollow fiber system of tuberculosis
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug

Abbreviation	Definition
INR	International normalized ratio
IRB	Institutional Review Board
IRE	Immediately reportable event
LAM	Lipoarabinomannan
MAD	Multiple ascending dose
MDR-TB	Multidrug-resistant tuberculosis
MGIT	Mycobacteria Growth Indicator Tube®
MIC	Minimum inhibitory concentration
mITT	Modified intent-to-treat
NOAEL	No observed adverse effect level
OBR	Optimized background regimen
Otsuka	Otsuka Pharmaceutical Co, Ltd
PET/CT	Positron emission tomography/computerized axial tomography
PK/PD	Pharmacokinetics/pharmacodynamics
PQC	Product quality complaint
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's method
RBC	Red blood cell
RHEZ	Rifampin, isoniazid, ethambutol, and pyrazinamide
RS ratio	Ribosomal ribonucleic acid synthesis ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus
SCC	Sputum culture conversion
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TIW	Thrice-weekly
ULN	Upper limit of normal
WBC	White blood cell

10.5 Appendix 5: Schedule of Sputum Collections for All Treatment Arms

Sample:		Sputum - MGIT Culture/ LAM	Sputum - MGIT Culture/ LAM	Sputum - RS Ratio
Collected by:		Participant at home	Site staff	Site staff
Day	-14 to -2	-	X (eligibility assessment only)	-
	-1	-	X	X
	1	-	X	X
Week	1	X	X	X
	2	X	X	X
	3	X	X	X
	4	X	X	X
	5	X	X	X
	6	X	X	X
	7	X	X	X
	8	X	X	X
	10	X	X	X
	12	X	X	X
	13	X	X	X
	15	X	X	X
	17	X	X	X
	19	X	X	X
	21	X	X	X
	23	X	X	X
	26	X	X	X
	28	X	X	X
Week	30 to 52/ET	X	X	X

10.6 Appendix 6: Completer Category Information

Treatment completer, trial completer	Randomized participant who has taken at least one dose of IMP/RHEZ Does not discontinue treatment in the treatment period (17weeks for IMP/26 weeks for RHEZ) Has at least some assessments at the 17 week/26week end-of-treatment visit (completes end-of-treatment visit) Continues on trial till the end-of-study visit at 12 months post-randomization; completes end-of-study assessments
Treatment non-completer, trial completer	Randomized participant who has taken at least one dose of IMP/RHEZ Discontinues treatment prior to the end of the treatment period (17 weeks for IMP/26 weeks for RHEZ) Continues on trial till the end-of-study visit at 12 months post-randomization; completes end-of-study assessments
Treatment completer, trial non-completer	Randomized participant who has taken at least one dose of IMP/RHEZ Does not discontinue treatment in the treatment period (17 weeks for IMP/26 weeks for RHEZ) Has at least some assessments at the 17week /26week end-of-treatment visit (completes end-of-treatment visit) May or may not continue on trial after end-of-treatment visit. Does not continue till the end-of-study visit at 12 months post-randomization; does not complete end-of-study assessments Includes participants who do not complete 12 months of post-randomization follow-up for any reason: participants who die after end-of-treatment visit; participants LTFU after end-of-treatment visit; participants who withdraw/are withdrawn from the study after end-of-treatment.
Treatment non-completer, trial non-completer	Randomized participant not treated with IMP/RHEZ OR at least one dose of IMP/RHEZ If study treatment was started, discontinues treatment prior to the end of the treatment period (17 weeks for IMP/26 weeks for RHEZ) May or may not continue on trial after discontinuing treatment. If continues on study, discontinues prior to end-of-study visit at 12 months post-randomization; does not complete end-of-study assessments at the 12-month timepoint. Includes participants who: participants who die/are LTFU/withdraw/are withdrawn prior to 17/26 weeks treatment period participants who die/are LTFU/withdraw/are withdrawn after discontinuing treatment (prior to 17/26 weeks) but prior to 12 months post-randomization

10.7 Appendix 7: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB/IEC. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB/IEC, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators will wait for IRB/IEC approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of participants, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately after agreement by the sponsor and investigator, followed by IRB/IEC notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB/IEC, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the participant, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB/IEC, repeat written informed consent will be obtained from participants enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

10.7.1 Protocol Amendment(s)/Administrative Change(s)

Please see Appendix 1, Appendix 2, and Appendix 3.

11 References

1 World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization; 2020.

2 Sirturo (bedaquiline) [US Prescribing Information]. Titusville, NJ: Janssen Therapeutics, Division of Janssen Products, LP; May 2020.

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5 Otsuka Pharmaceutical Development and Commercialization, Inc. OPC-167832 Investigator's Brochure, Edition 6. Otsuka Report, issued 20 Apr 2021.

6 Aventis Pharma (Pty) Ltd. Rifafour e-275 tablets Package Insert. South African Electronic Package Inserts. Published 11 Feb 2002.

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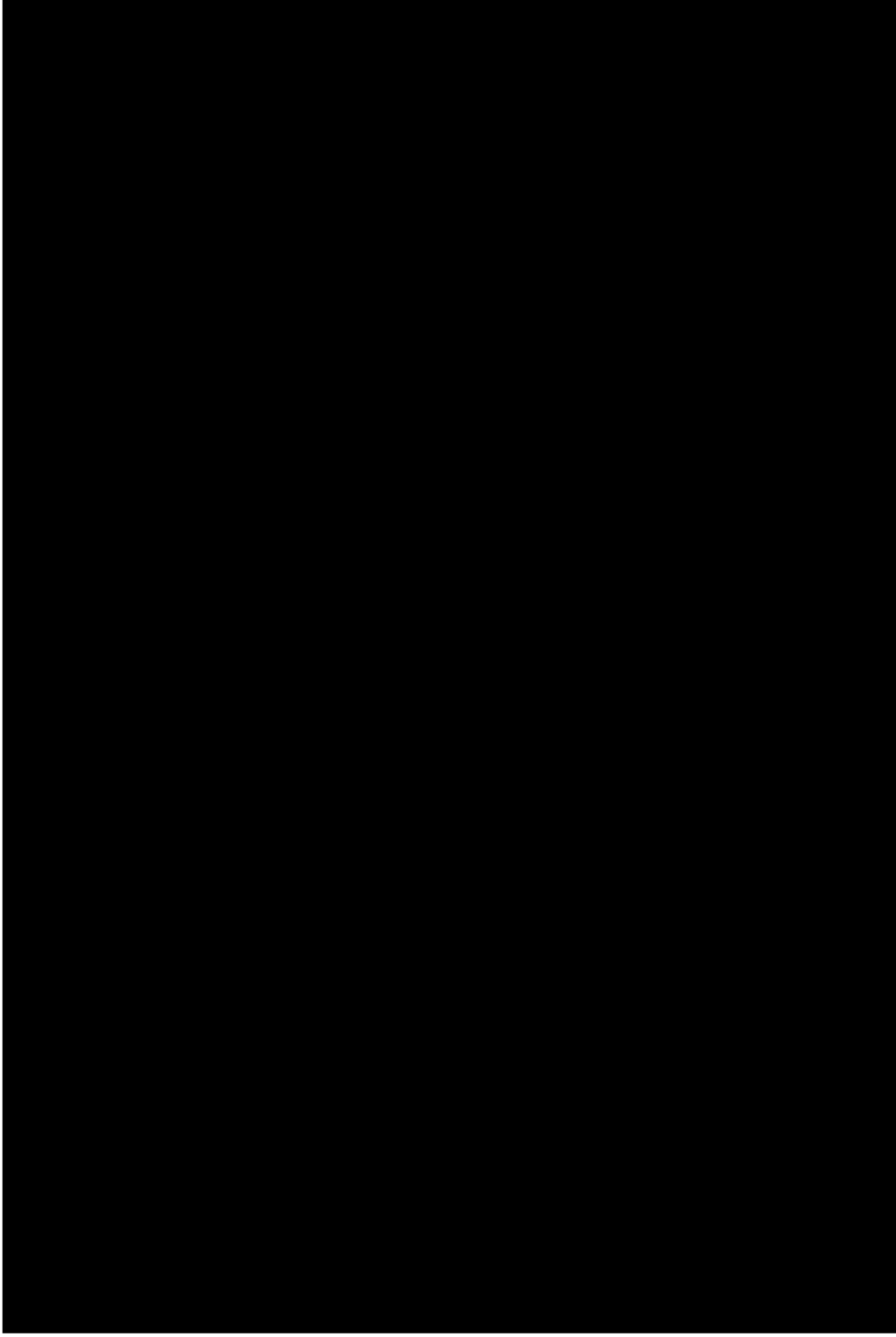
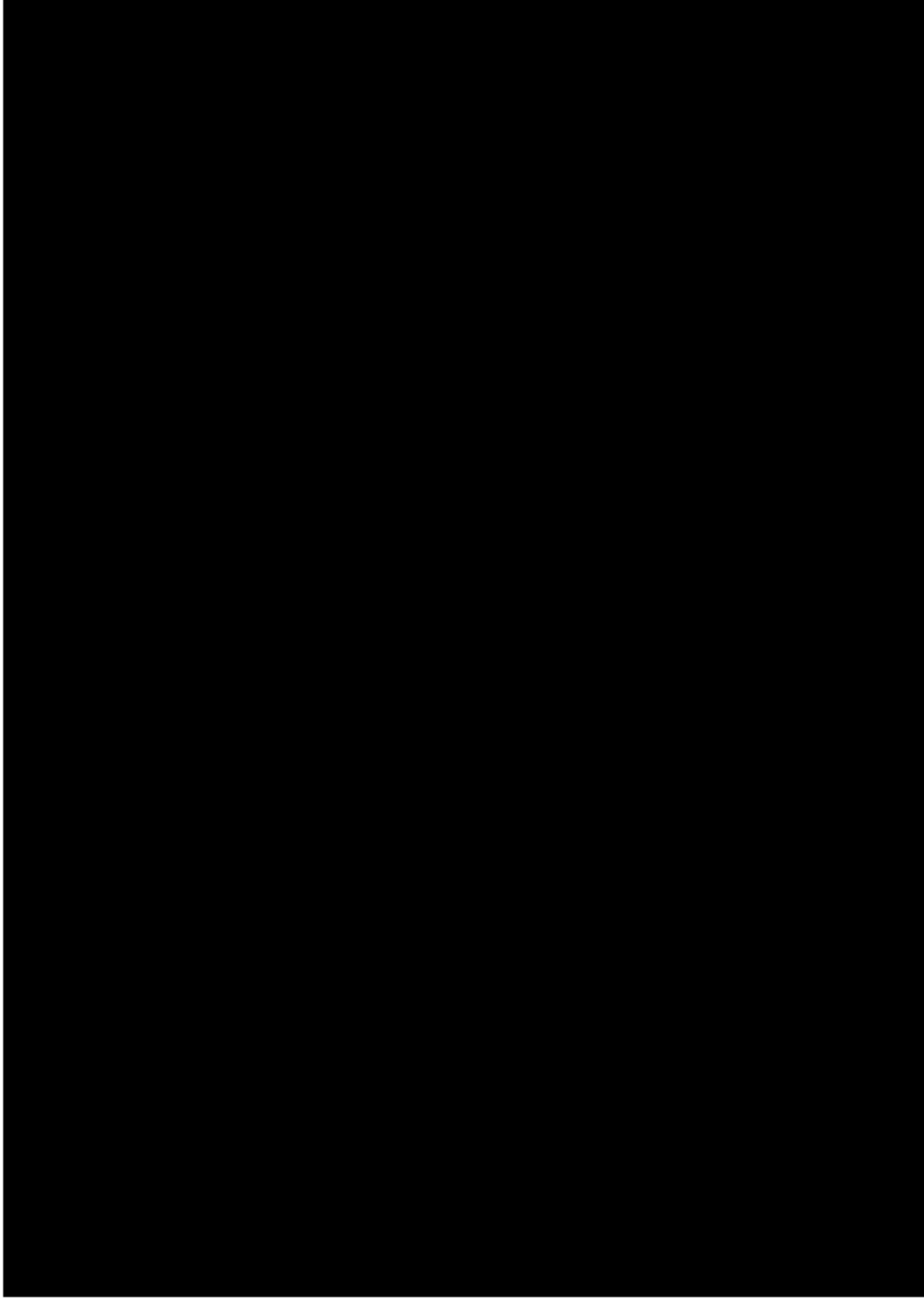
9 United States Department of Health and Human Services, Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events; 2017.

10 European Medicines Agency, Science Medicines Health. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. London, England: European Medicines Agency; 2017.





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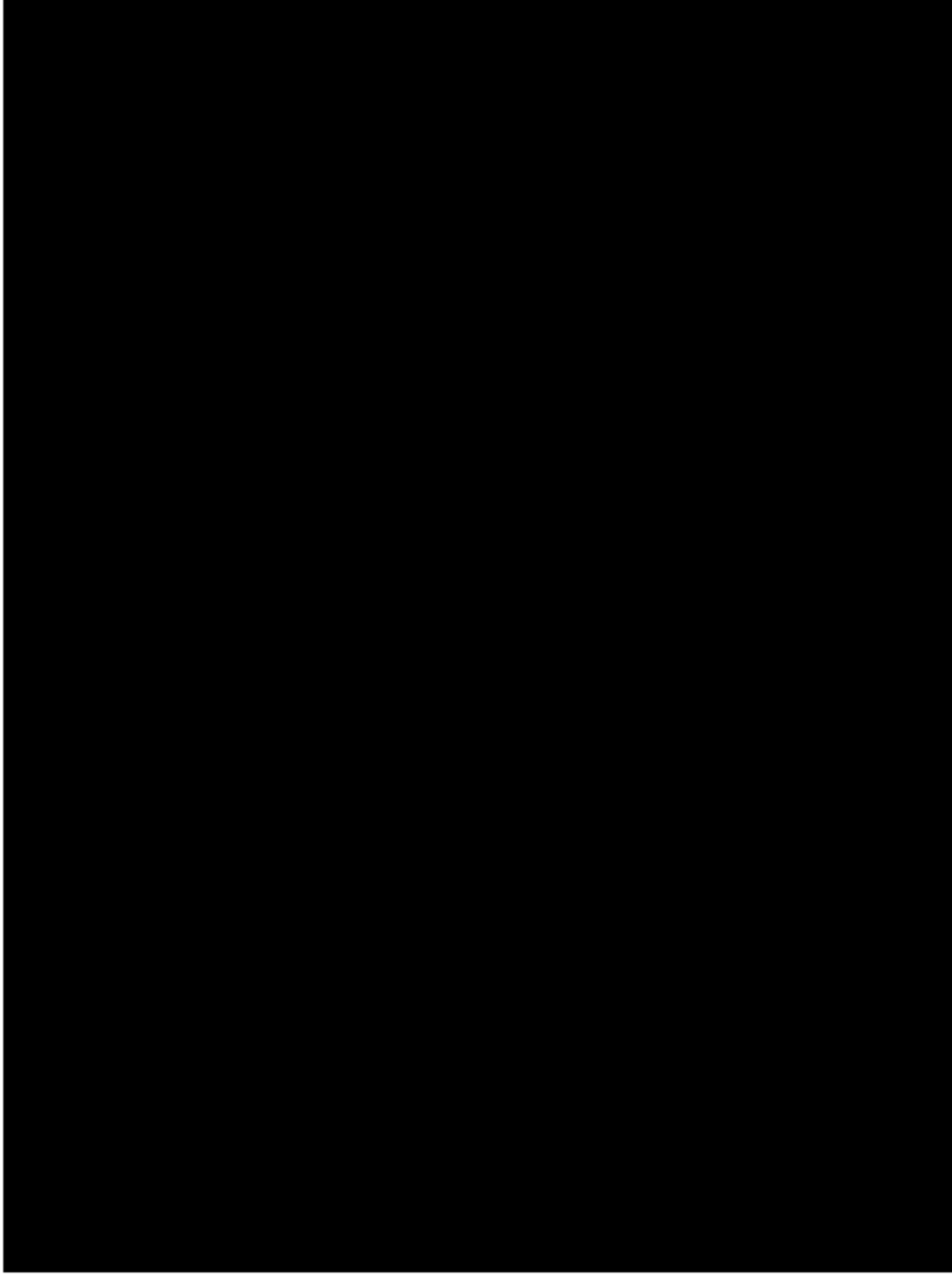

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, OPC-167832, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or receive a favorable opinion by the Independent Ethics Committee (IEC) responsible for such matters in the clinical trial facility where OPC-167832 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB/IEC-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for participants screened or enrolled in the trial.

I agree to await IRB/IEC approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to participants, I will implement the amendment immediately, and provide the information to the IRB/IEC within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB/IEC for informational purposes only, if required by local regulations.

I agree to provide all participants with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: Protocol 323-201-00006 Amendment 3

Document Number: 1000231647

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
Jingli Song	Biostatistics Approval	22-Feb-2023 17:46:27
Takuva Simbarashe	Clinical Approval	22-Feb-2023 20:43:57
Zheng Bo	Clinical Pharmacology Approval	22-Feb-2023 21:02:36