Janssen Pharmaceutical K.K. *

Clinical Protocol

Protocol Title

A Phase 2/3, Multicenter, Randomized, Open-label, Active-controlled Study to Evaluate the Efficacy and Safety of Bedaquiline Administered as Part of a Treatment Regimen With Clarithromycin and Ethambutol in Adult Patients With Treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD)

Short Title

Bedaquiline/CAM/EB Study in Treatment-refractory MAC-LD Patients

Protocol TMC207NTM3002; Phase 2/3

AMENDMENT 8

TMC207 (Bedaquiline)

*This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 8 December 2022
Prepared by: Janssen Pharmaceutical K.K.
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 8	08-Dec-2022
Amendment 7	30-June-2022
Amendment 6	20-Apr-2022
Amendment 5	09-Dec-2021
Amendment 4	30-Sep-2021
Amendment 3	08-Jul-2021
Amendment 2	14-Apr-2021
Amendment 1	21-Oct-2020
Original Protocol	01-Jul-2020

Amendment 8 (8 December 2022)

Overall Rationale for the Amendment: The major rationale for the amendment is to change in the study design from Japan study to a multi-country study taking into participation of South Korea and Taiwan, to reconsideration the inclusion/exclusion criteria, and to change the sample size based on the changing the statistical power. In accordance with these changes, the statistical analysis plan is also revised.

The changes made to the clinical protocol TMC207NTM3002 as part of Protocol Amendment 8 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.8 Appendix 8: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 4.1 Overall Design 5 Study Population 6.8 Concomitant Therapy	• The study will consist of a screening period of ~~63~~70 days (~~9~~10 weeks) • ~~-W9~~-W10 ~~-63~~-70 to 0 (figure omitted) • Footnote a. Screening evaluations must be performed within ~~63~~70 days (~~9~~10 weeks) prior to baseline (Day 1). These ~~9~~10 weeks include 14 days of rifamycin W/O for participants to whom it is applicable. If screening period exceeds ~~9~~10 weeks for reasons such as time required to obtain the result of microbiology assessment of screening, the screening period may be extended up to ~~14~~15 weeks. • Screening for eligible participants will be performed within ~~9~~10 weeks before administration of the study intervention. • Concomitant therapies administered after signing informed consent (~~63~~70 days before first dose of study intervention, including the extension period if screening period is extended) and prestudy therapies for pulmonary MAC disease administered prior to signing informed consent must be recorded at screening.	1-week extension in consideration of transportation period of samples from South Korea and Taiwan
1.1 Synopsis 4.1 Overall Design 9.2 Sample Size Determination	• A target of ~~180~~124 participants with treatment-refractory MAC-LD will be enrolled in this study. • A sample size of ~~180~~124 participants (~~90~~62 in Group A: the BDQ containing regimen, ~~90~~62 in Group B: the rifamycin-containing regimen) will have a power of about ~~90~~80% to show superiority for a 20% difference in proportion of participants having sputum conversion at Week 24 based on a chi-square test (at the 5% 2-sided significance level) on the intent-to-treat (ITT) population.	Change in target sample size according to change in statistical power

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall Design 6.3 Measures to Minimize Bias: Randomization and Blinding	• Participants who meet all the eligibility criteria will be randomized in a 1:1 (Treatment Group A [Group A]: Treatment Group B [Group B]) ratio stratified by country: • The randomization will be balanced by using randomly permuted blocks and will be stratified by country.	Stratification by country for the enrollment in multi-country study
1.3 Schedule of Activities (SoA)	Footnote c. Assessments planned on Day 1 except for blood sampling for PK which is performed after dosing must generally be performed prior to first dose of study intervention.	Clarification of applicable tests
	Footnote m. Two sputum samples should be collected at each visit time point except for Week 2, 6, and 10. One should be collected in the early morning ~~(~~at home ~~or at the study site)~~ and the other sample(s) at the study site. If sputum collection at home is impossible, 2 samples will be collected at the study site. If sputum can be produced more easily in the evening/night than in the early morning, it is acceptable to store the sample obtained in the previous day of visit in a refrigerator, bring it to the study site, and submit it on the following day. Samples collected at home or the study site can be spontaneous, ~~or~~ induced or aspirated. In case 2 sputum sample collection is not feasible at Week 2, 6, and 10, either no sample or 1 sample collection is allowed. Sputum samples will be shipped to the central microbiology laboratory where all cultures will be performed on solid and on liquid media. The same applies to sputum collections at OPW 2, 6 and 10 in the optional cohort. And in case a sputum sample is collected in routine clinical practice before obtaining informed consent on the day of informed consent, it is acceptable to submit as a sputum sample for the study after obtaining the participant's consent and recorded.	Clarification of sputum collection methods, etc.
	Footnote v. Extra visits will be required for participants meeting certain grading thresholds for changes in QTcF. All ECGs will be performed in triplicate (3 ECGs within 5 minutes) and must be of good quality (stable baseline, free of interference and artefact). The ECG machine dedicated for this study must be used. All tracings will be transmitted for blinded central analysis. ECG at 2-4 hours post-dose of BDQ and CAM will be obtained at Week 2, Week 12, Week 24 and Week 48. ECG at pre-dose of BDQ and CAM ~~(0 hours)~~ will be obtained at Day 1, Week 4, Week 6, Week 8, Week 16 and Week 32. Those ECG should be performed within 20 minutes prior to PK blood sampling at every time point whenever possible. ECG will be performed before blood sampling at the other visit where time points of ECG measurement are not specified.	Clarification of target drugs
2 Introduction	In South Korea, "KOREAN GUIDELINE FOR TUBERCULOSIS 4th EDITION" is published in 2020,[50] and in Taiwan, "Consensus Statement of Nontuberculous Mycobacterial Lung Disease in Taiwan" is published in 2020.[51] Both diagnostic criteria for NTM-LD and chemotherapy for MAC-LD in both countries are in accordance with an official ATS/IDSA statement,[14] and chemotherapy mainly with 3 drugs consisted of macrolide (CAM or AZM), rifamycin (RFP or RBT), and EB, is recommended as the standard therapy.	Addition current status of the diagnostic criteria and chemotherapy for MAC-LD in South Korea and Taiwan
2.1 Study Rationale	The diagnostic criteria and chemotherapy for MAC-LD in the world are in accordance with an official ATS/IDSA statement,[14] and there is no difference in the diagnostic criteria. For chemotherapy, regimen consisting of 3 drugs such as macrolide (CAM or AZM), rifamycin (RFP or RBT), and EB is recommended as SOC. Although there are some differences in the dosage and administration of drugs among countries, it is not a major factor that causes differences in the efficacy.	Addition the rationale on the change to multi-country study

Section Number and Name	Description of Change	Brief Rationale
	Therefore, it may be considered that there is no major regional difference in the therapeutic outcome for MAC-LD. In April 2020, a post-phase II study consultation was held with the Pharmaceuticals and Medical Devices Agency (PMDA), and the study was started as a Japan study. However, in view of the severe circumstance for the progress of the study due to the repeated outbreaks of COVID-19 etc., additional PMDA consultation was held in November 2022. Based on the advice from PMDA, the study design is changed to conduct as a multi-country clinical study including the investigational sites in South Korea and Taiwan.	
2 Introduction 2.2 Background 2.2.1 Comparator/ Combination Therapy 2.3 Benefit-risk Assessment 4.1 Overall Design	• For the most comprehensive nonclinical and clinical information regarding BDQ, refer to the latest version of the Investigator's Brochure (IB)[40] addendum, and ~~Japanese~~ local package insert of SIRTURO (BDQ). • For the most comprehensive nonclinical and clinical information regarding BDQ, refer to the latest version of the IB,[40] addendum, and the ~~Japanese~~ local package insert ~~to support the use of BDQ for the chemotherapy for NTM-LD~~. • ~~Rifampicin~~ RFP and RBT have been approved for TB and NTM-LD including MAC-LD or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] • ~~Clarithromycin~~ CAM is one of the macrolide antibiotics and approved for broader infectious disease including MAC infection or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] • ~~Ethambutol~~ EB has been approved for TB and NTM including MAC or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] • For further information regarding above drugs, refer to each ~~Japanese~~ local package insert. • More detailed information about the known and expected benefits and risks of BDQ may be found in the IB,[40] addendum, and ~~Japanese~~ local package insert of SIRTURO (BDQ). • Upon completion of the 60-week study intervention period, the study is completed, but the participant may continue SOC of ~~Japanese~~ local guidelines or medical practice at each study site for at least 1 year after culture conversion at the discretion of the investigators.	Revision in association with the change to multi-country study
4.2 Scientific Rationale for Study Design	• The South Korean and Taiwanese guidelines recommend a 3-drug regimen consisting of macrolide (CAM or AZM), RFP or RBT, and EB as the SOC.[50, 51] Therefore, ~~this~~3-drug regimen, consisting of CAM as macrolide is selected as control arm. • The ~~Japanese~~ local guidelines for MAC-LD treatment in Japan, South Korea ,Taiwan and an Official ATS/IDSA statement currently recommend treating until patients have been on SOC for 1 year after culture conversion, but there is no evidence to support this treatment duration.[41, 50, 51, 14] • Upon completion of the 60-week study intervention period, the study is completed, but the participant may continue SOC of ~~Japanese~~ local guidelines in Japan, South Korea and Taiwan or medical practice at each study site for least 1 year after culture conversion at the discretion of the investigators after study completion.	Addition in association with the change to multi-country study
4.4 End of Study Definition	Following completion of the study, the participant may continue the SOC per ~~Japanese~~ local guidelines or medical practice at each study	

Section Number and Name	Description of Change	Brief Rationale
	site for at least 1 year after culture conversion, at the discretion of the investigator.	
4.2 Scientific Rationale for Study Design 5.1 Inclusion Criteria	• The present study will enroll patients with treatment-refractory MAC-LD defined as participants who are sputum culture positive for MAC despite at least 6 months ~~and no more than 36 months~~ of MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within the last 12 months. • 5.1 Criterion modified per Amendment 8. 5.2 Has at least 2 positive sputum cultures of MAC (sputum cultures to be taken at least 4 weeks apart): · one obtained within 12 months prior to screening, which was documented while being treated for MAC-LD for a total of at least 6 months ~~and no longer than 36 months~~. · one at screening (by central microbiology laboratory). • 6.1 Criterion modified per Amendment 8. 6.2 Received at least 6 months ~~and no more than 36 months~~ of consecutive MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within 12 months prior to screening. Note: Participants must be compliant with medication intake for at least 75% of the total doses for prescribed SOC (including intermittent regimen) recommended by local guidelines ~~a given treatment~~.	Elimination of upper limit of prior treatment period in Inclusion Criterion 5, and modification of related descriptions
5.2 Exclusion Criteria	5. Criterion modified per Amendment 8. 5.1 Treatment already includes an injectable/inhaled aminoglycoside within 3 months prior to screening or the investigator deems the participant to be a candidate for an injectable/inhaled aminoglycoside ~~at~~ during screening period or at Day 1.	Clarified language regarding use of aminoglycosides
	6. Criterion modified per Amendment 8. 6.1 Has a history of documented macrolide-resistant MAC strain within 24 months prior to screening or at screening. For CAM, MIC of ≥32 µg/mL indicates resistance according to the Clinical and Laboratory Standards Institute [CLSI] M24 guidelines.[9,46,47] Note: In case a subject has ≥2 documented DST results within 24 months prior to screening, the subject is eligible if the latest result is susceptible and DST at screening is confirmed susceptible.	Addition of note on handling of multiple records of DST
	15. Criterion modified per Amendment 8. 15.1 Has contraindications to the use of CAM, EB, RFP or RBT per ~~Japanese~~ local prescribing information in Japan, South Korea or Taiwan.	Revision in association with the change to multi-country study
5.4 Screening Failures	Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, including candidates whose microbiological testing at screening is not eligible, such as culture negative, resistance to CAM, etc.	Clarification of rescreening rules
6.1 Study Interventions Administered	Rifamycin (RFP or RBT) will be taken according to the investigator's instructions ~~as per Japanese package insert~~. Combination drugs will not be provided by the sponsor and marketed product at study sites should be administered. Participants will be instructed to take their assigned dose of the study intervention or comparator and combination drugs, per Table 2. Additions to Table 2 (dosage and administration, etc. of study interventions in South Korea and Taiwan) are omitted.	Revision in association with the change to multi-country study, and addition of dosage and administration etc. of study

Section Number and Name	Description of Change	Brief Rationale
		interventions in South Korea and Taiwan
6.3 Measures to Minimize Bias: Randomization and Blinding	In order to maintain the blind, the investigator should not perform microbiological tests for acid-fast bacillus at the study site after Day 1 until completion of the assessments other than microbiological assessments at the Week 24 except in emergency situations related to subject safety or chemotherapy.	Clarification of microbiological testing rules during the blinded period
6.7 Treatment of Overdose	Refer to the ~~Japanese~~ local package insert of the comparator rifamycin (RFP or RBT) for advice on treatment of overdose.	Revision in association with the change to multi-country study
6.8 Concomitant Therapy	• Antibacterial drugs, such as fluoroquinolones, linezolid that may be effective for MAC-LD other than the specified concomitant medications are prohibited during the study treatment period. • clofazimine (increased QT prolongation is reported in co-administration with BDQ)	Addition of prohibition of antibacterial drugs that may be effective for MAC-LD, and clofazimine
8.1.2 Clinical Assessments in MAC-LD	This is to calculate the percentage of participants who have changed to an individualized treatment regimen ~~in accordance with SOC of Japanese guidelines or medical practice at each study site~~ as defined by SOC of local guidelines or protocol (Section 6.8.1) in both groups and participants who have switched to BDQ-containing regimen in Group B.	Revision in association with the change to multi-country study and modification based on consistency of description
8.2.3 Electrocardiograms	• If triplicate ECGs confirm a mean QTcF ≥500 ms or an increase from baseline of >60 ms, the following will be done: • if after 2 weeks mean QTcF is ≥500 ms or increase from baseline of >60 ms, the investigator must permanently stop the study intervention, and continue weekly triplicate ECGs until resolution. Weekly triplicate ECG monitoring for participants who have recovered from QTcF ≥500 ms or increase from baseline of >60 ms may be discontinued if over 3 consecutive weeks the triplicate ECGs demonstrate a mean QTcF <500 ms or one time increase of ≤60 ms. Participants who meet these criteria can be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA). If mean QTcF <500 ms or increase of ≤60 ms is not demonstrated, then weekly triplicate ECGs will be continued at least until the end of the last dose of BDQ plus 4 weeks due to the long half-life of BDQ. At that point, if mean QTcF <500 ms or increase of ≤60 ms is demonstrated, weekly triplicate ECGs can be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA). Otherwise if mean QTcF <500 ms or increase of ≤60 ms is not demonstrated, the investigator judges whether weekly triplicate ECGs will be continued or be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA).	Clarification of response to increase of >60 ms
1.1 Synopsis 9.4.3 Primary Endpoint	The Cochran-Mantel-Haenszel ~~chi-square~~ test stratified by region (Japan, non-Japan) at the 5% 2-sided significance level will be used to compare sputum culture conversion rate in MGIT at Week 24.	Reconsideration of the statistical analysis plan in

Section Number and Name	Description of Change	Brief Rationale
9.4.4 Secondary Endpoints	• The percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media will be calculated after Week 4. The percentage of participants who achieved sputum culture conversion at Week 24 and completed 48-week BDQ-containing regimen and achieved sputum culture conversion at Week 60 in Group A will be compared with the percentage of participants who completed 60-week SOC regimen and achieved sputum culture conversion at Week 60 in Group B using the Cochran-Mantel-Haenszel test stratified by region (Japan, non-Japan) ~~chi-square test (the Fisher's exact test will be used in case of rare events)~~. • The percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media will be calculated at each visit after Week 2, respectively. A generalized linear model including treatment, region (Japan, non-Japan), time, and treatment-by-time interaction as fixed effects will be applied for the number of negative culture participants and the number of all participants at each timepoint and comparison between treatment groups will be performed using the appropriate contrast for the percentage of negative culture participants at Week 24. • Kaplan-Meier estimates will be generated for the time to sputum culture conversion up to Week 24 and Week 48. The difference between the treatment groups will be compared using the log-rank test stratified by region (Japan, non-Japan) for the time to sputum culture conversion up to Week 24.	association with the change to multi-country study
Throughout the protocol	Minor changes and clarifications were made.	Minor errors and unclear descriptions were noted.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2/3, Multicenter, Randomized, Open-label, Active-controlled Study to Evaluate the Efficacy and Safety of Bedaquiline Administered as Part of a Treatment Regimen With Clarithromycin and Ethambutol in Adult Patients With Treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD)

Short Title: Bedaquiline (BDQ)/CAM/EB Study in Treatment-refractory MAC-LD patients.

(Bedaquiline) TMC207 is a diarylquinoline derivative and a novel antimycobacterial agent, with in vitro activity against a wide range of *Mycobacterium* (M) species, including *Mycobacterium tuberculosis* (*M. tuberculosis)*, *M. avium* complex (MAC), *M. kansasii*, and *M. abscessus*. Infection with the latter 3 nontuberculous organisms can result in nontuberculous mycobacterial (NTM) lung disease (LD), which is distinct from the pulmonary infection caused by *M. tuberculosis*, for which BDQ is currently indicated.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Microbiological assessment in MGIT: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT at Week 24.
Secondary	
• Microbiological assessment in 7H10 or 7H11 agar media: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in 7H10 or 7H11 agar media at Week 24.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Change from baseline in patient-reported health status on total score of SGRQ at Week 24.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD up to Week 48.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 48. • Percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media, respectively, at each visit after Week 2 per Schedule of Activities. • Time to sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least

Objectives	Endpoints
	25 days apart) in MGIT up to Week 48. • Time to positivity in MGIT up to Week 48.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 48 and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Percentage of participants who undergo a change in their MAC-LD treatment regimen by Week 24, by Week 48 (Group A) and by Week 60 (Group B).
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 60.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 60.
• To evaluate the safety and tolerability of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Safety and tolerability based on assessment of AEs, clinical laboratory assessments, 12-lead ECG, vital signs, physical examination, visual examination, and audiology up to Week 60.
• To evaluate the PK of BDQ (and metabolite M2), and CAM (and metabolite 4-OH-CAM [optional]).	• PK exposures of BDQ (and metabolite M2 [optional]) at Day 1, Weeks 2, 8, 12, 24, and 48, and CAM (and metabolite 4-OH-CAM [optional]) at Day 1, Weeks 2, 8, 12, and 24.
Exploratory	
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment refractory MAC - LD assessed by QOL-B NTM module.	• Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60.
• To evaluate the occurrence of culture reversion (relapse or reinfection) in participants who previously had sputum conversion.	• Rate of culture reversion (relapse or reinfection) up to Week 60.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered	• Percentage of participants having MAC isolates with acquired

Objectives	Endpoints
as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	resistance to CAM detected by a phenotypic method up to Week 60. • Percentage of participants having MAC isolates with increased MICs to BDQ (at least 4 fold increase) up to Week 60.
• To evaluate PK/PD relationships for safety and efficacy of BDQ (and CAM [optional]).	• Exposure, and safety and efficacy (PK/PD) relationship assessments of BDQ (and CAM [optional]) by Week 24.
• To determine the mechanisms of resistance in participants' MAC isolates with increased BDQ MICs by sequencing both *atpE, mmpT5* and other genes (if available).	• Evolution of the *atpE, mmpT5* and other gene sequences up to Week 60.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB for participants who achieved sputum culture conversion (at Weeks 24, 48, and 60).	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 24, 48, and 60. • Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Change from baseline in chest CT findings at Weeks 24, 48, and 60.

Note:
1) Although not included in the above objectives and endpoints, the efficacy and safety at OPW24 (Week 24 of study intervention treatment) and OPW48 (the last dose of study intervention) in the optional cohort will be evaluated as additional analysis in the similar manner with efficacy and safety at Week 24 and Week 48.
2) Group A= Treatment group consisting of BDQ + CAM + EB
3) Group B= Treatment group consisting of rifamycin (RFP or RBT) + CAM + EB
Key: AEs=adverse event; atpE=ATP synthase subunit c; BDQ=bedaquiline; CAM=clarithromycin; CT=computed tomography; EB=ethambutol; ECG=electrocardiogram; MAC=*Mycobacterium avium* complex; MAC-LD=MAC lung disease; MGIT=mycobacterium growth indicator tube; MIC=minimal inhibitory concentration; mmpT5=mycobacterial membrane protein transporter-5; NTM=nontuberculous mycobacterial; OPW=week in optional cohort; PD=pharmacodynamics; PK=pharmacokinetics; QOL-B=Quality of Life-Bronchiectasis; RBT=rifabutin; RFP=rifampicin; SoA=schedule of activities; SGRQ= St. George's Respiratory Questionnaire.

Hypothesis

The hypothesis of this study is that BDQ -containing regimen is superior to rifamycin-containing regimen and increases the proportion of participants with sputum culture conversion in mycobacteria growth indicator tube (MGIT) at Week 24 as compared to rifamycin-containing regimen.

OVERALL DESIGN

This is a multicenter, randomized, open-label, active-controlled study to evaluate efficacy and safety of BDQ compared with rifamycin administered as part of a treatment regimen with clarithromycin (CAM) and ethambutol (EB) for 48 weeks in adult participants with treatment -refractory MAC-LD. The study will consist of a screening period of 70 days (10 weeks) (including rifamycin washout period of 14 days for participants to whom this is applicable), an open-label treatment period of 48 weeks (baseline visit [Day 1] to Week 48) in Group A or 60 weeks (Day 1 to Week 60) in Group B, and follow-up period of 12 weeks in Group A. Participants will return for study visits biweekly in the first 12 weeks, and then every 4 weeks until Week 60. In addition, this study provides an option to receive BDQ -containing regimen for non-converters in Group B based on the result of microbiological test up to Week 24 as the optional cohort. OPW-2 in optional cohort will be initiation of 2-week washout period in optional cohort.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study.

A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) who reach the Week-24 time point or discontinued earlier or switched to individualized treatment regimen. This futility analysis is nonbinding and the IDMC will recommend the continuation or termination of the study based on the whole package of information, which also includes other efficacy and safety assessments. Sponsor will decide the continuation or termination of the study based on the recommendation by IDMC.

NUMBER OF PARTICIPANTS

A target of 124 participants with treatment-refractory MAC-LD will be enrolled in this study.

TREATMENT GROUPS AND DURATION

Participants who meet all the eligibility criteria will be randomized in a 1:1 (Treatment Group A [Group A]: Treatment Group B [Group B]) ratio stratified by country:

- Group A: BDQ + CAM + EB
- Group B: rifamycin (rifampicin [RFP] or rifabutin [RBT]) + CAM + EB

EFFICACY EVALUATIONS

Microbiology assessments (MAC-LD Treatment Outcome), clinical assessments in MAC-LD, percentage of participants who undergo a change in their MAC-LD treatment regimen, and a lung function assessment using a spirometry test, will be performed in this study.

PHARMACOKINETIC EVALUATIONS

Pharmacokinetic (PK) assessments for BDQ (and its active metabolite M2 [optional]) will be based on sparse sampling and will be performed using a Bayesian PK approach. A validated population PK model for BDQ and M2 has been developed that allows estimation of the main PK parameters (maximum plasma concentration [C_{max}], area under plasma concentration time curve [AUC], and minimum plasma concentration between 0 hour and the dosing interval τ [C_{trough}]) based on sparse samples drawn on various study visits. The plasma concentration of CAM and its active metabolite 4-OH CAM will be determined predose and around peak via predose and postdose blood sampling.

SAFETY EVALUATIONS

Safety assessments will include all adverse events (AEs), physical examination, measurement of body weight, visual examination and audiology, vital signs, electrocardiograms (ECGs), and clinical laboratory tests.

STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A sample size of 124 participants (62 in Group A: the BDQ containing regimen, 62 in Group B: the rifamycin-containing regimen) will have a power of about 80% to show superiority for a 20% difference in proportion of participants having sputum conversion at Week 24 based on a chi-square test (at the 5% 2-sided significance level) on the intent-to-treat (ITT) population.

All efficacy and safety data will be summarized by treatment groups (Groups A and B). For the Group B, data from optional cohort will be analyzed separately.

The Cochran-Mantel-Haenszel test stratified by region (Japan, non-Japan) at the 5% 2-sided significance level will be used to compare sputum culture conversion rate in MGIT at Week 24. A generalized linear model including treatment, region (Japan, non-Japan), time, and treatment-by-time interaction as fixed effects will be applied for the number of sputum culture negative participants and the number of all participants at each timepoint and comparison between treatment groups will be performed using the appropriate contrast for the percentage of negative participants at Week 24. Kaplan Meier estimates will be generated for the time to sputum culture conversion up to Week 24 and Week 48. The changes from baseline in total score of St. George's Respiratory Questionnaire (SGRQ) and respective domain scores will be summarized descriptively at Weeks 24, 48, and 60.

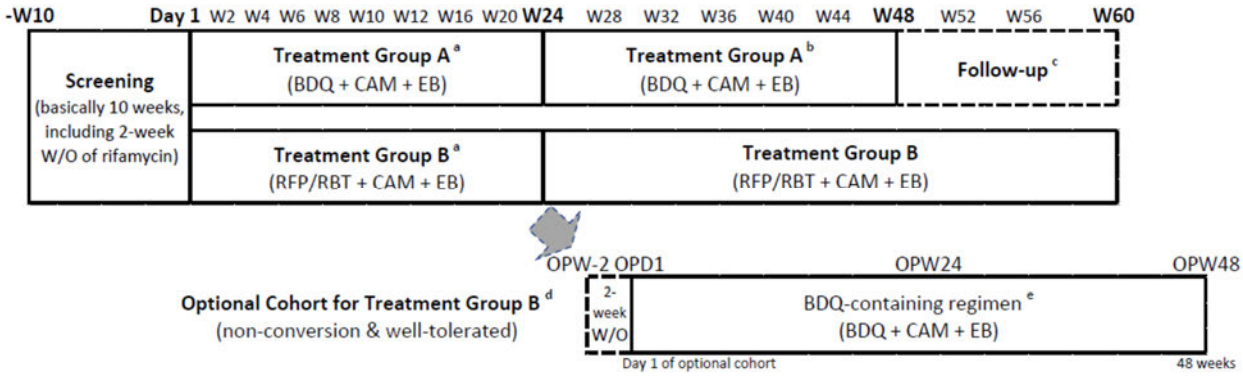
For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus postintervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. Vital signs including temperature (axillary), heart rate, respiratory rate, oxygen saturation, and blood pressure (systolic and diastolic) values and their changes from baseline, including percentage of participants with values beyond clinically important limits will be summarized. Physical examination findings, visual acuity, color discrimination, visual field, fundoscopy, and audiometry data will also be descriptively presented.

The pharmacokinetic/pharmacodynamic (PK/PD) analyses may be performed at earlier time points as necessary to support efficacy and safety findings. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of BDQ and M2 (if applicable) for Group A, and will be calculated for predose and 2 to 4 hours postdose plasma concentrations on Day 1, Weeks 2, 8, 12, 24, and 48 of BDQ, and CAM and 4-OH CAM for both Groups A and B.

The Statistical Analysis Plan (SAP) will describe the planned interim (futility) analyses in detail. Details of the futility analysis (including classification of lack of efficacy) and criterion will be included in the IDMC charter and SAP.

1.2. Schema

Figure 1: Schematic Overview of the Study



Key: BDQ=bedaquiline; CAM=clarithromycin; CT=computed tomography; EB=ethambutol; IDMC=Independent Data Monitoring Committee; MAC=*Mycobacterium avium* complex; MAC-LD=MAC lung disease; max=maximum; OPW=week in optional cohort; RBT=rifabutin; RFP= rifampicin; W=Week; W/O=washout

Note:

1) OPW-2 - Initiation of 2-week washout period in optional cohort
2) OPD1 - Date of starting dose in optional cohort
3) OPW24 - Week 24 in optional cohort
4) OPW48 - Week 48 in optional cohort

[a] Prior to Week 24, participants who are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on non-conversion and clinical worsening) or the occurrence of AE will be considered treatment failures and can switch to an individualized treatment regimen (see Section 6.8.1), at the discretion of the investigator in consultation with IDMC.

[b] After Week 24 assessment, all participants who are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on non-conversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen (see Section 6.8.1) at the discretion of the investigator.

[c] After completion of 48-week treatment, converters who achieved culture conversion at Week 48 in the Group A will be followed for 12 weeks as drug-free period. Participants who failed to achieve sputum culture conversion (non-converters) by Week 48 and continue chemotherapy will be discontinued from the study and switched to another treatment regimen.

[d] At Week 24, non-converters in the Group B, will be considered to switch to BDQ-containing regimen at the discretion of the investigators. When the investigator changes to BDQ-containing regimen, 2-week washout of used rifamycin is required before initiation of BDQ-containing regimen.

[e] All participants who are judged to have difficulty continuing their BDQ-containing regimen due to failure to respond (based on non-conversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen (see Section 6.8.1) at the discretion of the investigators.

1.3. Schedule of Activities (SoA)

	Screening [a]	Investigation [b]																Follow-up (Group A)/ Investigation (Group B)			Early discontinuation/ Switch to ITR [f]
Day (D)/Week (W)	-W10 to D0	Baseline D1 [c]	W2	W4	W6	W8	W10	W12	W16[d]	W20[d]	W24[d]	W28[d]	W32[d]	W36[d]	W40[d]	W44[d]	W48[d,e]	W52[d]	W56[d]	W60[d]	
Study day	-70 to 0	1	15±2	29±2	43±2	57±2	71±2	85±2	113±3	141±3	169±3	197±4	225±4	253±4	281±4	309±4	337±4	365±4	393±4	421±4	before W60
Screening/administrative																					
Informed consent [g]	X																				
Inclusion/exclusion criteria [h]	X	X																			
Medical history and demographics [i]	X																				
Prestudy therapy	X																				
Pregnancy test (WOCBP only)[j]	X	X						X			X			X			X			X	X
FSH test [k]	X																				
HIV infection status	X																				
Hepatitis B and C	X																				
Study intervention/administration																					
Randomization		X																			
Dispense/administer study intervention [f]		Timing will be at prespecified intervals, as described in the clinical trial protocol.																			
Study intervention accountability [l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[l]	X[l]	X[l]	X
Concomitant therapy	Continuously																				
Microbiological assessment																					
Sputum collection [m] for	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• Identification and speciation [n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• MGIT [o], agar media	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• Drug susceptibility testing [p]	X	X	The testing will be performed on positive isolates at Week 24 as well as the last culture positive isolates in case of participants with non-conversion and recurrence (relapse/reinfection). In addition, it will be performed on positive isolates at early discontinuation (if available).																		
• VNTR or WGS [q]	X		In case of recurrence (relapse/reinfection), and if acquired resistance (at least 4-fold increased MIC) to BDQ is observed, VNTR and/or WGS will be performed on both baseline and postbaseline isolates.																		
Clinical assessment																					
SGRQ, QOL-B NTM module		X									X						X			X	(X)
Lung function test		X[r]									X						X			X	(X)
Chest CT [s]	X										X						X			X	(X)
Pharmacokinetics (PK)																					
Blood sampling for PK of BDQ (Group A)		X[u]	X[u]	X[t]	X[t]	X[u]		X[u]	X[t]		X[u]		X[t]				X[u]				
Blood sampling for PK of CAM		X[u]	X[u]			X[u]		X[u]			X[u]										
Safety assessment																					
Adverse events	Continuously																				
12-lead ECG [v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations, vital signs [w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests [x]	X	X		X		X		X			X			X			X			X	X

	Screening [a]	Investigation [b]																Follow-up (Group A)/ Investigation (Group B)			Early discon-tinuation/ Switch to ITR [f]
Day (D)/Week (W)	**-W10 to D0**	**Baseline D1 [c]**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16[d]**	**W20[d]**	**W24[d]**	**W28[d]**	**W32[d]**	**W36[d]**	**W40[d]**	**W44[d]**	**W48[d,e]**	**W52[d]**	**W56[d]**	**W60[d]**	
Study day	**-70 to 0**	**1**	**15±2**	**29±2**	**43±2**	**57±2**	**71±2**	**85±2**	**113±3**	**141±3**	**169±3**	**197±4**	**225±4**	**253±4**	**281±4**	**309±4**	**337±4**	**365±4**	**393±4**	**421±4**	**before W60**
Audiology, visual examinations [y]		X		X[ee]		X[ee]		X			X			X			X			X	(X)
Fundoscopy [dd]		X									X						X			X	(X)

Note: (X)=If available

Key: CAM=clarithromycin; CT=computed tomography; D=day; ECG=electrocardiogram; FSH=follicle-stimulating hormone; HIV= human immunodeficiency virus, ITR=Individualized treatment regimen; MGIT=mycobacterium growth indicator tube; MIC= minimal inhibitory concentration; NTM=nontuberculous mycobacterial; PK=pharmacokinetics; QOL-B=Quality of Life-Bronchiectasis; SGRQ= St. George's Respiratory Questionnaire; SoA=schedule of activities; VNTR: variable number tandem repeat, W=week; WGS: whole genome sequencing; WOCBP: woman of childbearing potential.

1.3.1. Schedule of Activities (SoA) in the Optional Cohort

	Washout [z]	Optional Investigation																
Day (D)/Week (W)	from OPW-2	Baseline (OPD1) [aa]	OPW2	OPW4	OPW6	OPW8	OPW10	OPW12	OPW16 [d]	OPW20 [d]	OPW24 [d]	OPW28 [d]	OPW32 [d]	OPW36 [d]	OPW40 [d]	OPW44 [d]	OPW48 [d,bb]	Early discontinuation/ Switch to ITR [r]
Study day (optional cohort)	-14 to 0	1	15±2	29±2	43±2	57±2	71±2	85±2	113±3	141±3	169±3	197±4	225±4	253±4	281±4	309±4	337±4	before OPW48
Washout																		
Washout of rifamycin	X																	
Study intervention/administration																		
Dispense/administer study intervention		Timing will be at prespecified intervals, as described in the clinical trial protocol.																
Study intervention accountability	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	Continuously																	
Microbiological assessment																		
Sputum collection [m] for		X [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• Identification and speciation [n]		X [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• MGIT [o], agar media		X [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
• Drug susceptibility testing [p]		X [cc]	The testing will be performed on the last culture positive isolates in case of participants with non-conversion and recurrence (relapse/reinfection). In addition, it will be performed on positive isolates at early discontinuation (if available).															
• VNTR or WGS [q]	In case of recurrence (relapse/reinfection), and if acquired resistance (at least 4-fold increased MIC) to BDQ is observed, VNTR and/or WGS will be performed on both baseline and postbaseline isolates.																	
Clinical assessment																		
SGRQ, QOL-B NTM module		X [cc]									X						X	(X)
Lung function test		X [cc]									X						X	(X)
Chest CT		X [cc]									X						X	(X)
Safety assessment																		
Adverse events	Continuously																	
12-lead ECG [v]		X [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examinations, vital signs [w]		X [cc]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests [x]		X [cc]		X		X		X			X			X			X	X
Pregnancy test (WOCBP only)		X [cc]						X			X			X			X	X
Audiology, visual examinations [y]		X [cc]		X [ee]		X [ee]		X			X			X			X	(X)
Fundoscopy [dd]		X [cc]									X						X	(X)

Note: (X)=If available, X=In principle, no additional test is required as OPD1 as data of Week 24 will be used as the baseline

Key: CAM=clarithromycin; CT=computed tomography; D=day; DST=drug susceptibility testing; ECG=electrocardiogram; FSH=follicle stimulating hormone, ITR=Individualized treatment regimen; MAC=*Mycobacterium avium* complex; MAC-LD=MAC lung disease; MALDI-TOF MS= Matrix-Assisted Laser Desorption/Ionization-Time Of Flight mass spectrometry; MGIT=mycobacterium growth indicator tube; MIC=minimal inhibitory concentration; NTM=nontuberculous mycobacterial; OPD=day in optional cohort; OPW=week in optional cohort; QOL-B=Quality of Life-Bronchiectasis; QTcF= QT corrected according to Fridericia's formula; SGRQ= St. George's Respiratory Questionnaire; SoA=schedule of activities; VNTR: variable number tandem repeat, W=week; WGS: whole genome sequencing; WOCBP: woman of childbearing potential.

Footnotes:

a. Screening evaluations must be performed within 70 days (10 weeks) prior to baseline (Day 1). These 10 weeks include 14 days of rifamycin W/O for participants to whom it is applicable. If screening period exceeds 10 weeks for reasons such as time required to obtain the result of microbiology assessment of screening, the screening period may be extended up to 15 weeks.
b. If required during the 48-week treatment period, participants can have a change in their treatment regimen, in which MAC-LD treatment may continue in accordance with standard of care or NTM treatment guidelines. All decisions on treatment regimen change should be made based on clinical worsening supported by microbiology data by the investigator. Participants requiring a treatment regimen change will be followed up for safety only, but all assessments should be performed according to the protocol.
c. Assessments planned on Day 1 except for blood sampling for PK which is performed after dosing must generally be performed prior to first dose of study intervention.
d. Every 4-week visit must be scheduled after more than 25 days from the previous visit.
e. The participants who have been treated with BDQ-containing regimen (Group A) through Week 48 and culture converted, will transfer to the follow-up period. The participants who have been treated with rifamycin-containing regimen (Group B) through Week 48 will continue to be treated up to Week 60.
f. Early discontinuation visit is to be scheduled within 7 days of the investigator's discretion to discontinue treatment with study intervention (including the day of discontinuation, other than withdrawal of consent). Visit for switch to individualized treatment regimen is to be scheduled within 7 days after discontinuing the assigned treatment regimen (including the day of switch) and before the start of individualized treatment regimen.
g. Must be signed before first study-related activity.
h. Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.
i. Medical and surgical history, including NTM exposure history, NTM treatment history, and MAC-LD.
j. β-hCG test will be performed only at screening and Day 1 whereas urine pregnancy test at timepoints described in SoA other than screening and Day 1.
k. FSH test is performed only for postmenopausal women.
l. After Week 48, only participants in Group B will continue to administer study intervention, and study intervention accountability will be continued up to Week 60.
m. Two sputum samples should be collected at each visit time point except for Week 2, 6, and 10. One should be collected in the early morning at home and the other sample(s) at the study site. If sputum collection at home is impossible, 2 samples will be collected at the study site. If sputum can be produced more easily in the evening/night than in the early morning, it is acceptable to store the sample obtained in the previous day of visit in a refrigerator, bring it to the study site, and submit it on the following day. Samples collected at home or the study site can be spontaneous, induced or aspirated. In case 2 sputum sample collection is not feasible at Week 2, 6, and 10, either no sample or 1 sample collection is allowed. Sputum samples will be shipped to the central microbiology laboratory where all cultures will be performed on solid and on liquid media. The same applies to sputum collections at OPW 2, 6 and 10 in the optional cohort. And in case a sputum sample is collected in routine clinical practice before obtaining informed consent on the day of informed consent, it is acceptable to submit as a sputum sample for the study after obtaining the participant's consent and recorded.
n. Identification and speciation of MAC will be done by MALDI-TOF MS at screening, baseline, and postbaseline for all positive sputum culture(s)
o. BACTEC MGIT™ will be used for qualitative culturing in an automated mycobacterial detection system.
p. Drug susceptibility testing (DST) will be done on culture positive isolates at screening, baseline, and at Week 24. The testing will be done on the last culture positive isolates in case of participants with non-conversion and recurrence (relapse/reinfection). In addition, the testing will be done on positive isolates at early discontinuation (if available). In the optional cohort, DST will be done on the last culture positive isolates in case of participants with non-conversion and recurrence (relapse/reinfection), as well as positive isolates at early discontinuation (if available).
q. In case of recurrence (relapse/reinfection) or in case of acquired resistance (at least 4-fold increased MIC) to BDQ is indicated by DST result, baseline and postbaseline isolates will be identified using WGS or VNTR if necessary. If more than 1 postbaseline positive culture (isolate) showing resistant is available the last culture positive sample will be tested for VNTR and/or WGS in addition to the baseline culture positive sample.
r. Lung function test on Day 1 will be acceptable within 1 week prior to Day 1.
s. Chest CT scans taken within 6 months prior to screening are acceptable.
t. Single sparse blood samples will be collected for measurement of plasma concentrations of BDQ (and M2 [optional]). These samples can be taken at any time after intake of BDQ on the day, but the date and time of the second to last and the last administration of BDQ and CAM, respectively, and the date and time of blood draw must be recorded.
u. Two blood samples will be drawn: one just before intake of BDQ or first intake of CAM in the visit, and the second sample between 2 to 4 hours after the intake. The date and time of the last study drug administrations of BDQ and CAM, respectively, prior to the first PK samples and the date and time of the study drug administrations immediately after the first PK samples must be recorded. The date and time of the blood draw must be recorded.
v. Extra visits will be required for participants meeting certain grading thresholds for changes in QTcF. All ECGs will be performed in triplicate (3 ECGs within 5 minutes) and must be of good quality (stable baseline, free of interference and artefact). The ECG machine dedicated for this study must be used. All tracings will be transmitted for blinded central analysis. ECG at 2-4 hours post-dose of BDQ and CAM will be obtained at Week 2, Week 12, Week 24 and Week 48. ECG at pre-dose of BDQ and CAM will be obtained at Day 1, Week 4, Week 6, Week 8, Week 16 and Week 32. Those ECG should be performed within 20 minutes prior to PK blood sampling at every time point whenever possible. ECG will be performed before blood sampling at the other visit where time points of ECG measurement are not specified.
w. Examination of height (screening only), body weight measurement, observation for skin events/reactions, assessments performed as part of the clinical course of NTM related disease (body temperature, heart rate, respiratory rate, and oxygen saturation) and additional assessments (systolic blood pressure and diastolic blood pressure). Physical examination and vital signs will be performed before intake of study intervention and blood sampling.
x. Including hematology, chemistry and urinalysis.
y. Including visual acuity, color discrimination, visual field. Audiology and visual examinations within 4 week prior to Day 1 and within 4 days prior or after each visit other than Day 1 will be acceptable.
z. After Week 24 assessment, all participants in the Group B who are non-conversion and well-tolerated, will be considered to receive the BDQ-containing regimen at the discretion of the investigators. When the investigator changes to BDQ-containing regimen, 2-week washout of treated rifamycin must be given before initiation of BDQ-containing regimen. The investigators can postpone the decision to transfer

to the optional cohort for up to Week 32 in order to confirm a sputum culture positive at Week 24, if necessary. If decision to transfer to the optional cohort exceeds Week 32 for reasons such as time required to obtain the result of microbiology assessment of Week 24, the period may be extended. If necessary, consider study date of OPD1 by adding the number of days required to switch to the optional cohort to study date of Week 24.

aa. OPD1 is Day 1 for participants who are transferred to optional cohort. Assessments planned on OPD1 must be performed prior to first dose of BDQ. The investigators can postpone the decision to switch to the optional cohort for up to Week 32 in order to confirm sputum culture positive at Week 24. If decision to transfer to the optional cohort exceeds Week 32 for reasons such as time required to obtain the result of microbiology assessment of Week 24, the period may be extended.

bb. Upon completion of the 48-week optional treatment period, the observation of each participant will be completed.

cc. In principle, testing data at Week 24 will be used as that of OPD1, so it is not necessary to perform another test as OPD1. If the transition period is extended due to confirmation of the result of sputum culture, the result of microbiology assessment of Week 24 will be used as that of OPD1, the latest data (Week 28, etc) will be used when specified testing other than the microbiology assessment have been performed after Week 24 in Group B.

dd. Fundoscopy within 4 week prior to Day 1 and within 4 days prior or after each visit other than Day 1 will be acceptable.

ee. Audiology must be done only in subjects who are taking aminoglycoside

2. INTRODUCTION

Bedaquiline (BDQ) is a Mycobacterium-specific adenosine 5'-triphosphate (ATP) synthase inhibitor that was developed as part of a combination therapy for pulmonary tuberculosis (TB) due to infection with multi-drug resistant (MDR) *Mycobacterium tuberculosis (M. tuberculosis)*. Bedaquiline fumarate (TMC207) was first approved on 28 December 2012 in the United States (US) under the provisions of accelerated approval regulations. Conditional Marketing Authorization in the European Union (EU) was granted on 5 March 2014, approval for market authorization in Japan was on 19 January 2018, and over 60 approvals worldwide for the treatment of pulmonary MDR-TB in adults as of part of combination therapy have been granted. Bedaquiline is marketed under the trade name SIRTURO®.

Bedaquiline is a diarylquinoline derivative and a novel antimycobacterial agent, with in vitro activity against a wide range of *Mycobacterium* (M) species, including *M. tuberculosis*, *M. avium* complex (MAC), *M. kansasii*, and *M. abscessus*. Infection with the latter 3 nontuberculous organisms can result in nontuberculous mycobacterial lung disease (NTM-LD), which is distinct from the pulmonary infection caused by *M. tuberculosis*, for which BDQ is currently indicated. Nontuberculous mycobacteria are a collection of naturally occurring organisms with the potential to cause hard-to-treat pulmonary infections. The bacteria exist in the environment, commonly in water and soil, and often colonize natural water sources such as indoor water systems, hot tubs, and pools.[8,13]

Mycobacterium avium complex comprises a group of slow growing mycobacteria including *M. avium and M. intracellulare*. Infection with MAC is the most common cause of NTM-LD worldwide (although there are regional differences). The prevalence and incidence of NTM-LD associated with MAC are increasing worldwide in both immunocompromised and immunocompetent individuals, with and without preexisting lung disease.[1,18,34] The incidence rate of NTM-LD in Japan in 2014 was estimated to be 14.7 cases per 100,000 person-years, which is approximately 2.6 times the incidence rate reported in 2007,[35] and the rate of MAC infection in NTM-LD was 88%.[26] Japan is a high-burden country of NTM-LD.

MAC lung disease (MAC-LD) has 2 main clinical presentations: one is nodular-bronchiectatic (NB) type which tends to affect the middle-aged, postmenopausal, and elderly female population; and the other is fibro-cavitary (FC) type which is most often seen in patients with underlying lung disease such as cystic fibrosis, bronchiectasis, previous TB, and chronic obstructive pulmonary disease (COPD).[27,44] Some patients with predominantly NB type may also have cavities, which is referred to as cavitary NB type.[12,22,29] This mixed clinical presentation is however not considered as a separate category. Clinical symptoms vary in scope and intensity but commonly include chronic recurrent cough, often with purulent sputum and/or hemoptysis, and dyspnea. Systemic symptoms include malaise, fatigue, weight loss, fever, and chest pain in advanced disease.[28] The diagnosis of NTM-LD is based on the following 2 criteria in Japan; clinical criteria (radiological findings, exclusion of other diagnosis) and bacteriology criteria (eg, positive culture results).[42] However, both an official ATS/IDSA statement (published by the American Thoracic Society [ATS] and the Infectious Diseases Society of America [IDSA] in 2007) and the Japanese

guidelines (published by the Japanese Society for Tuberculosis and the Japanese Respiratory Society in 2012) state that treatment need not necessarily commence as soon as the diagnostic criteria are met.[14,41] The decision to initiate treatment should be based on an assessment of the potential risks and benefits of a prolonged course of multiple antibiotics for the individual patient.[41]

Treatment of MAC-LD remains challenging and involves prolonged antibiotic therapy, with a combination of at least 3 antibiotics. In an official ATS/IDSA statement, it is stated that the cornerstones of MAC therapy are the macrolides (clarithromycin [CAM] or azithromycin [AZM]) and ethambutol (EB), and then these agents are combined with companion drugs, usually rifamycin (rifampicin [RFP] or rifabutin [RBT]), and possibly an injectable aminoglycoside.[14] The British Thoracic Society guidelines published in 2017, also recommend the treatment with RFP, EB, CAM or AZM, and intravenous or nebulised amikacin (AMK) (consideration of use) for MAC-LD.[16] However, the macrolides, rifamycin, and EB are not approved for the treatment of NTM-LD in the US and EU, but are used off-label as these drugs are approved for the treatment of disseminated MAC disease in human immunodeficiency virus (HIV) positive patients.[14,16]

On the other hand, the Japanese guidelines recommend a treatment regimen for MAC-LD based on CAM, RFP (RBT is as an alternative to RFP), and EB; if necessary injectable aminoglycosides (streptomycin [SM] or kanamycin [KM]) can be added.[41] In Japan, CAM, RFP, RBT, EB, SM, and AMK liposome inhalation suspension (ALIS) are approved for the treatment of MAC-LD. Kanamycin is listed in the Japanese guidelines, but KM is not approved for the treatment of MAC-LD.[41] Amikacin is not listed in the Japanese guidelines, but injectable AMK is reimbursed for the treatment of MAC-LD as from February 2019 and ALIS is approved for the treatment of MAC-LD in March 2021.[33] In addition, AZM is recommended as one of macrolides in US and UK, but the Japanese guidelines do not recommend the use of AZM, as it is approved for the prophylaxis and treatment of disseminated MAC disease with acquired immunodeficiency syndrome (AIDS), but is not approved for the treatment of MAC-LD without AIDS (but reimbursement for MAC-LD is acceptable in Japan from 26 February 2020).[41] In conclusion, there are limited antibiotics approved for the treatment of MAC-LD in Japan.

In South Korea, "KOREAN GUIDELINE FOR TUBERCULOSIS 4th EDITION" is published in 2020,[50] and in Taiwan, "Consensus Statement of Nontuberculous Mycobacterial Lung Disease in Taiwan" is published in 2020.[51] Both diagnostic criteria for NTM-LD and chemotherapy for MAC-LD in both countries are in accordance with an official ATS/IDSA statement,[14] and chemotherapy mainly with 3 drugs consisted of macrolide (CAM or AZM), rifamycin (RFP or RBT), and EB, is recommended as the standard therapy.

In addition, the inclusion of RBT or RFP, a moderate or strong inducer of hepatic cytochrome P450 (CYP) 3A4 enzymes, in the MAC-LD treatment regimen complicates the administration of other important drugs to treat underlying conditions in patients with MAC-LD.

For the most comprehensive nonclinical and clinical information regarding BDQ, refer to the latest version of the Investigator's Brochure (IB)[40] addendum, and local package insert of SIRTURO (BDQ).

The term “study drug” throughout the protocol refers to BDQ. The term “study intervention” throughout the protocol refers to BDQ and rifamycin (RFP or RBT) as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Protocol Supplementary Information, which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

MAC-LD can vary widely in severity, ranging from asymptomatic to severe, the disease is frequently (but slowly) progressive and can lead to deterioration in lung function, reduced physical function and health-related quality of life (HRQOL), and an increased risk of mortality.[11,28] Patients with MAC-LD, particularly those with poor lung function or cavitary disease, have been shown to have a significantly impaired HRQOL.[19] Management and complete eradication of the infection remains extremely challenging; despite treatment, the persistence of the underlying disease and the presence of the organism in the environment often renders patients susceptible to recurrence. Other comorbid factors and adverse side effects combined with toxicity due to the treatment drugs lead to poor quality of life for patients.

In general, standard treatment for MAC-LD is long and frequently associated with drug-related toxicities,[3,24] with the most common toxicities of the recommended regimen including gastrointestinal disorders, liver disorders, and eye disorders.[13,41] The Japanese guidelines currently recommend a 3-drug regimen, consisting of CAM, RFP or RBT, and EB, as standard of care (SOC).[41] Although limited by variable and inconsistent drug combinations, the relationship between in vitro macrolide susceptibility and clinical response (based on sputum conversion) for MAC-LD was demonstrated in the CAM monotherapy and CAM-containing regimens in HIV-negative patients with MAC-LD.[13,41] Most first-line anti-TB drugs have 10 to 100 times less in vitro activity against MAC isolates than against *M. tuberculosis*.[13] With the exception of CAM, drug susceptibility testing (DST), from which the therapeutic efficacy of agents used in the treatment of MAC-LD, has not been established.[13,41]

As isolates of MAC have only a single copy of the ribosomal ribonucleic acid operon in their genome, macrolide monotherapy carries a significant risk for the development of mutational resistance, which is extremely difficult to treat.[13] Hence, it is crucial to include companion drugs with the macrolide in order to prevent the emergence of macrolide-resistant MAC isolates. Therefore, drugs with less activity against MAC are included in the recommended treatment regimen. The contribution of EB to the efficacy of the regimen is unknown but may be minimal, although EB was shown to delay the emergence of resistance in a mouse study.[6] Rifamycins have been shown to have a lower bactericidal activity against MAC than against *M. tuberculosis* in vitro. The minimal inhibitory concentration (MIC) of RFP was demonstrated to be 16 µg/mL for MAC compared to 0.2 µg/mL for *M. tuberculosis* for several strains.[20] Additionally, in chemotherapeutic experiments in beige mice infected with MAC, RFP, and RBT displayed no reduction in the colony-forming unit (CFU) counts in the organs of the beige mouse model after 28 days of treatment, while CAM resulted in a reduced CFU count of more than 1 $\log_{10}$ unit from the

pretreatment values after 28 days of treatment.[20] Moreover, the inclusion in a regimen of any rifamycin, all of which are potent inducers of CYP3A4 enzymes, can result in drug-drug interactions (DDIs), which further complicates therapy.

Overall, the treatment success rate in treatment-refractory patients with the current treatment has been unsatisfactory and many patients remain culture positive despite prolonged therapy.[24] The Japanese guidelines for MAC-LD treatment currently recommend treating until patients have been on SOC for 1 year after culture conversion, but there is no evidence to support this treatment duration.[41]

As mentioned, the treatment of MAC-LD is essentially empirical as there are very few published randomized controlled trials, specifically a lack of trials evaluating treatment in patients who are not infected with HIV.[13,41] Given the issues and lack of robustness of the current recommended treatment regimen, the inclusion of a single new antibiotic with activity against MAC could have a significant impact on overall treatment efficacy and safety. Due to its novel mode of action (inhibition of ATP synthase), BDQ defines a new class of anti-TB compounds. Currently, no other drugs belonging to the same pharmacologic class are available and therefore the potential for cross-resistance is minimal. Because of the conserved nature of ATP synthase in mycobacteria, BDQ also shows activity against other mycobacteria including MAC[2] and BDQ has shown to have activity against MAC in an experimental murine model.[30] Studies have also shown that BDQ has a low MIC with regard to MAC[7,23], and that the minimal bactericidal concentration ranges between 1 to 2 mg/L for some clinical strains[31] and >128 mg/L for MAC 101 strain,[30] suggesting it has at least bacteriostatic activity against MAC.

The standard duration of administration with BDQ for the treatment of MDR-TB with a known bactericidal effect is 24 weeks, whereas the duration of administration with BDQ for MAC-LD, which has been suggested to have a bacteriostatic effect, needs to be longer, and is therefore set at 48 weeks.

The sponsor expects that the substitution of BDQ for rifamycin in the MAC-LD treatment regimen with CAM and EB will show higher culture conversion rate and enable shortening of the MAC-LD treatment period (as well as avoid DDIs caused by rifamycin). Hence, the present study (TMC207NTM3002) will evaluate the efficacy and safety of BDQ as part of a regimen including CAM and EB after 48 weeks of treatment of the study intervention. This 48-week BDQ treatment period is same as the maximum duration in the sponsor-initiated clinical study in Japanese participants with MDR-TB (Study TMC207TBC2001).[43]

The diagnostic criteria and chemotherapy for MAC-LD in the world are in accordance with an official ATS/IDSA statement,[14] and there is no difference in the diagnostic criteria. For chemotherapy, regimen consisting of 3 drugs such as macrolide (CAM or AZM), rifamycin (RFP or RBT), and EB is recommended as SOC. Although there are some differences in the dosage and administration of drugs among countries, it is not a major factor that causes differences in the efficacy. Therefore, it may be considered that there is no major regional difference in the therapeutic outcome for MAC-LD.

In April 2020, a post-phase II study consultation was held with the Pharmaceuticals and Medical Devices Agency (PMDA), and the study was started as a Japan study. However, in view of the severe circumstance for the progress of the study due to the repeated outbreaks of COVID-19 etc., additional PMDA consultation was held in November 2022. Based on the advice from PMDA, the study design is changed to conduct as a multi-country clinical study including the investigational sites in South Korea and Taiwan.

2.2. Background

Bedaquiline Nonclinical Studies

Microbiologic Profile

Bedaquiline is a potent inhibitor of MAC in vitro with a MIC lower than that of approved antimycobacterial agents. Its spectrum is unique in its specificity to mycobacteria, including species important in humans such as *M. tuberculosis*, *M. kansasii*, and the fast growers *M. fortuitum* and *M. abscessus*. The target and mechanism of action of BDQ are different from those of other anti-TB agents. In BDQ mutant strains (*M. tuberculosis,* MAC, and *M. smegmatis*), the *atpE* gene, which encodes a part of the F0 subunit of ATP synthase, was affected. This indicates that BDQ inhibits the proton pump of *M. tuberculosis* ATP synthase. Furthermore, the distinct target of BDQ means that there is no cross-resistance with existing antimycobacterial drugs.

Bedaquiline has potent bacteriostatic activity after 1 month of treatment in the MAC-established infection mouse model. Four months of treatment improved the activity of AMK alone, CAM+AMK, AMK+BDQ, and CAM+AMK+BDQ, all achieving bactericidal activity. The activity of BDQ monotherapy did not improve and was still bacteriostatic. The triple combination CAM+AMK+BDQ activity was better when compared to CAM alone or BDQ alone but not to AMK alone.

Toxicology

Repeated dose toxicity studies were performed up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. Recovery was studied in rats and dogs.

Bedaquiline and its N-monodesmethyl metabolite (N-monodesmethylbedaquiline [M2]) have the characteristics of a cationic amphiphilic drug and therefore induce phospholipidosis, mainly in cells of the mononuclear phagocytic system. Changes in the mononuclear phagocytic system were seen in all species and consisted of the accumulation of pigment-laden and/or foamy macrophages in various tissues, but mostly in lymphoid tissue (lymph nodes and spleen), lungs, liver, stomach, skeletal muscle, pancreas, and/or uterus. Ultrastructural examination was done on numerous tissues from mice, rats, and dogs. Phospholipidosis is mainly regarded as an adaptive phenomenon rather than a toxic response. It is described to be slowly reversible upon treatment cessation and this was confirmed for BDQ by at least partial recovery seen in dog and rat studies.

A main target organ of toxicity was the skeletal muscle, which showed degenerative/necrotic lesions in mice, rats, and dogs. The changes have been described as varying from multifocal to widespread and were accompanied by clear increases in aspartate aminotransferase (AST), total

creatine phosphokinase (CPK), and myoglobin. This myopathy only occurred after prolonged or high dose administration and was usually reversible after treatment cessation or a decrease in dose.

Pharmacokinetic Profile

After single oral administration in rats, mice, dogs, and monkeys, absorption of BDQ was rather rapid. Oral bioavailability was approximately 70% to 80% in mice and rats and 40% in dogs and monkeys. The plasma concentration profiles of BDQ showed a multiphasic decline with a long terminal elimination half-life ($t_{1/2\ term}$) ranging from 1 to 3 days in mice to 40 days in dogs. The dose was slowly excreted in urine and feces after oral administration of ^{14}C-labeled BDQ to rats, dogs, and monkeys, most of the dose being recovered in feces. The overall recovery of radioactivity was 56% in dogs and 71% in monkeys at 2 weeks after dosing, and 90% in male rats and 72% in female rats at 216 hours.

After repeated oral administration, the systemic exposure to M2 in mice (area under the plasma concentration-time curve [AUC]) was 2 to 7 times higher than that to unchanged BDQ. Bedaquiline exposure increased less than dose proportionally and M2 exposure increased almost dose proportionally. In rats and dogs, the exposure to M2 was either comparable or up to 2 times lower than that to BDQ and the exposure of the 2 compounds increased dose proportionally to less than dose proportionally. The *N*-didesmethyl metabolite (M3) plasma levels represented about 10% of those of BDQ in dogs and at least 25% in rats. The M3 metabolite was not investigated in mice.

Tissue uptake was low in the brain after single oral administration of ^{14}C-labeled BDQ in pigmented male rats and monkeys. High tissue concentrations were associated with the adrenal gland, lung, spleen, and liver. The decline of the concentrations of total radioactive substances in most tissues was parallel to the plasma concentration decline. Following repeated oral administration of BDQ to mouse, rat, and dog, the BDQ trough concentration ratios tissue/blood (T/B) were above 30 in lung, spleen, lymph nodes, and thymus, and the tissue concentrations of M2 were generally higher than those of unchanged BDQ. The tissue concentrations of the 2 compounds increased more than dose proportionally at high dose levels.

In vitro and *in vivo* metabolism studies showed that BDQ was subjected primarily to oxidative metabolism leading mainly to M2. Cytochrome P450 3A4 (CYP3A4) was the major CYP form involved in vitro in the metabolism of BDQ and the further metabolism of M2. In juvenile rats, BDQ was less extensively metabolized than in adult rats, in agreement with CYP3A ontogeny.

No induction of CYP1A2, CYP3A4, CYP2C9, and CYP2C19 activities at concentrations up to 10 µM of BDQ was observed in cultures of cryopreserved primary human hepatocytes.

Investigation of the BDQ-mediated inhibition of CYP activity in a pooled batch of human liver microsomes demonstrated slight or no direct inhibition of the CYP activity and no mechanism-based inhibition was observed. M2 showed some moderate potential to inhibit CYP activity using human liver microsomes, mainly CYP2B6, CYP2D6, and CYP2C19 (50% inhibitory concentration=3-13 µM). However, inhibition of CYP activity by M2 *in vivo* in

humans should be limited since exposure to M2 in humans is low (maximum concentration [C_{max}] <0.5 µg/mL or 0.9 µM).

Clinical Studies

Phase 1 Studies

Pooled analyses were done for 8 Phase 1 studies in healthy subjects (5 single-dose studies and 3 multiple-dose studies). The pooled analysis included data from 217 healthy subjects, of whom, 189 received at least 1 dose of BDQ up to 700 mg. Five studies were not included in the Phase 1 pooled analysis: C117 was an open-label, DDI study in 16 HIV-1 infected subjects (without TB infection). This single-sequence DDI Phase 1 study was conducted to investigate the potential interaction between steady-state nevirapine and a single-dose of 400 mg BDQ. C112 was an open-label, single-dose study in 8 healthy subjects and in 8 subjects with moderate hepatic impairment. TBC1003 was a double-blind, single-dose study in 88 healthy subjects to evaluate the effect of a single supratherapeutic (800 mg) dose BDQ on the QT/corrected QT (QTc) interval. A total of 44 subjects received BDQ. TBC1002 was an open-label 3-way crossover study in 36 healthy adults to assess the relative bioavailability of 2 pediatric formulations of BDQ after single-dose administration of 100 mg, with and without food. NTM1001 was an open-label, DDI study in 16 healthy subjects. This single-sequence DDI Phase 1 study was conducted to investigate the potential interaction between steady-state CAM and a single-dose of 100 mg BDQ.

Bedaquiline was well absorbed with t_{max} at approximately 5 hours postdose. The C_{max} and AUC increased proportionally up to the highest doses studied (700 mg single dose and 400 mg once daily [qd] multiple doses). Accumulation from Day 1 to Day 14 was approximately 2-fold expressed as increase in AUC, corresponding to an effective half-life of about 24 hours. From Phase 2 study, 4 weeks after ceasing BDQ intake, the mean BDQ and M2 concentrations were reduced by approximately 40% compared to the end of the BDQ treatment period. At the last follow-up visit (Week 120), BDQ and M2 plasma concentrations were approximately 15% and 20% of the median Week 24 plasma concentrations, respectively. The average $t_{1/2\ term}$ of BDQ and M2, was estimated as 5.5 months and 5.3 months, respectively.

Administration of BDQ as the tablet formulation with food increased the relative bioavailability (by 95%) compared to administration without food.

Drug-drug interaction studies confirmed the role of CYP3A4 in the metabolism of BDQ to M2. A study with RFP (a CYP3A4 inducer) showed that the exposure (AUC_{336h}) to single dose BDQ as well as M2 was significantly reduced (by 52% and 25%, respectively). Furthermore, co-administration of ketoconazole, lopinavir/low-dose ritonavir (LPV/rtv), or CAM (CYP3A4 inhibitors) increased the systemic exposure to BDQ. After 3 days of co-administration with ketoconazole, exposure (AUC_{24h}) to BDQ increased by 22%, without a significant effect on M2. The combined intake of a single-dose of BDQ and LPV/rtv caused an increase in exposure (AUC_{last}) of BDQ by 22%, while for M2 exposure was decreased by 41% compared to intake of BDQ alone. After 5 days of co-administration with CAM, no impact on rate and extent of absorption (C_{max} and t_{max}) of BDQ were observed, while it led to an increase in BDQ plasma

exposure of 12% for AUC_{72h} and 14% for AUC_{240h} and to a decrease of 52% for C_{max} and 51% and 42% for AUC_{72h} and AUC_{240h}, respectively, of M2.

In the pooled Phase 1 studies, BDQ was generally safe and well tolerated. In the pooled group of subjects treated with BDQ alone, adverse event (AEs) were reported in 60.3% of subjects and most frequently related to system organ class of nervous system disorders (24.3%) and gastrointestinal disorders (16.9%). Within these classes, the most frequent AE was headache (18.0%). In the single-dose BDQ alone pooled treatment group, AEs were most frequently (in at least 15% of subjects) related to the system organ class of nervous system disorders (25.0%). The most frequently reported AE was headache (18.9%). Except for nasal congestion and nasopharyngitis, which were reported in 5.3% of subjects, all other AEs were reported in less than 5% of subjects. In the pooling of the multiple-dose studies, the number of subjects with at least 1 AE was 55.6%. Adverse events were most frequently related to the system organ classes of gastrointestinal disorders (28.9%), nervous system disorders (17.8%), and general disorders and administration site conditions (15.6%). Within these classes, the most frequently reported AEs were headache (15.6%) and dry mouth (11.1%).

Efficacy/Safety Studies

There are a few publications about the use of BDQ in patients with NTM-LD. However, no controlled studies by the sponsor have been conducted to investigate the efficacy and safety of BDQ in MAC-LD.

Overall clinical safety of BDQ administered as 400 mg once daily for 2 weeks and 200 mg dosed thrice a week up to an additional 22 weeks was generally safe and well tolerated in adults as part of combination therapy of pulmonary TB due to MDR *M. tuberculosis*.

Upon analysis of the placebo-controlled Phase 2b study C208 Stage 2, an imbalance in the number of deaths was identified between the BDQ group (n=10; 12.7%) and the placebo group (n=3; 3.7%) despite better microbiologic outcomes in the BDQ group. The reason for the increased overall mortality in the BDQ group in this study is as yet unclear given that the causes of death were varied (TB was the only cause of death reported in more than 1 subject), and there was a wide range in time to death since last intake of BDQ/placebo (range, 2-911 days). In addition, all deaths in the BDQ arm were considered not related to study intervention by the investigator. Overall, 16 subjects (6.9%) died during or after participation in study C209; all deaths were considered not or doubtfully related to BDQ by the investigator. Three (5.3%) subjects died during the completed TBC3001 study, all after the end of the Investigational Treatment phase, all 3 fatal serious adverse events (SAEs) were assessed as not related to BDQ by the investigator.

Based on review as confirmed by an external hepatologist,[10] it can be concluded that BDQ has a signal for liver injury manifested by increases in AST and to a lesser extent alanine transaminase (ALT). Transaminase elevations are not unexpected given the number of other hepatotoxic drugs in the background regimen and based on the publication by Keshavjee et al (2012),[22] which describes a 16.5% incidence of hepatotoxicity during MDR-TB treatment. There were no significant changes or treatment-related effects in other clinical laboratory tests, vital signs, and most electrocardiogram (ECG) parameters. The QT corrected according to Fridericia's formula

(QTcF) interval was shown to increase modestly (mean 10-15 ms increase from baseline) after treatment with BDQ.

For the most comprehensive nonclinical and clinical information regarding BDQ, refer to the latest version of the IB,[40] addendum, and the local package insert.

2.2.1. Comparator/Combination Therapy

Comparator:

Rifampicin (RFP)/Rifabutin (RBT)

RFP and RBT have been approved for TB and NTM-LD including MAC-LD or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] Rifampicin and RBT are strong or moderate inducers of CYP3A4 enzymes. Frequent AEs of RFP are gastrointestinal disorders, AST increased, ALT increased, rash, liver disorder, pyrexia, thrombocytopenia, and headache. Frequent AEs of RBT are nausea, leukopenia, pancytopenia, hypertriglyceridemia, and immune reconstitution inflammatory syndrome.

Combination:

Clarithromycin (CAM)

CAM is one of the macrolide antibiotics and approved for broader infectious disease including MAC infection or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] Frequent AEs of CAM are gastrointestinal symptoms such as abdominal pain and diarrhea. The major laboratory changes were ALT increased, AST increased, and eosinophils increased.

Ethambutol (EB)

EB has been approved for TB and NTM including MAC or recommended for use in local guidelines in Japan, South Korea and Taiwan.[41, 50, 51] Known clinically significant AEs are visual impairment, severe liver disorder, shock, anaphylactic shock, interstitial pneumonia, eosinophilic pneumonia, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythroderma, and thrombocytopenia.

For further information regarding above drugs, refer to each local package insert.

2.3. Benefit-risk Assessment

Although BDQ has demonstrated antimicrobial activity against MAC in vitro and in the mouse model, clinical efficacy of BDQ in MAC-LD patients has not been established yet. Participants in this study may experience clinical benefit from the treatment of MAC-LD. Result from these studies may be useful in developing novel therapy for treatment-refractory MAC-LD.

The following adverse drug reactions related to BDQ therapy were identified:

- Very common: nausea, arthralgia, headache, vomiting, and dizziness.
- Common: ECG QT prolonged, diarrhea, transaminases increased, and myalgia

More detailed information about the known and expected benefits and risks of BDQ may be found in the IB,[40] addendum, and local package insert of SIRTURO (BDQ).

2.3.1. Risks for Study Participation

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Benefit of BDQ-containing regimen regarding the clinical course of MAC-LD might not be shown.	Clinical efficacy of BDQ in treatment-refractory MAC-LD patients has not been evaluated in human clinical study yet and efficacy is not demonstrated.	• A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) to minimize the number of exposure participants in case benefit/risk balance are unfavorable. • Unblinding IDMC review will be implemented. • Investigator can switch to individual regimen based on the result of non-conversion and clinical worsening.
Participants who are randomized to treatment Group B need to continue SOC by Week 24 regardless of the low culture conversion rates.	Based on the result of clinical study in AMK liposome inhalation suspension (ALIS, Arikayce®), culture conversion rate in SOC were about 10%.[15]	• Non-converter in treatment Group B will be assigned to optional cohort to receive the BDQ containing regimen. • Investigator can switch to individual regimen based on the result of based on non-conversion and clinical worsening.
Risks Due to Study Intervention (BDQ and RFP/RBT) and Combination Drugs (CAM and EB)		
QT prolongation due to administration of BDQ and/or CAM	QT prolongation was identified as known risk and has been observed in nonclinical and clinical studies in MDR-TB patients (see IB[40]).	• Triplicate ECG will be assessed and monitored by IDMC frequently. • Discontinuation of study intervention and combination drugs will be required based on the result of ECG.
Risks Due to Study Procedures		
Blood sampling will be increased compared to standard medication. Blood drawing may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and, rarely, infection at the site where the blood is taken.	As with all clinical studies requiring blood sampling, there are risks associated with venipuncture and multiple blood sample collection.	The total blood volume to be collected is considered to be an acceptable amount of blood over this time period from the population in this study.
Risks Due to Other Causes		
Risk for emerging BDQ-resistant MAC.	Risk for emerging BDQ-resistant strains in MAC-LD patients is possible and will be evaluated in	• Emergence of resistance will be evaluated in non-converters.

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
	this study. Appropriateness of dosage and treatment duration will be evaluated in this study. BDQ resistant strains were identified in clinical studies in MDR-TB patients.	• Switch to individualized treatment based on the result of microbiological assessment and clinical worsening is allowed in this study. • Conduct drug susceptibility test and gene analysis to detect the resistance.
Visual impairment is a known risk in EB.	-	Visual examinations and fundoscopy will be assessed.
For an individualized treatment regimen in treatment Group A, aminoglycosides may be added to the BDQ-containing regimen.	The antimicrobial activity of BDQ in combination with aminoglycosides against MAC has been confirmed from the results of a nonclinical study,[30] but its clinical efficacy has not been evaluated yet and its efficacy has not been demonstrated. In multidrug therapy approved for the treatment of pulmonary MDR-TB in Japan and overseas, aminoglycosides have been recommended as one of the agents to be used concomitantly with multidrug therapy including BDQ[48,49,] and no safety issues have been observed. However, the clinical safety in patients with pulmonary MAC disease has not yet been evaluated and its safety has not been demonstrated.	During the study, study visits are scheduled at least once every 4 weeks to perform specified safety assessments.

Key: AMK=amikacin; BDQ=bedaquiline; CAM=clarithromycin; EB=ethambutol; ECG=electrocardiogram; IB=investigator's brochure; IDMC=Independent Data Monitoring Committee; MDR-TB=multi-drug resistant tuberculosis; MAC-LD=*Mycobacterium avium* complex-lung disease; SOC=standard of care.

2.3.2. Benefits for Study Participation

As described in Section 2.1, the treatment options for the target population are very limited and there is an unmet medical need. BDQ-containing treatment regimens may be a new treatment option for treatment-refractory patients. From this perspective, study participation may provide the benefit for participants to potentially improve their clinical course. The contribution to participate in this study may be useful to develop new therapy in MAC-LD.

2.3.3. Benefit-risk Assessment for Study Participation

Based on the available data and proposed safety measures, the overall benefit/risk assessment for this study is acceptable for the following reasons:

- Only participants who meet all inclusion criteria and none of the exclusion criteria (specified in Section 5) will be allowed to participate in this study, The selection criteria include adequate provisions to minimize the risk and protect the well-being of participants in the study.
- Safety will be closely monitored throughout the study:

  - In general, safety evaluations will be performed at scheduled visits during the study as indicated in the Section 1.3.
  - Triplicate ECG will be assessed at scheduled visits during the study. The result of ECG will be read by not only investigators but also central ECG monitors. Independent Data Monitoring Committee (IDMC) will review the data frequently.

- A futility analysis will be implemented to evaluate early the benefit/risk balance.
- Optional cohort is planned to ensure the opportunity to receive the BDQ containing regimen for Group B participants who could not achieve sputum culture conversion at Week 24.
- Participants can switch to individualized treatment based on the result of microbiological assessment and clinical worsening at the discretion of investigators.
- Any clinically significant abnormalities (including those persisting at the end of the study/early withdrawal) will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with BDQ are justified by the anticipated benefits that may be afforded to participants with MAC-LD.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• Microbiological assessment in MGIT: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT at Week 24.
Secondary	
• Microbiological assessment in 7H10 or 7H11 agar media: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in 7H10 or 7H11 agar media at Week 24.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 24.	• Change from baseline in patient-reported health status on total score of SGRQ at Week 24.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD up to Week 48.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 48.

Objectives	Endpoints
	• Percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media, respectively, at each visit after Week 2 per SoA. • Time to sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT up to Week 48. • Time to positivity in MGIT up to Week 48.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 48 and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Percentage of participants who undergo a change in their MAC-LD treatment regimen by Week 24, by Week 48 (Group A), and by Week 60 (Group B).
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD at Week 60.	• Percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media at Week 60.
• To evaluate the safety and tolerability of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Safety and tolerability based on assessment of AEs, clinical laboratory assessments, 12-lead ECG, vital signs, physical examination, visual examination, and audiology up to Week 60.
• To evaluate the PK of BDQ (and metabolite M2), and CAM (and metabolite 4-OH-CAM [optional]).	• PK exposures of BDQ (and metabolite M2 [optional]) at Day 1, Weeks 2, 8, 12, 24, and 48, and CAM (and metabolite 4-OH-CAM [optional]) at Day 1, Weeks 2, 8, 12, and 24.
Exploratory	
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment refractory MAC-LD assessed by QOL-B NTM module.	• Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60.

Objectives	Endpoints
• To evaluate the occurrence of culture reversion (relapse or reinfection) in participants who previously had sputum conversion.	• Rate of culture reversion (relapse or reinfection) up to Week 60.
• Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB in adult participants with treatment-refractory MAC-LD.	• Percentage of participants having MAC isolates with acquired resistance to CAM detected by a phenotypic method up to Week 60. • Percentage of participants having MAC isolates with increased MICs to BDQ (at least 4-fold increase) up to Week 60.
• To evaluate PK/PD relationships for safety and efficacy of BDQ (and CAM [optional]).	• Exposure, and safety and efficacy (PK/PD) relationship assessments of BDQ (and CAM [optional]) by Week 24.
• To determine the mechanisms of resistance in participants' MAC isolates with increased BDQ MICs by sequencing both *atpE, mmpT5* and other genes (if available).	• Evolution of the *atpE mmpT5* and other gene sequences up to Weeks 60.
• Clinical assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB for participants who achieved sputum culture conversion (at Weeks 24, 48, and 60).	• Change from baseline in patient-reported health status on total score of SGRQ at Weeks 24, 48, and 60. • Change from baseline in patient reported health status on score of QOL-B NTM module at Weeks 24, 48, and 60. • Change from baseline in lung function parameters at Weeks 24, 48, and 60. • Change from baseline in chest CT findings at Weeks 24, 48, and 60.

Note:
1) Although not included in the above Objectives and Endpoints, the efficacy and safety at OPW24 (Week 24 of study intervention treatment) and OPW48 (the last dose of study intervention) in the optional cohort will be evaluated as additional analysis in the similar manner with efficacy and safety at Week 24 and Week 48.
2) Group A=Treatment group consisting of BDQ + CAM + EB
3) Group B=Treatment group consisting of rifamycin (RFP or RBT) + CAM + EB
Key: AEs=adverse event; atpE=ATP synthase subunit c; BDQ=bedaquiline; CAM=clarithromycin; CT=computed tomography; EB=ethambutol; ECG=electrocardiogram; MAC=*Mycobacterium avium* complex; MAC-LD=MAC lung disease; MGIT=mycobacterium growth indicator tube; MIC=minimal inhibitory concentration; mmpT5=mycobacterial membrane protein transporter-5; NTM=nontuberculous mycobacterial; OPW=week in optional cohort; PD=pharmacodynamics; PK=pharmacokinetics; QOL-B=Quality of Life-Bronchiectasis; RBT=rifabutin; RFP=rifampicin; SoA=schedule of activities; SGRQ= St. George's Respiratory Questionnaire.

Refer to Section 8, STUDY ASSESSMENTS AND PROCEDURES for evaluations related to endpoints.

HYPOTHESIS

The hypothesis of this study is that BDQ-containing regimen is superior to rifamycin-containing regimen and increases the proportion of participants with sputum culture conversion in MGIT at Week 24 as compared to rifamycin-containing regimen.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, open-label, active-controlled study to evaluate efficacy and safety of BDQ compared with rifamycin administered as part of a treatment regimen with CAM and EB for 48 weeks in adult participants with treatment-refractory MAC-LD.

- A target of 124 participants with treatment-refractory MAC-LD will be enrolled in this study. Participants who meet all the eligibility criteria will be randomized in a 1:1 (Treatment Group A [Group A]: Treatment Group B [Group B]) ratio:
  - Group A: BDQ + CAM + EB
  - Group B: rifamycin (RFP or RBT) + CAM + EB

For dosing details, refer to Section 6, STUDY INTERVENTION AND CONCOMITANT THERAPY.

Participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by country. The investigator and participant will be blinded for microbiological assessments until each participant has completed the other assessments at Week 24. If during the treatment period, the participant presents with clinical worsening, unblinding for microbiology assessments is allowed at the discretion of the investigator. For the microbiological blinding procedures, refer Section 6.3.

Participants who are taking rifamycin before start of the study intervention will be required to discontinue rifamycin to allow for a minimum of 14-day washout period. This safety measure is implemented to avoid DDIs between rifamycin and BDQ. Bedaquiline is a substrate of CYP3A4 (which is the main metabolic pathway for elimination) and co-administration with strong inducers such as rifamycin are contraindicated as they substantially reduce BDQ levels.

The study will consist of a screening period of 70 days (10 weeks) (including rifamycin washout period of 14 days for participants to whom this is applicable), an open-label treatment period of 48 weeks (baseline visit [Day 1] to Week 48) in Group A or 60 weeks (Day 1 to Week 60) in Group B, and a follow-up period of 12 weeks in Group A. Participants will return for study visits biweekly in the first 12 weeks and then every 4 weeks until Week 60. In addition, this study provides an option to receive BDQ-containing regimen for non-converters in Group B at Week 24 as the optional cohort. OPW-2 in optional cohort will be initiation of 2-week washout period in optional cohort.

Participants requiring a treatment regimen change will be considered treatment failures for subsequent endpoints and will be followed up for safety only, but all assessments should be performed according to the protocol. In addition to the option to switch to the optional cohort in Group B and withdrawal from the study, individualized treatment regimen was set up to as a regimen that may be used when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on non-conversion supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by the results such as chest computed tomography [CT] scan) or the occurrence of AE. Since the microbiological results are blinded, if the investigators consider the regimen change based on the clinical worsening of symptoms related to MAC-LD supported by the result of chest CT scan and so on, the investigators can consult with IDMC before the change. Specific switching criteria, treatment options, visits and assessments before and after switching, and follow-up will be detailed in Section 6.8.1, Individualized Treatment Regimen.

Upon completion of the 48-week treatment period, the participants in Group A who achieved culture conversion will transfer to the follow-up period of 12 weeks. During the follow-up period, the convertors will be treatment free for MAC-LD in order to confirm the durability of culture conversion. Non-converters at Week 48 in Group A will be discontinued from the study and switched to another treatment regimen if they continue chemotherapy because the duration of BDQ treatment is 48 weeks. On the other hand, the participants in Group B will continue the study intervention up to Week 60. Upon completion of the 60-week study intervention period, the study is completed, but the participant may continue SOC of local guidelines or medical practice at each study site for at least 1 year after culture conversion at the discretion of the investigators.

In addition, this study provides an option to receive BDQ-containing regimen (BDQ + CAM + EB) for non-converters in Group B at Week 24 as the optional cohort. The participants may continue Group B regimen, switch to an individualized treatment regimen, or BDQ-containing regimen in the optional cohort at the discretion of the investigators. The criteria for switching to optional cohort after Week 24 are detailed in Section 6.8.2. When the investigator changes to BDQ-containing regimen, 2-week washout of rifamycin is required before initiation of BDQ-containing regimen. The participants switching to BDQ-containing regimen will be considered treatment failures for rifamycin-containing regimen and will be followed up for efficacy and safety for BDQ-containing regimen.

In this optional cohort, during the 48-week treatment period (from Day 1 in optional cohort [OPD1] to Week 48 in optional cohort [OPW48]) of the study, participants may be changed to individualized treatment regimen. The investigators can postpone the decision to transfer to the optional cohort for up to Week 32 in order to confirm a sputum culture positive at Week 24, if necessary. Regardless of delay in the transition phase, the treatment duration of the optional cohort will be for 48 weeks.

All participants who switched to the optional cohort will be considered as treatment failure to rifamycin-containing regimen.

Key efficacy assessments include sputum culture conversion in MGIT and 7H10 or 7H11, St. George's Respiratory Questionnaire (SGRQ), and lung function (refer to Section 8.1, Efficacy Assessments). Key safety assessments will include the monitoring of AEs, physical examinations, measurement of body weight, vital sign measurements, clinical laboratory tests, 12-lead ECGs, and visual/audiology test (refer to Section 8.2, Safety Assessments).

An IDMC will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

Study Population

A recent study in treatment-refractory patients (including cavitary patients) documented a sputum culture conversion rate of 8.9% by month 6 of guideline-based therapy.[15] This patient population therefore represents not only an area of unmet medical need, but also a suitable group to establish whether BDQ is active against human MAC infections. The present study will enroll patients with treatment-refractory MAC-LD defined as participants who are sputum culture positive for MAC despite at least 6 months of MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within the last 12 months.

Regardless of the predominant radiographical MAC-LD clinical presentation (FC type or NB type), the presence of cavities may be correlated with different treatment outcome compared to the noncavitary NB type.[25] Additionally, cavity size may be negatively correlated with treatment outcome, as demonstrated in participants with drug susceptible TB.[5,39] To uniformly evaluate clinical efficacy, participants with one or more cavities ≥2 cm on a chest CT scan taken within the last 6 months will be excluded from this study. Patients with large cavity have a poor prognosis and surgical therapy in addition to chemotherapy can be considered immediately after diagnosis.

Dose Selection

Refer to Section 4.3, Justification for Dose.

Blinding, Control, Study Phase/Periods, Treatment Groups

The Japanese guidelines currently recommend a 3-drug regimen, consisting of CAM, RFP or RBT, and EB, as SOC.[41] The South Korean and Taiwanese guidelines recommend a 3-drug regimen consisting of macrolide (CAM or AZM), RFP or RBT, and EB as the SOC. [50, 51] Therefore, 3-drug regimen, consisting of CAM as macrolide is selected as control arm.

This study will be conducted by an open-label design. Because rifamycin, which is included in the control regimen, is known to cause a reddish coloration of the urine, feces, sputum, sweat, serum, and discoloration of soft contact lenses, blinding of the study drug/comparator is practically impossible due to the wide area of coloration effects. The primary endpoint at Week 24 is sputum culture conversion, which will be assessed based on the results of culture at the central microbiology laboratory. These microbiological results will be blinded to the investigator and

participants until the completion of the other assessments at Week 24. Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The planned treatment duration of BDQ (48-week BDQ treatment period) is same as the maximum duration in the sponsor-conducted clinical study in Japanese participants with MDR-TB (Study TMC207TBC2001).[43] Overall, the treatment success rate in treatment-refractory patients with the current treatment has been unsatisfactory and many patients remain culture positive despite prolonged therapy.[24] The local guidelines for MAC-LD treatment in Japan, South Korea ,Taiwan and an Official ATS/IDSA statement currently recommend treating until patients have been on SOC for 1 year after culture conversion, but there is no evidence to support this treatment duration.[41, 50, 51, 14]

The standard duration of administration with BDQ for the treatment of MDR-TB with a known bactericidal effect is 24 weeks, whereas the duration of administration with BDQ for MAC-LD, where a bacteriostatic effect is suggested, needs to be longer, and is therefore set at 48 weeks and drug free follow-up period for 3 months is planned to evaluate the recurrences after completion of treatment to evaluate appropriate treatment duration. On the other hand, the participants in Group B who achieved culture conversion at Week 24 will continue up to Week 60. This 60-week duration is consistent with the end of follow-up period in Group A. Upon completion of the 60-week study intervention period, the study is completed, but the participant may continue SOC of local guidelines in Japan, South Korea and Taiwan or medical practice at each study site for least 1 year after culture conversion at the discretion of the investigators after study completion.

In addition, participants who have not achieved culture conversion in Group A (BDQ-containing regimen) will continue their assigned regimen until Week 48, unless they have difficulty continuing due to failure to respond (see Section 6.8.1, based on non-conversion and clinical worsening) or the occurrence of AE related to the regimen. If participants were judged to have difficulty continuing due to failure to respond to the regimen or the occurrence of the regimen related AE, at the discretion of investigators, there will be options to discontinue from the study or switch to an individualized treatment regimen (in principle, add on injectable SM, injectable or inhalation suspension of AMK).

The participants in Group B (rifamycin-containing regimen) who do not achieve culture conversion up to Week 24 and continue the study, will have the option, at discretion of investigator, to (1) continue rifamycin-containing regimen, (2) switch to individualized treatment regimen (see Section 6.8.1, in principle, add on injectable SM, injectable or inhalation suspension of AMK), (3) switch to BDQ-containing regimen after 2-week washout of rifamycin. The latter option is called the "optional cohort" (see Section 6.8.2). The target population is refractory participants, who received at least 6-month SOC before this study and received the rifamycin-containing regimen up to Week 24 and SOC for at least 1 year but could not achieve culture conversion. Therefore, in consideration of the benefits for non-converters in Group B, an opportunity to switch to the optional cohort at Week 24 after the completion of the assessments will be provided. All

participants switched to individualized treatment regimen or the optional cohort will be considered as "treatment failures".

Efficacy Measures

To date, the surrogate markers predictive of clinical treatment response in MAC-LD have not been established. In 2018, a consensus paper on treatment outcome definitions was released which proposed key outcome parameters to be used in the treatment of NTM-LD.[44] The microbiological consensus definition for culture conversion is the finding of at least 3 consecutive negative mycobacterial cultures from respiratory samples, collected at least 4 weeks apart (at least 25 days apart in consideration of allowed visiting window), during antimycobacterial treatment (the sampling date of the first negative culture is then the date of culture conversion).[44] In the present study, the primary endpoint for the primary analysis at Week 24 is the percentage of participants achieving sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) (ie, 6 months after start of study intervention). The recent study using semiquantitative cultures to monitor treatment effect suggests that a lack of microbiological response after 6 months of treatment is a very accurate predictor of treatment failure (nonresponse) at 12 months and beyond. The percentage of participants achieving sputum culture conversion at Week 48 (ie, 12 months after start of study intervention) is the secondary efficacy endpoint for the assessment of the sustainability of sputum culture conversion. In addition, the secondary efficacy endpoint for clinical assessment is the change from baseline in patient-reported health status on the total score of SGRQ and the extrapolatory efficacy endpoint for clinical assessment is the change from baseline in patient-reported health status on the score of QOL-B NTM module at Weeks 24, 48, and 60.[14]

The burden of living with MAC-LD and the complicated, prolonged therapy associated with its treatment has a significant impact on patient's HRQOL. Assessing HRQOL is an important aspect of patient assessment and management, which involves evaluating a patient's satisfaction with domains of health, including the perception of performance in physical function, emotional state, social interaction, and somatic sensation domains.[4,32] The present study will evaluate the HRQOL in participants with MAC-LD using the SGRQ[21,45] and the QOL-B NTM module.[17,38] The SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in participants with obstructive airway disease.[21,45] The NTM module was developed specifically for NTM symptoms and consists of NTM symptoms, body image, digestive symptoms, and eating problems.[17,38] However, as QOL-B NTM module has only been preliminarily validated and no consensus has been reached at present, this will be handled as an exploratory measurement tool in this study.

4.2.1. Study-specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The primary ethical concern is to continue the standard regimen which may not be effective in treatment-refractory MAC-LD for at least Week 24 in case participants will be randomized to Group B. Although this study plans to perform the primary analysis at Week 24, an optional cohort of participants randomized to standard therapy who have not achieved culture conversion at Week 24 will be provided in which they will receive the BDQ combination regimen. Participants who are not converted at Week 24 will be selected at the discretion of the investigator to either continue with the treatment regimen used through Week 24, switch to an individualized treatment regimen, or proceed to an optional cohort and receive the BDQ combination regimen. All participants, except those who continue on the same treatment regimen through Week 24, will be treated as failures. This cohort was set as a rescue measure for participants assigned to the standard therapy because the sputum culture conversion rate by the standard therapy was low and the likelihood of conversion was low even if the treatment was continued for longer than 24 weeks.

Addition of aminoglycosides (injectable SM, injectable or inhalation suspension of AMK) is permitted as an individualized treatment regimen in either treatment group if participants are judged to have difficulty continuing the designated treatment regimen due to failure to respond (based on non-conversion and clinical worsening) or the occurrence of the regimen related AE, at the discretion of investigators. Addition of aminoglycosides in Group B is recommended by the Japanese guideline,[41] and is expected to be clinically efficacious in participants with clinical worsening. On the other hand, addition of aminoglycosides to the regimen in Group A has been confirmed to have antimicrobial activity based on nonclinical studies, but its clinical efficacy has not been confirmed at present. Regarding safety, in the Japanese and oversea guidelines on approved drug therapies for the treatment of pulmonary MDR-TB,[48,49] AMK and SM are recommended as agents to be used in combination with multiple drug therapies including BDQ, and there have been no reports of any problems concerning drug interactions and new adverse reactions associated with the combination use. However, experience in the treatment of pulmonary MAC disease is limited, and safety monitoring participants will be performed at least every 4 weeks until study completion or early discontinuation according to Section 1.3, Schedule of Activities (SoA), Since treatment options for participants who failed to respond are limited, addition of aminoglycosides, which is expected to convert and improve clinical symptoms, was selected as an individualized treatment regimen.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the Japanese Red Cross Society.

4.3. Justification for Dose

The dosage and administration of BDQ of this study in adult participants with treatment-refractory MAC-LD (BDQ 400 mg once daily in the first 2 weeks, followed by BDQ 200 mg twice weekly in Weeks 3-48) was determined based on the PK results of DDI study between CAM and BDQ and simulation using the previously developed population pharmacokinetic (popPK) model of BDQ.

In this study, the replacement of RFP in the current standard therapy regimen (CAM + EB + RFP) with BDQ (CAM + EB + BDQ) for the participants with treatment-refractory MAC-LD is planned. BDQ is a CYP3A4 substrate and co-administration with CAM (CYP3A4 inhibitor), one of the standard therapies for MAC-LD, increases BDQ exposure. Thus, a popPK model was developed to simulate the exposure of BDQ in combination with CAM. As the popPK model of BDQ, a model based on the non-Japanese data from Phase 1 and Phase 2 studies conducted at the timing of development for the participants with MDR-TB was used. Applying this model to the results from NTM1001, a 37% decrease in BDQ clearance was estimated when CAM was co-administered. The model was used to explore the dosage and administration of BDQ in this study. Bedaquiline exposures were targeted to be similar to those expected with the MDR-TB dosing regimen (BDQ 400 mg once daily in the first 2 weeks, followed by BDQ 200 mg three times weekly in Weeks 3-24) for the following reasons:

- There were no safety concerns in the Phase 2 clinical studies in non-Japanese and Japanese participants with MDR-TB.
- Based on the postmarketing safety information of BDQ in Japan, there has been no safety concern in participants with MDR-TB, even when administered for longer than 24 weeks.

In this assessment, several dose regimens were simulated. When BDQ PK was simulated for 1,000 participants under the dose regimen of "BDQ 400 mg once daily in the first 2 weeks, followed by BDQ 200 mg twice weekly in Weeks 3 to 48 (in combination with CAM 500 mg twice daily)", the exposure was consistent with that expected with the dosage regimen for pulmonary MDR-TB (Table 1).

Table 1: The Ratios of Mean BDQ Exposures From Simulations of the Dose and Administration of BDQ for the Patients With MDR-TB (MDR-TB regimen) and the Dose and Administration of BDQ for the Patients With MAC-LD in This Study (MAC-LD regimen)

Time since first BDQ dose	The ratio[a] of C_{trough}[b]	The ratio[a] of C_{max}	The ratio[a] of AUC
Week 2	1.15	1.06	1.11[c]
Week 24	0.97	0.98	0.93[d]
Week 48	0.99	0.99	0.95[d]

Key: AUC=area under curve; CAM=clarithromycin; C_{max}=maximum plasma concentration; C_{trough}=minimum plasma concentration between 0 hour and the dosing interval τ; MAC-LD=*Mycobacterium avium* complex-lung disease; MDR-TB=multi-drug resistant tuberculosis.

Note: In MDR-TB regimen, BDQ was administered as 400 mg once daily in the first 2 weeks, followed by BDQ 200 mg three times weekly in Weeks 3 to 24 (without co-administration of CAM).

MAC-LD regimen: BDQ 400 mg once daily in the first 2 weeks, followed by BDQ 200 mg twice weekly in Week 3 to 48 (with co-administration of CAM [500 mg twice daily]).

[a]: The mean exposure of MAC-LD regimen/ the mean exposure of MDR-TB regimen

[b]: Plasma trough concentration

[c]: AUC_{24h}

[d]: AUC_{168h}.

As a result, BDQ dosing regimen for this study was proposed as "400 mg once daily for the first 2 weeks in combination with CAM followed by BDQ administered at 200 mg twice weekly for the next 46 weeks, with an interval of at least 72 hours".

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed assessments at Week 60 of the open-label phase or at OPW48 of the optional cohort. Following completion of the study, the participant may continue the SOC per local guidelines or medical practice at each study site for at least 1 year after culture conversion, at the discretion of the investigator.

5. STUDY POPULATION

Screening for eligible participants will be performed within 10 weeks before administration of the study intervention.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. Male or female.
2. 20 to 79 years of age, inclusive.
3. Has body weight ≥40 kg at screening and on Day 1.
4. Has radiological evidence consistent with NTM-LD based on a chest CT scan taken within 6 months prior to screening or at screening.
5. Criterion modified per Amendment 4.

5.1 Criterion modified per Amendment 8.

5.2 Has at least 2 positive sputum cultures of MAC (sputum cultures to be taken at least 4 weeks apart):

- one obtained within 12 months prior to screening, which was documented while being treated for MAC-LD for a total of at least 6 months.

- one at screening (by central microbiology laboratory).

6. Criterion modified per Amendment 4.

6.1 Criterion modified per Amendment 8.

6.2 Received at least 6 months of consecutive MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within 12 months prior to screening.

Note: Participants must be compliant with medication intake for at least 75% of the total doses for prescribed SOC (including intermittent regimen) recommended by local guidelines. Participants who have missed more than 25% of their doses during a given treatment period for any reason (including noncompliance by participants, interruption due to an AE at the discretion of physician, and others) can only be enrolled if approved by the sponsor's medical monitor.

7. No presence of cognitive dysfunction that would impact the completion of the patient-reported outcome (PRO) assessments.

8. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

9. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) test at screening and on Day 1.

10. A woman using oral contraceptives must use an additional contraceptive method (as required in Inclusion Criterion 11).

11. A woman must be (as defined in Section 10.5, Appendix 5: Contraceptive Guidance).

a. Not of childbearing potential

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 90 days after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of the study intervention. Examples of highly effective methods of contraception are located in Section 10.5, Appendix 5: Contraceptive Guidance.

12. a woman must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for at least 90 days after receiving the last dose of study intervention.

13. a male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for at least 90 days after receiving the last dose of study intervention (male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak).

14. a male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 90 days after receiving the last dose of study intervention.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Had previous exposure to BDQ.

2. Has active TB disease.

3. Has cystic fibrosis, medically unstable respiratory disease (eg, COPD, bronchiectasis, asthma).

   Note: Medically unstable respiratory disease is defined as their symptom/sign are not controlled with medication for their respiratory disease and exacerbation was observed within 6 months prior to screening.

4. Has one or more cavities ≥2 cm in diameter on a chest CT scan taken within 6 months prior to screening or at screening.

5. Criterion modified per Amendment 8.

5.1 Treatment already includes an injectable/inhaled aminoglycoside within 3 months prior to screening or the investigator deems the participant to be a candidate for an injectable/inhaled aminoglycoside during screening period or at Day 1.

6. Criterion modified per Amendment 8.

6.1 Has a history of documented macrolide-resistant MAC strain within 24 months prior to screening or at screening. For CAM, MIC of ≥32 µg/mL indicates resistance according to the Clinical and Laboratory Standards Institute [CLSI] M24 guidelines.[9,46,47]

Note: In case a subject has ≥2 documented DST results within 24 months prior to screening, the subject is eligible if the latest result is susceptible and DST at screening is confirmed susceptible.

7. Has a history of a myocardial infarction, or a presence of any clinically significant cardiac disease, as determined by the investigator.

8. Has experienced one or more of the following risk factors for QT prolongation:

- personal or family history of Long QT Syndrome
- personal history of cardiac disease, symptomatic or asymptomatic arrhythmias, with the exception of sinus arrhythmia
- a confirmed prolongation of the QT or QT interval corrected according to QTcF ≥450 milliseconds (ms) in the screening ECG (retesting to reassess eligibility will be allowed once using an unscheduled visit during the screening period)
- pathologic Q-waves (defined as Q-wave >40 ms or depth >0.4-0.5 mV)
- evidence of ventricular pre-excitation (eg, Wolff Parkinson White syndrome)
- electrocardiographic evidence of complete or clinically significant incomplete left bundle branch block or right bundle branch block
- evidence of second- or third-degree heart block
- intraventricular conduction delay with QRS duration >120 ms
- bradycardia as defined by sinus rate less than 50 beats per minute
- syncope (ie, cardiac syncope not including syncope due to vasovagal or epileptic causes)
- risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, or hypomagnesemia)

9. Has a relevant history or current condition that might interfere with drug absorption, distribution, metabolism, or excretion such as malabsorption syndrome or renal, or hepatic disease.

10. Has active malignancy (primary or metastatic) or any other malignancy requiring chemotherapy or radiotherapy within 1 year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).

11. Has known allergies, hypersensitivity, or intolerance to BDQ, CAM, EB, RFP or RBT (refer to IB[40] and addendum of BDQ, and package insert of each drug).

12. Has the following toxicities during the screening period:

- Serum creatinine is >1.5 × upper limit of normal (ULN)

- Aspartate aminotransferase (AST) is >3.0 × ULN
- Alanine aminotransferase (ALT) is >3.0 × ULN
- Alkaline phosphatase (ALP) is >3.0 × ULN
- Total bilirubin is >2.0 × ULN or >1.5 × ULN when accompanied by any increase over ULN in other liver function test

13. Has a history of HIV antibody positive, tests positive for HIV at screening, a history of hepatitis B surface antigen (HBsAg), or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease, or tests positive for HBsAg or anti-HCV at screening. A participant who has completed treatment for hepatitis C and has been cured is eligible.
14. Has a history of drug or alcohol abuse that, in the investigator's opinion, would compromise the participant's safety or compliance to the study protocol procedures.

15. Criterion modified per Amendment 8.

15.1 Has contraindications to the use of CAM, EB, RFP or RBT per local prescribing information in Japan, South Korea or Taiwan.

16. Has taken any prohibited therapies as noted in Section 6.8, Concomitant Therapy before the planned first dose of study intervention.

17. Received an investigational study intervention or used an invasive investigational medical device within 60 days before the planned first dose of study intervention or is currently enrolled in an investigational study.

18. Is pregnant, or breast-feeding, while enrolled in this study or within 90 days after the last dose of study intervention.

19. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention or who is unwilling to use acceptable methods of contraception as outlined in Section 10.5, Appendix 5: Contraceptive Guidance.

20. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

21. Has preplanned surgery or procedures that would interfere with the conduct of the study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

22. Employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

23. Is co-infected with NTM species other than MAC on sputum culture at screening.

    Note: If both MAC and NTM species other than MAC were detected on screening sputum culture, and previous test result(s) suggested possible contamination such as NTM species other than MAC was not detected before screening, a retesting of screening sputum culture (repeat of sputum collection and sputum culture) will be allowed once. The time required for retesting will not be included in the duration of the screening period (9 weeks).

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and at baseline (Day 1). If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study.

NOTE: Retesting of abnormal laboratory, ECG and physical examination values that may lead to exclusion will be allowed once. Retesting will take place during an unscheduled visit in the screening period. If the repeat test meets the study enrollment criteria, the participant can be included in the study.

NOTE: If a subject is excluded due to COVID-19 related circumstances during the screening period, the reason for screen failure should be recorded as exclusion criterion number 25 on the eCRF (refer to COVID-19 Appendix).

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Activity

1. Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

2. Strenuous exercise may affect study specified assessments and safety laboratory results; for this reason, strenuous exercise should be avoided within 24 hours before all planned study visits and during stays in the study site.

3. Avoid donating blood for at least 30 days after last dose of BDQ of the study.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, including candidates whose microbiological testing at screening is not eligible, such as culture negative, resistance to CAM, etc. Rescreened participants should be assigned a different participant number with the initial screening.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

The study drug BDQ and the comparator rifamycin (RFP and RBT) will be provided as tablets for oral administration. BDQ will be taken with food in the morning at approximately the same time each day, depending on visit and visit assessments. Rifamycin (RFP or RBT) will be taken according to the investigator's instructions. Combination drugs will not be provided by the sponsor and marketed product at study sites should be administered. Participants will be instructed to take their assigned dose of the study intervention or comparator and combination drugs, per Table 2.

Table 2: Dosage and Administration Table for Study Interventions and Combination Drugs

Group	Group A	Group B		Group A and Group B	
Intervention Name	BDQ (TMC207) [a,b]	Rifamycin [a,b,c]		clarithromycin (CAM)	ethambutol (EB)
		rifampicin (RFP)	rifabutin (RBT)		
Category	Study Interventions (Investigational Medicinal Product)			Non-Investigational Medicinal Product	
	Study drug	Comparator		Combination drugs	
Formulation and strengths	100 mg tablet	150 mg capsule	150 mg capsule	200 or 250 mg tablet	125, 250, 400 or 800 mg tablet
Dosage level(s)	JP, SK, TW: Loading phase (Week 1-2): 400 mg qd, Maintenance phase (Week 3-48): 200 mg biw with at least 72 hours between doses	JP, SK, TW: 450 mg qd, Maximum daily dose 600 mg	JP: 300 mg qd SK, TW: 150 or 300 mg qd	JP: 800 mg/day [d] (400 mg bid) SK, TW: 1,000 mg/day [d] (500 mg bid)	JP: 500-750 mg qd, Maximum daily dose 1.0 g SK, TW: 15 mg/kg [e] qd
Route of administration	Oral	Oral	Oral	Oral	Oral
Sourcing	Provided centrally by the sponsor			Provided locally by the trial site	

[a] Participants who are taking rifamycin before start of treatment with BDQ will be required to discontinue rifamycin to allow for a minimum 14-day washout period to avoid DDIs between rifamycin and BDQ.
[b] Bedaquiline and rifamycin (RFP/RBT) will be provided under the responsibility of the sponsor.
[c] RFP is basically administered in all countries, but RBT will be considered if RFP is ineffective or cannot be used in Japan or at the discretion of the investigator in South Korea and Taiwan. The dose of RBT is based on the recommended dose in each country; 300 mg/day in Japan, and 300 mg/day for ≥50 kg and 150 mg/day for <50 kg in South Korea and Taiwan.
[d] Daily dose of CAM on Day 1 is 800 mg (400 mg bid) in Japan and 1,000 mg (500 mg bid) in South Korea and Taiwan. If a dose reduction is required due to AEs after the start of treatment, the daily dose of CAM may be reduced to 750 mg (South Korea and Taiwan) or 600 mg (Japan) at the discretion of the investigator.
[e] Based on 15 mg/kg, the daily dose will be determined at the discretion of the investigator.

Key: JP=Japan; SK=South Korea; TW=Taiwan; AE=adverse event; BDQ=bedaquiline; bid: bis in die (twice a day), biw: bis in week (twice a week); qd: quaque die (once a day), CAM=clarithromycin; EB=ethambutol; RBT=rifabutin; RFP=rifampicin; DDI= drug-drug interactions

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

BDQ will be manufactured and provided under the responsibility of the sponsor. Refer to the IB[40] for a list of excipients of BDQ. Rifamycin (RFP or RBT) will be provided under the responsibility of the sponsor. Refer to the respective Japanese package insert for a list of excipients of Rifamycin (RFP or RBT).

For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention must be stored in the original blister sheet or container within the designated temperature range indicated by label of the kit in order to protect from light.

Refer to the pharmacy manual/study intervention and procedures manual for additional guidance on study intervention preparation, handling, and storage.

Preparation, handling, and storage of combination drugs (CAM and EB) will be in accordance with procedures of the study sites.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant and the return of study intervention from the participant must be documented on the study intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. The participants must return unused study intervention to the study site.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention and study intervention returned by the participant must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention or used returned study intervention for destruction will be documented on the study intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the study intervention return form.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

It is an open-label study; however, participants will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by country.

Blinding

As this is an open-label study, blinding procedures are not applicable. However, the microbiological results from Week 2 to Week 24 will be blinded to the investigators, site staffs and participants until the completion of the other assessments at Week 24 by the investigators. In order to maintain the blind, the investigator should not perform microbiological tests for acid-fast

bacillus at the study site after Day 1 until completion of the assessments other than microbiological assessments at the Week 24 except in emergency situations related to subject safety or chemotherapy. In case the investigators need to know the microbiological result to decide if participants should be switched to an individualized treatment regimen or continue the study treatment regimen, due to clinical worsening, the investigators can access the microbiological result from the central laboratory (for the detailed procedure, refer to the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test). Sponsor except for specific personnel listed below must keep the blinding of all the microbiological assessment after Week 2 until unblinding takes place for the primary analysis.

In addition, sponsor personnel involved in monitoring of the study sites and personnel involved in management operation of the central laboratory etc. are excluded from maintenance of blinding for microbiology assessments, taking into account that sponsor needs to confirm that investigators and etc. comply with the protocol and the decision to switch to individualized treatment regimen and the optional cohort is made based on the appropriate process. Details will be provided in the statistical analysis plan (SAP).

The interim (futility) analysis is detailed in Section 9.5, Interim Analysis.

6.4. Study Intervention Compliance

Table 3 provides instructions for when BDQ doses are missed or interrupted. Bedaquiline in the optional cohort will be administered according to Group A regimen. Interruption or missing dose of comparator or combination drug will be managed by investigators based on local practice and labeling.

Table 3: BDQ Missed Dose and Interruption Instructions

BDQ Missed Dose		BDQ Interruption	
Loading Phase (Weeks 1-2)		Loading Phase (Weeks 1-2)	
Participant notices missed dose within 12 hours of planned intake time	Participant notices missed dose 12 hours or later after planned intake time	BDQ interruption ≤14 days	BDQ interruption >14 days
⇩	⇩	⇩	⇩
Take missed dose and then resume dosing schedule	Do not take missed dose and resume dosing schedule	Continue dosing from last dose taken to complete total doses required in Loading Phase (previous doses taken into account)	Restart from beginning of Loading Phase to complete total doses required in Loading Phase (previous doses not taken into account)
		More than 1 interruption is not allowed (considered as treatment failures, 1 interruption is acceptable) Restarting is not permitted after interruptions of >30 days (considered as treatment failures)	
Maintenance Phase (Weeks 3-48)		Maintenance Phase (Weeks 3-48)	
Participant notices missed dose in same dosing week of missed dose	Participant notices missed dose after dosing week of missed dose	BDQ interruption ≤14 days	BDQ interruption between 15 to 30 days
⇩	⇩	⇩	⇩
Take missed dose as soon as possible and then resume dosing schedule	Do not take missed dose and resume dosing schedule	Dosing can be resumed after interruptions of up to 30 days. All interruptions must be reported to the sponsor within 3 working days of the study site becoming aware More than 1 interruption of 15 to 30 days is not allowed (considered as treatment failures, 1 interruption is acceptable) Restarting is not permitted after interruptions of >30 days (considered as treatment failures)	

Note: BDQ in the optional cohort will be administered according to Group A regimen.

Study intervention compliance will be assessed by counting tablets and/or capsules returned and using participant diary during the site visits and documented in the source documents. The use of study intervention captured in participant diary will be recorded in the eCRF.

Combination drug compliance will be assessed by participant diary during the site visits and documented in the source documents. The use of combination drug captured in participant diary will be recorded in the eCRF.

6.5. Dose Modification

Any dose/dosage adjustment as described in Section 6.1, Study Interventions Administered, should be overseen by medically-qualified study-site personnel (principal or subinvestigator unless an immediate safety risk appears to be present).

In case a dose reduction is necessary, the study drug will be administered per Section 6.1.

6.6. Continued Access to Study Intervention After the End of the Study

Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to determine standard of care.

6.7. Treatment of Overdose

There is no experience with the treatment of acute overdose with BDQ.

For this study, any dose of BDQ greater than 400 mg within a 24-hour time period (-12 hour) from first day to 14 days after the first dose and 200 mg within a 72-hour time period (-24 hour) from 15 days will be considered an overdose. The sponsor does not recommend specific intervention for an overdose. Removal of unabsorbed BDQ may be achieved by gastric lavage or aided by the administration of activated charcoal. Since BDQ is highly protein-bound, dialysis is not likely to significantly remove BDQ from plasma.

Refer to the local package insert of the comparator rifamycin (RFP or RBT) for advice on treatment of overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with Medical Monitor, whether study intervention should be interrupted or dose should be reduced.
- Closely monitor the participant for AE/SAE and laboratory abnormalities. General measures to support basic vital functions including monitoring of vital signs and ECG (QT interval) should be taken in case of deliberate or accidental overdose.
- Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Concomitant therapies administered after signing informed consent (70 days before first dose of study intervention, including the extension period if screening period is extended) and prestudy therapies for pulmonary MAC disease administered prior to signing informed consent must be recorded at screening.

Concomitant therapies must be recorded throughout the study from signing of the ICF up to the last study visit. Concomitant therapies should also be recorded beyond the last follow-up visit only in conjunction with new or worsening AEs and SAEs that meet the criteria outlined in Serious

Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; nonpharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the Concomitant Therapy Section of the eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. For any concomitant therapy given as a treatment for a new condition or worsening of an existing condition, the condition must be documented in the Adverse Event Section of the eCRF. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

It is important to record the use of biotin because of its potential to affect certain laboratory assays when high levels of biotin are present in serum/plasma samples, leading to incorrect test results for certain laboratory parameters. All prior and concomitant treatment with MAC-LD drugs will be recorded. For participants who were previously diagnosed with MAC-LD and are being treated or will start treatment at screening, the start date and details of their treatment regimen must be recorded. Participants who are taking rifamycin before start of the study intervention will be required to discontinue rifamycin to allow for a minimum 14-day washout period (to avoid DDIs between rifamycins and BDQ). Participants who are transferred to the optional cohort will be required to discontinue rifamycin to allow for a minimum 14-day washout period before start of the BDQ-containing regimen.

If contraindicated medication(s) listed in each package insert of comparator/combination drugs (RFP, RBT, CAM, or EB) are received during screening, the contraindicated medication(s) are prohibited from 7 days prior to Day 1 up to the last dose of the medications including study intervention.

Antibacterial drugs, such as fluoroquinolones, linezolid that may be effective for MAC-LD other than the specified concomitant medications are prohibited during the study treatment period.

When injectable aminoglycoside is used as part of an individualized treatment regimen, injectable KM is prohibited throughout the study period, because it is not approved for the treatment of NTM-LD. Injectable SM, injectable or inhalation suspension of AMK is acceptable as part of an individualized treatment regimen. The use of injectable SM, injectable or inhalation suspension of AMK for any purposes other than as part of an individualized treatment regimen is prohibited.

The following medications are prohibited from 2 weeks prior to Day 1 up to the last dose of study intervention (see note):

- systemic use of moderate and strong CYP3A4 inhibitors (eg, azole antifungals: ketoconazole, fluconazole, voriconazole, itraconazole; ketolides such as telithromycin; and macrolide antibiotics [except CAM]) for more than 2 weeks.

- systemic use of strong CYP3A4 inducers (eg, phenytoin, carbamazepine, phenobarbital, St. John's wort [*Hypericum perforatum*], and systemic, multiple dosing of dexamethasone), except rifamycins for those randomized to the rifamycin-containing regimen.

NOTE: For participants receiving BDQ, the above prohibited medication can be (re-)started 1 month after stopping BDQ.

NOTE: The examples of potent CYP3A4 inhibitors and inducers do not form a complete list. The investigator should consult the prescribing information for study interventions and combination drugs (CAM and EB) and, if necessary, contact the appropriate sponsor representative.

The following medications are prohibited because of their potential for QTc prolongation. These medications are not allowed from 7 days prior to Day 1 up to the last dose of study interventions and combination drugs (CAM and EB) (including individualized treatment regimens):

- antiarrhythmics Class IA (eg, quinidine, hydroquinidine, disopyramide)
- antiarrhythmics Class III (eg, amiodarone, sotalol, dofetilide, ibutilide)
- neuroleptics: phenothiazines thioridazine, haloperidol, chlorpromazine, trifluoperazine, pericycline, prochlorperazine, fluphenazine, sertindole, and pimozide
- quinolone antimalarials (eg, chloroquine and quinacrine)
- moxifloxacin (prohibited from the initiation date of BDQ treatment up to 1 month after the last dose of BDQ)
- antimicrobials: erythromycin intravenous (IV), pentamidine, delamanid
- tricyclic antidepressants, including amitriptyline, doxepin, desipramine, imipramine, and clomipramine
- prokinetic cisapride
- nonsedating antihistamines: astemizole, terfenadine, and mizolastine
- clofazimine (increased QT prolongation is reported in co-administration with BDQ)

NOTE: The above list of drugs with known risk of QT prolongation is based on drugs that may be commonly used during the treatment of NTM-LD. The investigator should consult current publicly available drug information to identify other drugs with potential QT prolongation. The list of potential QT prolonging drugs is long and subject to change. Clinical interpretation of known and potential additive risks is required.

The following medications are prohibited because of their potential for muscle damage (myopathy) from 7 days prior to Day 1 up to the last dose of study interventions and combination drugs (CAM and EB) (including individualized treatment regimens) (see note):

- 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins)
- griseofulvin

NOTE: All prohibited medications with a risk for muscle damage (myopathy) can be (re-)started 1 month after BDQ discontinuation.

Hepatotoxic medications should be used with caution, especially during the treatment period in participants with signs of hepatotoxicity (eg, participants with transaminase elevations). Alternative medications should be used if possible.

For participants who change their treatment regimen, latest package inserts should be consulted for contraindicated medication(s) or medication(s) that is not recommended for concomitant use.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.1. Individualized Treatment Regimen

In addition to the option to switch to the optional cohort in Group B and withdrawal from the study, individualized treatment regimen was set up to as a regimen that may be used when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on non-conversion supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by the results such as chest computed tomography [CT] scan) or the occurrence of AE.

During the study, if deemed necessary by the investigator to switch to individualized treatment regimen (in principle, add on SM, injectable or inhalation suspension of AMK. Regimens that may be selected for each treatment group are listed below) and continue treatment, it can be done by obtaining re-consent from the participant (refer to Sections 1.2 and 4.1). Participants should meet one of the following criteria to switch to individualized treatment regimen. (Note: Refer to Section 6.3 for blinding method of the microbiological assessment result).

- Continuation of assigned treatment regimen is difficult because participants are non-converters based on the result of microbiological test (ie, positive) and have clinical worsening of symptom associated with MAC-LD based on the findings in chest CT scan and so on, at the discretion of investigators.
- Continuation of assigned treatment regimen is difficult due to AE related to drug in assigned regimen, at the discretion of investigators.

Individualized treatment regimens permitted in this study are described in below. Investigators should select the appropriate regimens for participants in each treatment group or if no regimen is considered appropriate the participants should be discontinued from the study.

Group A (Assigned treatment regimen: BDQ + CAM + EB)

- BDQ + CAM + EB + aminoglycosides (add one of injectable SM, injectable or inhalation suspension of AMK)
- BDQ + CAM + aminoglycosides (same as above)
- BDQ + CAM (when difficult to continue treatment with EB and no clinical worsening)

Group B (Assigned treatment regimen: Rifamycin + CAM + EB)

- Rifamycin + CAM + EB + aminoglycoside (same as above)

- Rifamycin+ CAM + aminoglycoside (same as above)
- Rifamycin + CAM (when difficult to continue treatment with EB and no clinical worsening)

Note: From the viewpoint of preventing the development of CAM resistance, a regimen with EB discontinuation should be carefully considered.

If an investigator judges that it is necessary to use treatment regimens other than those listed above, such as discontinuation of study intervention, discontinuation of CAM or switching CAM to AZM (prohibited medication), the participant should be discontinued from the study and treatment regimens available at the study site will be provided.

Prior to switching to an individualized treatment regimen, visit and assessments for switch to individualized treatment regimen must be done as shown in Section 1.3, Schedule of Activities (SoA). After switching, a participants will continue their usual schedule for assigned treatment regimen. Note that participants in Group A who have switched to individualized treatment regimen can continue up to Week 48, participants in Group B can continue up to Week 60.

6.8.2. Optional Cohort

To maximize the benefit and minimize the risk, participants in treatment Group B can switch to optional cohort after completion of Week 24 assessment. The decision to switch to optional cohort can be made by Week 32 (refer to Sections 1.2, 1.3 and 4.1). Participants must meet all of the following criteria at the timing of the decision to switch to optional cohort. Before starting BDQ administration, a washout of rifamycin for 2 weeks is required and BDQ administration in optional cohort should start by OPD1.

- Participants are non-converter based on the result of microbiological test (ie, positive) up to Week 24.
- Participants do not have condition described in Section 7.1.
- Participants do not experience any AE associated with CAM and/or EB that causes discontinuation of CAM and/or EB at the discretion of investigators.

Switching from an individualized treatment regimen to the optional cohort is not permitted.

Switching to an individualized treatment regimen is permitted if the criteria described in Section 6.8.1 are met, even after switching to the optional cohort.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention.

- The participant has a QTcF prolongation (defined as a QTcF value ≥500 ms, or an increase from baseline of >60 ms) at any given time point (confirmed by repeat ECGs).
- The participant requires treatment with any of the prohibited medications listed in Section 6.8, Concomitant Therapy.
- The participant becomes pregnant. Refer to Section 10.5, Appendix 5: Contraceptive Guidance.
- Noncompliance with study intervention administration as defined in Table 3.
- The participants discontinued administration of study intervention before Week 48 in Group A, Week 60 in Group B or OPW48 in optional cohort.

If a participant discontinues study intervention before Week 48 in Group A, Week 60 in Group B or OPW48 in the optional cohort, the participant will receive the assessments of early discontinuation or withdrawal.

The early discontinuation visit assessment will be performed within 7 days of the investigator's discretion to discontinue treatment with study intervention, unless the participant withdraws consent. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1.1. Liver Chemistry Stopping Criteria

Refer to Section 8.2.6 Management of Common Expected Toxicities.

7.1.2. QTc Stopping Criteria

Refer to Section 8.2.3, Electrocardiograms.

7.1.3. Temporary Discontinuation

Participants will be temporarily discontinued from study treatment at the investigator's discretion. Few situations are specified in Section 8.2.3, Electrocardiograms and Section 8.2.6 Management of Common Expected Toxicities.

7.1.4. Rechallenge

Instructions on BDQ interruption and resumption are specified in Table 3.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will NOT be automatically withdrawn from the study if he or she has to discontinue study intervention before Week 48 (Group A), Week 60 (Group B), or OPW48 (the optional cohort). A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document.

Participants will be encouraged to complete the early discontinuation visit assessments, which is to be scheduled within 7 days of investigator's discretion to discontinue treatment with study intervention. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of Consent

A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

7.2.1. Withdrawal From the Use of Research Samples

Collection of optional samples for research is not planned in the study.

7.3. Lost to Follow-up

To reduce the chances of a participant being deemed lost to follow-up, prior to randomization attempts should be made to obtain contact information from each participant, eg, home, work, and mobile telephone numbers, and email addresses for both the participant as well as appropriate family members.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (SoA) summarizes the frequency and timing of efficacy, PK, and safety measurements applicable to this study.

The following time windows are allowed:

- For visit Weeks 2, 4, 6, 8, 10, and 12 (±2 days)
- For visit Weeks 16, 20, and 24 (±3 days)
- For visit Weeks 28, 32, 36, 40, 44, 48, 52, 56, and 60 (±4 days)

In case of scheduling visit according to above time windows, the investigators should ensure that 4-week sputum collection interval does not fall below 25 days.

All PRO (SGRQ and QOL-B NTM module) assessments should be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant perceptions. The questionnaires will be completed by the investigator after interviewing the participant and the data will be entered into the eCRF by the investigator/study-site personnel. Refer to the PRO completion guidelines for instructions on the administration of PROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: noninvasive procedures should be collected first before invasive procedure (questionnaire/interview/ECG, vital sign/physical examination/CT scan/audiology/visual examinations/fundoscopy, then sputum sample collection, and blood sampling). ECG and blood collections for PK assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and eCRF.

The total blood volume for the study is approximately 68 to 115.5 mL (52 mL [Group A] for pharmacokinetics and 20 mL [Group B], and 2 mL for pregnancy testing [women of childbearing potential only]).

The total blood volume to be collected from each participant will be approximately 68 to 115.5 mL.

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 115.5 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

If the unscheduled PK samples are taken, the date and the time of the blood draw must be recorded.

Table 4: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	Number of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and posttreatment assessments)			
- Hematology	2[d]	9-12	18-24
- Serum chemistry[b]	2.5	9-12	22.5-30
Serology (HIV, hepatitis)	7.5	1	7.5
Serum β-hCG pregnancy tests (for women of child-bearing potential only)	1	2	2
Pharmacokinetic samples	2	10-26	20-52
Approximate Total[c]			68-115.5

[a]. Calculated as number of samples multiplied by amount of blood per sample.
[b]. Serum chemistry excludes serology (HIV, hepatitis) and serum β-hCG pregnancy tests.
[c]. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
[d]. Depending on local laboratory.
Key: β-hCG=beta human chorionic gonadotropin; HIV=human immunodeficiency virus

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Section 1.3, Schedule of Activities (SoA) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual. Procedures for the collection, handling, and shipment of microbiological samples (sputum), as well as disclosure of blinded data are described in the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test.

Study-specific Materials

The investigator will be provided with the following supplies:

- IB and IB Addendum
- Pharmacy manual/study intervention and procedures manual
- Laboratory manual
- Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture, Including Collection of Samples for Microbiology Test
- PRO questionnaires and PRO completion guidelines
- eCRF completion guidelines
- ICF
- Protocol Supplementary Information

8.1. Efficacy Assessments

Microbiology assessments (MAC-LD Treatment Outcome), clinical assessments in MAC-LD, percentage of participants who undergo a change in their MAC-LD treatment regimen, and a lung function assessment using a spirometry test, will be performed in this study.

8.1.1. Microbiology Assessments (MAC-LD Treatment Outcome)

Sputum sample will be collected at the timepoints shown in Section 1.3, Schedule of Activities (SoA). Instructions for the collection, handling, storage, and shipment of samples for microbiological assessment can be found in the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture, Including Collection of Samples for Microbiology Test. All sample collection and processing will be performed according to the approved operating procedures.

Qualitative Culture for MAC (Mycobacteria Growth Indicator Tube [MGIT])

This is to assess participants' response to treatment by measuring the microbiological response (culture positive or negative) using liquid medium in MGIT. In addition, time to sputum culture conversion and time to positivity are calculated for MGIT.

Qualitative Culture for MAC (7H10 or 7H11 Agar Media)

This is to assess participants' response to treatment by measuring the microbiological response (culture positive or negative) using 7H10 or 7H11 agar media.

Identification and Speciation Of MAC

This is for identification and speciation of MAC by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) for MAC from MGIT, 7H10 or 7H11 agar, and positive sputum cultures.

Resistance Determinations

This is to determine susceptibility of MAC isolates to BDQ, CAM, EB, rifamycins, and other NTM drugs (if possible) by DST using the broth-based microdilution method according to the Clinical and Laboratory Standards Institute [CLSI] M24 guidelines.[9,46,47]

Genotyping or Fingerprinting of Isolates

This is to assess if baseline and postbaseline isolates are the same or different in case of resistance occurring at postbaseline and in case cultures become positive after having been negative, genotyping using variable number tandem repeat (VNTR) or whole genome sequencing (WGS) will be performed.

8.1.2. Clinical Assessments in MAC-LD

SGRQ

CCI [redacted]

[redacted]

Paper-based SGRQ will be provided by the sponsor. It will be recommended that the paper questionnaire be received from the investigator or study staff at the site visit indicated in Section 1.3, Schedule of Activities (SoA) and that subject perform a self-assessment in a waiting room, etc. in an environment where the subject can be instructed on the contents including the assessment period of the questionnaire. It will be allowed that the investigator may also complete the assessment by interviewing (read out each question as written) and obtain the answers from the subject, if the investigator judges that the subject's understanding of the questionnaire including the assessment period is insufficient, etc.

The SGRQ author instructs in the SGRQ manual that "Do not allow patients to take the SGRQ home to be completed since the sponsor cannot be sure that it will be completed without the help of family or friends".

QOL-B and NTM module

[redacted]

Paper based QOL-B and NTM module will be provided by the sponsor. It will be recommended that the paper questionnaire be received from the investigator or study staff at the site visit indicated in Section 1.3, Schedule of Activities (SoA) and that subject perform a self-assessment in a waiting room, etc. in an environment where the subject can be instructed on the contents including the assessment period of the questionnaire. It will be allowed that the investigator may also complete the assessment by interviewing (read out each question as written) and obtain the answers from the subject, if the investigator judges that the subject's understanding of the questionnaire including the assessment period is insufficient, etc.

Percentage of participants who undergo a change in their MAC-LD treatment regimen

This is to calculate the percentage of participants who have changed to an individualized treatment regimen as defined by SOC of local guidelines or protocol (Section 6.8.1) in both groups and participants who have switched to BDQ-containing regimen in Group B.

Lung function assessment

The lung function parameters including forced expiratory volume in one second, forced vital capacity, inspiratory capacity, functional residual capacity, and total lung capacity, will be assessed.

Change from baseline in chest CT findings

The change from baseline in chest CT findings (improved, no change, or worsened) will be assessed and their respective percentages will be calculated. The investigators will evaluate comprehensively based on the spread of opacities, number/size of cavitary opacities, degree of bronchiectasis, etc.

8.2. Safety Assessments

Safety and tolerability will be evaluated throughout the study from signing of the ICF onwards until the last study-related activity (end of study/early withdrawal).

An IDMC will be established for this study to monitor the safety of participants. Details regarding the IDMC are provided in Committees Structure in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting and Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early discontinuation visit will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in Section 1.3, Schedule of Activities (SoA).

8.2.1. Physical Examinations

Physical examination of all body systems (including height and body weight measurement) and observation for skin events/reactions will be performed before the intake of BDQ and blood sampling at site visit indicated in Section 1.3, Schedule of Activities (SoA). Height will be measured at only screening.

8.2.2. Vital Signs

Body temperature (axillary), heart rate, respiratory rate, oxygen saturation, blood pressure (systolic and diastolic) will be assessed, preferably with same position and methodology throughout the study.

Blood pressure and heart rate measurements will be assessed supine or sedentary with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

During the collection of ECGs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine or sedentary position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: vital signs, ECG(s), blood draw.

At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes and must be of good quality (stable baseline, free of interference and artefact). ECGs will be recorded at a paper speed of 25 minute per second until 4 regular consecutive complexes are available. If the record is unclear due to the noise, ECGs will be repeated after 1 or 2 minutes, and the clearer recording will be adopted as an original recording. In principle, 2 original ECG recordings will be provided. One original recording will be stored at the study site and another will be sent to a central cardiologist designated by the sponsor for review. Submission of ECG to a central cardiologist will be done by transmission or send a hardcopy ECG if transmission is not possible for any reasons (refer ECG manual for details). The ECG machine dedicated for this study must be used. All tracings will be transmitted for blinded central analysis. Participants found to have a QTcF ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms on ECG at any point during the treatment period will be further investigated. The ECG should be repeated and if confirmed, the investigator should attempt to identify the cause, including checking and correcting abnormal K^+, Ca^{+2}, and Mg^{+2}. If the participant is taking any drugs suspected of causing QT prolongation, they should be withheld, and the tests repeated after sufficiently long washout to try to identify the cause. Any QTcF prolongation to ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms while on study intervention is considered a notable event and should be reported immediately to the sponsor.

Extra visits will be required for participants meeting certain grading thresholds for changes in QTcF. Additional unscheduled ECG evaluations may be made at the discretion of the investigator.

QTcF Prolongation

If a single ECG shows QTcF ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms, then complete additional triplicate ECGs, evaluate the mean QTcF, and record results on an unscheduled visit form.

If triplicate ECGs confirm a mean QTcF ≥500 ms or an increase from baseline of >60 ms, the following will be done:

- the investigator must assess potential causes of the abnormality including at a minimum a check and correction of electrolyte imbalances (K^{+}, Mg^{+2}, Ca^{+2}), review and adjust combination medications as necessary (eg, temporarily discontinuation of BDQ and CAM), and obtain weekly duplicate/triplicate ECGs until resolution,
- if after 2 weeks mean QTcF is ≥500 ms or increase from baseline of >60 ms, the investigator must permanently stop the study intervention, and continue weekly triplicate ECGs until resolution.

Weekly triplicate ECG monitoring for participants who have recovered from QTcF ≥500 ms or increase from baseline of >60 ms may be discontinued if over 3 consecutive weeks the triplicate ECGs demonstrate a mean QTcF <500 ms or one time increase of ≤60 ms. Participants who meet these criteria can be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA). If mean QTcF <500 ms or increase of ≤60 ms is not demonstrated, then weekly triplicate ECGs will be continued at least until the end of the last dose of BDQ plus 4 weeks due to the long half-life of BDQ. At that point, if mean QTcF <500 ms or increase of ≤60 ms is demonstrated, weekly triplicate ECGs can be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA). Otherwise if mean QTcF <500 ms or increase of ≤60 ms is not demonstrated, the investigator judges whether weekly triplicate ECGs will be continued or be switched to less frequent ECG monitoring per Section 1.3, Schedule of Activities (SoA).

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2, Appendix 2: Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents. The data of local laboratory test except for HBsAg and HCV antibody test and HIV test at screening must be recorded in eCRF.

8.2.5. Pregnancy Testing

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study.

8.2.6. Management of Common Expected Toxicities

For participants with AST and/or ALT elevations, pancreatic amylase elevation, gastrointestinal system toxicities, musculoskeletal system and cardiac muscle toxicities, and cardiac rhythm disturbances, the following should be done (refer Section 10.7, Appendix 7: A Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (November 2007)).

AST and/or ALT Elevation

<5.0 × ULN AST or ALT elevation with normal bilirubin:

Participants may continue to take the study intervention. Participants should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation. Clinical symptoms, AST,

ALT, and serum bilirubin should be monitored every 2 weeks until clinically stable as necessary to manage the participant's condition.

≥5.0 × ULN but ≤8.0 × ULN AST or ALT elevation or ≥3 ULN accompanied by bilirubin ≥2.0 × ULN:

Participants will be permanently discontinued from treatment of the suspected causative background agent or temporarily withhold study intervention at the investigator's discretion. Clinical symptoms, AST, ALT, and serum bilirubin should be monitored every 2 weeks until clinically stable as necessary to manage the participant's condition. If ALT, AST, and bilirubin do not improve or worsens within 2 weeks, the study intervention will be temporarily withheld for up to 2 weeks per investigator discretion. Additional tests should be performed to evaluate the cause of hepatitis (eg, hepatitis A, B, C). Liver enzymes, including serum bilirubin should be monitored as frequently as necessary to manage the participant's condition. If AST/ALT decreases to <5.0 × ULN, study intervention can be restarted once. Participants who fail to show improvement, demonstrated by no improvement in clinical course or persistent AST and ALT ≥5.0 × ULN values, or persistent AST/ALT ≥3.0 × ULN accompanied by bilirubin ≥2.0 × ULN (over 4 weeks) will have to permanently discontinue the study intervention. Participants should be followed until resolution or stabilization (return to baseline) of AST/ALT/bilirubin elevation.

>8.0 × ULN AST or ALT elevation

Per investigator discretion, the study intervention will be temporarily withheld for up to 2 weeks. Additional tests should be performed to evaluate the cause of hepatitis (eg, hepatitis A, B, C). Liver enzymes, including serum bilirubin should be monitored as frequently as necessary to manage the participant's condition. If AST/ALT decreases to <5.0 × ULN, study intervention can be restarted one time. Participants who fail to show improvement, demonstrated by no improvement in clinical course or persistent AST and ALT ≥5.0 × ULN values, or persistent AST/ALT ≥3 × ULN accompanied by bilirubin ≥2.0 × ULN will have to permanently discontinue the study intervention but can continue the study procedures. Participants should be followed until resolution or stabilization (return to baseline) of AST/ALT elevation.

Pancreatic Amylase Elevation

Grade 1 (>1.0 to ≤1.5 × ULN) or Grade 2 (>1.5 to ≤2.0 × ULN):

Participants may continue to take the study intervention and should be carefully evaluated and followed closely.

Grade 3 (>2.0 to ≤5.0 × ULN) or Grade 4 (>5.0 × ULN):

For asymptomatic Grade 3 pancreatic amylase elevations with no history or concomitant disease of pancreatitis, participants may continue to take the study intervention but should be carefully evaluated and followed closely. For confirmed Grade 4 elevations of pancreatic amylase, participants will have to permanently discontinue the study intervention. If there is clinical

evidence of pancreatitis and amylase of Grade 3 or higher, participants will have to permanently discontinue the study intervention.

Gastrointestinal System

In case of Grade 4 nausea (hospitalization required) or Grade 4 vomiting (physiologic consequences requiring hospitalization or requiring parenteral nutrition), the participant's continued participation in the study will be at the investigator's discretion.

Musculoskeletal System and Cardiac Muscle

Myalgia

Grade 1 (with no limitation of activity):

Participants may continue to take the study intervention and should be carefully evaluated and followed closely.

Grade 2 (muscle tenderness at site other than injection site or with moderate impairment of activity) or Grade 3 (severe muscle tenderness with marked impairment of activity) or Grade 4 (frank myonecrosis):

Participants will have to permanently discontinue the study intervention but can continue in the study. Creatinine phosphokinase should be fractionated for creatine kinase myocardial band (CPK-MB) subunit. Participants having confirmed ≥Grade 2 myalgia with Grade 3 (3.0 to 6.0 × ULN) elevation in CPK-MB, or Grade 4 (>6.0 × ULN) elevation in CPK-MB subunit will have to permanently discontinue the study intervention.

LDH and LDH-isoenzymes

For participants with lactate dehydrogenase (LDH) elevation >2.5 × ULN, LDH-isoenzymes will be assessed.

Cardiac Rhythm Disturbances

The following text describes the minimum requirements for the management of cardiac rhythm disturbances; however, additional management decisions are at the investigator's discretion.

Grade 1 (asymptomatic) or Grade 2 (asymptomatic, transient rhythm abnormality not requiring any treatment) cardiac rhythm disturbances:

Participants may continue to take the study intervention and should be carefully evaluated and followed closely.

Grade 3 (recurrent, persistent, symptomatic arrhythmia requiring treatment) or Grade 4 (unstable dysrhythmia requiring hospitalization and treatment) cardiac rhythm disturbances:

Participants will permanently discontinue the study intervention. QTcF prolongation that results in discontinuation of the study intervention will be reported as AE term of "QT prolonged" of

Grade 2 if no symptoms are present. If symptomatic, then a higher grade may be reported as per the definitions above.

8.2.7. Other Safety Evaluations

Visual examination including visual acuity testing, color discrimination, visual field testing, and fundoscopy and audiology will be assessed at study site visit indicated in Section 1.3, Schedule of Activities (SoA). The visual examination, audiology test, and fundoscopy at Day 1 can be assessed within 4 week prior to Day 1 and within 4 days prior or after each visit other than Day 1.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQC) from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver or surrogate) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All SAEs and PQCs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by

facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Institutional Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Reporting Form. If a participant becomes pregnant during the study, a determination regarding study intervention discontinuation must be made by the investigator in consultation with the sponsor.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Disease-related Events and Disease-related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

8.3.7. Adverse Events of Special Interest

The liver, skeletal muscle, heart, pancreas, and stomach have been identified as target organs in nonclinical toxicology studies. Careful monitoring of these organs should be included in clinical studies. Any abnormalities in the parameters related to these target organs are therefore considered as AEs of special interest. Because other compounds for treatment of MAC, with which BDQ will have to be administered, have been associated with rash, skin events are considered as AEs of special interest as well in the study.

8.4. Pharmacokinetics

Plasma samples will be used to evaluate the PK of BDQ (and M2 or additional metabolites, if warranted) and CAM (and its active metabolite 4-OH CAM, if warranted). Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.4.1. Evaluations

Single sparse blood samples will be collected for measurement of plasma concentrations of BDQ and M2 at Weeks 4, 6, 16, and 32 in Section 1.3, Schedule of Activities (SoA). On Day 1, Weeks 2, 8, 12, 24, and 48, 2 blood samples will also be drawn: the predose and 2 to 4 hours postdose plasma concentrations of BDQ and M2 for Group A, and CAM and 4-OH CAM for both Group A and B. The date and time of the second to last and the last administration of BDQ before the corresponding sample and the date and time of blood draw must be recorded. The date and time of the intake of CAM on the day of sampling and the day before sampling should be recorded. Using these blood samples per participant, the PK exposure of BDQ (if deemed necessary, M2) will be calculated, during the loading phase as well as during the maintenance phase.

Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

8.4.2. Analytical Procedures

Pharmacokinetics

Plasma samples will be analyzed to determine concentrations of BDQ, M2, CAM, and 4-OH CAM using a validated, specific, and sensitive liquid chromatographic-mass spectrometry method by or under the supervision of the sponsor.

If required, some plasma samples may be analyzed to document the presence of circulating metabolites of other analytes (eg, circulating metabolites or denatonium) using a qualified research method. In addition, plasma PK samples may be stored for future analysis of the metabolite profile or concomitant medications.

The bioanalytical report, including a description of the assay and a summary of the assay performance data, will be included in the final clinical study report as an addendum.

8.4.3. Pharmacokinetic Parameters and Evaluations

Parameters

Based on the individual plasma concentration-time data, using the actual dose taken and the actual sampling times, PK parameters (C_{max}, C_{trough} [trough concentration], AUCτ) of BDQ at Day 1, Weeks 2, 8, 12, 24, and 48 will be derived using population PK modelling. If deemed necessary, a similar analysis for C_{max}, C_{trough}, AUCτ will be performed for M2.

Baseline covariates (eg, body weight, age, sex) may be included in the model, if relevant.

The predose and 2 to 4 hours postdose plasma concentrations on Day 1, Weeks 2, 8, 12, 24, and 48 (for Week 48, BDQ and M2 only) of BDQ and M2 for Group A, and CAM and 4-OH CAM for both Group A and B will be listed.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between BDQ (and CAM [optional]) PK and MAC-LD treatment outcome and safety endpoints may be evaluated as appropriate. Pharmacokinetics/pharmacodynamics analyses will be performed on the collected data when all participants have reached Week 24 or discontinued earlier. The PK/PD analyses may be performed at earlier time points as necessary to support efficacy and safety findings. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. The results of the PK/PD evaluations will be presented in a separate report.

8.5. Genetics and Pharmacogenomics

Not applicable.

8.6. Biomarkers

Not applicable.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypothesis

The hypothesis of this study is that BDQ-containing regimen is superior to rifamycin-containing regimen and increases the proportion of participants with sputum culture conversion in MGIT at Week 24 as compared to the rifamycin-containing regimen.

9.2. Sample Size Determination

Based on the results of 2 clinical trials of ALIS (Phase 2[36] and Phase 3[15]) in an analogous population, it is anticipated that the rifamycin-containing regimen in this study will have a sputum culture conversion rate assumed to be equal to 10% after 24 weeks of treatment.

A sample size of 124 participants (62 in Group A: the BDQ containing regimen, 62 in Group B: the rifamycin-containing regimen) will have a power of about 80% to show superiority for a 20% difference in proportion of participants having sputum conversion at Week 24 based on a chi-square test (at the 5% 2-sided significance level) on the intent-to-treat (ITT) population.

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized in the study.
Intent-to-treat (ITT)	All randomized participants who take at least 1 dose of study intervention. ITT will be the primary population for efficacy analyses.
Per-protocol (PP)	All ITT population with at least 3 consecutive sputum collections taken at least 25 days apart after baseline. Participants who have major protocol deviations will be excluded from the PP population. More details will be provided in the SAP.
Safety	All participants who take at least 1 dose of study intervention.
PK	All safety population with at least 1 PK measurement.

9.4. Statistical Analyses

The SAP will be finalized prior to DBL and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

All efficacy and safety data will be summarized by treatment groups (Groups A and B). For the Group B, data from optional cohort will be analyzed separately.

9.4.2. Primary Estimand

The primary estimand, the main clinical quantity of interest to be estimated in this study, is defined by the following 5 components:

- Population: Adult patients with treatment-refractory MAC-LD.
- Endpoint: Proportion of participants with sputum culture conversion in MGIT at Week 24.
- Treatment: BDQ-containing regimen versus rifamycin-containing regimen.
- Intercurrent Events (ICE):
    a. Deaths, treatment discontinuation and treatment regimen changes prior to Week 24: all the ICEs will be handled by a composite strategy to treat the participants as non-convertors.

b. Major protocol deviations: all data will be used regardless of the occurrence of major protocol deviations (treatment policy strategy).

- Population Level Summary: The difference of proportions between treatment groups.

9.4.3. Primary Endpoint

Sputum Culture Conversion in MGIT at Week 24.

The Cochran-Mantel-Haenszel test stratified by region (Japan, non-Japan) at the 5% 2-sided significance level will be used to compare sputum culture conversion rate in MGIT at Week 24. Participants with missing sputum samples that impact the ability to assess sputum culture conversion (ie, 3 consecutive negative sputum cultures taken at least 25 days apart) will be imputed as non-convertors in the analysis. Participants requiring a treatment regimen change to individualized regimen will also be considered as non-convertors. A contaminated sputum culture or failed culture occurring between two negative cultures will be interpreted as "no data", and will be ignored for the assessment of the 3 consecutive negative cultures. More details will be provided in the SAP. Subgroup analyses will be performed for important baseline disease characteristics.

9.4.4. Secondary Endpoints

- Sputum culture conversion in MGIT and 7H10 or 7H11 agar media (other than MGIT at Week 24).

The percentage of participants with sputum culture conversion (defined as 3 consecutive negative sputum cultures taken at least 25 days apart) in MGIT and 7H10 or 7H11 agar media will be calculated after Week 4. The percentage of participants who achieved sputum culture conversion at Week 24 and completed 48-week BDQ-containing regimen and achieved sputum culture conversion at Week 60 in Group A will be compared with the percentage of participants who completed 60-week SOC regimen and achieved sputum culture conversion at Week 60 in Group B using the Cochran-Mantel-Haenszel test stratified by region (Japan, non-Japan).

- Sputum culture negativity in MGIT and 7H10 or 7H11 agar media.

The percentage of participants with sputum culture negativity in MGIT and 7H10 or 7H11 agar media will be calculated at each visit after Week 2, respectively. A generalized linear model including treatment, region (Japan, non-Japan), time, and treatment-by-time interaction as fixed effects will be applied for the number of negative culture participants and the number of all participants at each timepoint and comparison between treatment groups will be performed using the appropriate contrast for the percentage of negative culture participants at Week 24.

- Time to sputum culture conversion in MGIT.

Time to sputum culture conversion in MGIT is calculated as the interval in days between the initiation date of the study intervention and the sampling date of the first of the 3 consecutive negative sputum cultures from sputum samples collected at least 25 days apart.[44] Kaplan-Meier estimates will be generated for the time to sputum culture conversion up to Week 24 and Week 48. The difference between the treatment groups will be compared using the log-rank test stratified by region (Japan, non-Japan) for the time to sputum culture conversion up to Week 24. For

participants with no sputum culture conversion during the analysed period, time to culture conversion is censored on the last assessment day of the analysed period.

- Time to positivity in MGIT.

Time to positivity is calculated as the time required to positive signal in MGIT. A recent study showed a similar correlation between CFU and time to positivity with MAC.[37]

- SGRQ.

The changes from baseline in total score of SGRQ and domain scores will be summarized descriptively at Weeks 24, 48, and 60. For the total score of SGRQ at Week 24, the difference in the change from baseline between the treatment groups will be provided using an analysis of covariance (ANCOVA) model.

- Percentage of participants who undergo a change in their MAC-LD treatment regimen.

The percentage of participants who are changed from randomized treatment regimen to the individualized treatment regimen, including switched to the optional cohort is calculated.

9.4.5. Tertiary/Exploratory Endpoint

The changes from baseline in score of QOL-B NTM module and domain scores will be summarized descriptively at Weeks 24, 48, and 60.

For participants who achieved sputum culture conversion, the changes from baseline in the total score of SGRQ, the score of QOL-B NTM module, and chest CT findings will be evaluated.

The relationship between BDQ and CAM PK and MAC-LD treatment outcome and safety endpoints will be evaluated. PK/PD analyses will be performed on the collected data when all participants have reached Week 24 or discontinued earlier. The PK/PD analyses may be performed at earlier time points as necessary to support efficacy and safety findings. If there is any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships. The results of the PK/PD evaluations will be presented in a separate report. Other exploratory endpoints specified in Section 3, OBJECTIVES AND ENDPOINTS will be analyzed descriptively.

9.4.6. Safety Analyses

All safety analyses will be made on the Safety Population.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment period or that are a consequence of a preexisting condition that has worsened since baseline. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue study intervention due to an AE, or who experience a severe AE of at least Grade 3 or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus postintervention cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the laboratory abnormalities will be made. A listing of participants with any laboratory results outside the reference ranges will be provided. A listing of participants with any markedly abnormal laboratory results based on DMID scale (defined in SAP) will also be provided.

Electrocardiogram

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the predose ECG will be used as baseline).

Electrocardiogram data will be summarized by ECG parameter. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

The ECG variables that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and QTc interval using some of the following correction methods: QT corrected according to Bazett's formula (QTcB), QTcF.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval >450 milliseconds (ms), >480 ms, or >500 ms will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 ms or >60 ms.

All clinically relevant abnormalities in ECG waveform that are changes from the baseline readings will be reported (eg, changes in T-wave morphology or the occurrence of U-waves).

Vital Signs

Vital signs including temperature (axillary), heart rate, respiratory rate, oxygen saturation, and blood pressure (systolic and diastolic) (supine or sedentary after at least 5 minutes rest) values and changes from baseline will be summarized at each scheduled time point. The percentage of participants with values beyond clinically important limits based on DMID scale (defined in SAP) will be summarized.

Physical Examination, Visual Examination, and Audiology

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made. Visual acuity, color discrimination, visual field, fundoscopy, and audiometry data will be descriptively presented.

9.4.7. Other Analyses

An IDMC will be established as noted in Committees Structure in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

Pharmacokinetic Analyses

If feasible, population PK analysis of plasma BDQ (and M2 [optional]) concentration-time data of BDQ (and M2 [optional]) may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

A snapshot date for PK samples to be analyzed will be defined, if required. Samples collected before this date will be analyzed for BDQ (and M2 [optional]) and included in the population PK analysis. Samples collected after the snapshot date will be analyzed at a later date and may be included in a population PK re-analysis when they become available after database lock.

Data will be listed for all participants with available plasma concentrations per intervention group.

For each intervention group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for all individual derived PK parameters including exposure information of BDQ and M2 (if applicable) for Group A, and will be calculated for predose and 2 to 4 hours postdose plasma concentrations on Day 1, Weeks 2, 8, 12, 24, and 48 (for Week 48, BDQ and M2 only) of BDQ, and CAM and 4-OH CAM for both Groups A and B.

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All participants and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Mean and median plasma BDQ, M2, CAM and 4-OH CAM concentration time profiles will be plotted after the first dose of BDQ, and individual serum concentration time profiles may also be plotted.

9.5. Interim Analysis

The SAP will describe the planned interim (futility) analyses in greater detail.

A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) who reach the Week 24 time point or discontinued earlier or switched to individualized treatment regimen. This futility analysis is nonbinding and the IDMC will recommend the continuation or termination of the study based on the whole package of information, which also includes other efficacy and safety assessments.

In case lack of efficacy is concluded:

- enrollment in the study will be stopped.
- participants already enrolled will be switched to a treatment regimen at the discretion of the investigator.

In case no lack of efficacy is concluded:

- ongoing enrollment will continue.

Details of the futility analysis (including classification of lack of efficacy) and criterion will be included in the IDMC charter and SAP. The futility analysis will be prepared by a Statistical Support Group organized outside of the sponsor.

The primary analysis will be performed when all participants have reached Week 24 or have discontinued earlier than Week 24.

After the primary analysis, IAs are planned when:

- all participants have reached Week 48 or discontinued earlier or have switched to the optional cohort.
- all participants have reached Week 60 or discontinued earlier or have switched to the optional cohort.

The primary analysis and the analyses after Week 24 will be conducted by the sponsor. Additional interim analyses may be performed on request of health authorities or for preparing interactions with health authorities.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

*: The abbreviations for the medications, such as CAM are the one specified in the Japanese package insert of each medication and Japanese guidelines.

AE(s)	adverse event(s)
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMK*	amikacin
ALIS	amikacin liposome inhalation suspension
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adenosine 5'-triphosphate
ATS	the American Thoracic Society
AUC	area under the plasma concentration-time curve
AZM*	azithromycin
BDQ	bedaquiline (TMC207)
β-hCG	β-human chorionic gonadotropin
bid	bis in die (twice a day)
biw	bis in week (twice a week)
CAM*	clarithromycin
CFU	colony forming unit
C_{max}	maximum plasma concentration
CLSI	Clinical and Laboratory Standards Institute
COPD	chronic obstructive pulmonary disease
CPK	creatine phosphokinase
CPK-MB	CPK myocardial band
CT	computed tomography
C_{trough}	minimum plasma concentration between 0 hour and the dosing interval τ
CYP	cytochrome P450
DDI	drug-drug interaction
DMID	Division of Microbiology And Infectious Diseases
DST	drug susceptibility testing
EB	ethambutol
ECG	electrocardiogram
eCRF	electronic case report form
FC	fibro-cavitary
FEV1	forced expiratory volume in one second
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HRT	hormonal replacement therapy
IB	investigator's brochure
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonization

ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IDSA	the Infectious Diseases Society of America
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ITT	intent-to treat
KM*	kanamycin
LD	lung disease
LDH	lactic acid dehydrogenase
LPV	lopinavir
M	Mycobacterium
MAC	Mycobacterium avium complex
MALDI-TOF MS	matrix-assisted laser desorption ionization time of flight mass spectrometry
MDR	multi-drug resistant
MedDRA	Medical Dictionary for Regulatory Activities
MGIT	mycobacteria growth indicator tube
MIC	minimal inhibitory concentration
NB	nodular-bronchiectatic
NTM	nontuberculous mycobacterial
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PQC	product quality complaint
PROs	patient-reported outcomes
qd	quaque die (once daily)
QOL-B	quality of Life-Bronchiectasis
QTc	corrected QT
QTcB	QT corrected according to Bazett's formula
QTcF	QT corrected according to Fridericia's formula
QTL	quality tolerance limits
RBC	red blood cell
RBT*	rifabutin
RFP*	rifampicin
rtv	ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SGRQ	St. George's Respiratory Questionnaire
SM*	streptomycin
TB	tuberculosis
ULN	upper limit of normal
VNTR	variable number tandem repeat
WBC	white blood cell
WGS	whole genome sequencing
WOCBP	woman of childbearing potential

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in an eCRF as determined by the protocol. Data in this system may be considered source documentation.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to Section 1.3, Schedule of Activities (SoA) by the central and local laboratories:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology (Local Laboratory)</td><td>Platelet count
Red blood cell count (RBC)
Hemoglobin
Hematocrit</td><td><u>RBC Indexes:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the local laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the local laboratory. In addition, any other abnormal cells in a blood smear will also be reported.</td></tr>
<tr><td rowspan="2">Clinical Chemistry (Central Laboratory)</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Serum creatinine (screening and Day 1)
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin (direct, indirect)
Alkaline phosphatase (ALP)
Creatine phosphokinase (CPK)
CPK myocardial band (CPK-MB)
Lactic acid dehydrogenase (LDH)
Uric acid
Calcium
Calcium corrected for albumin*
Phosphate
Albumin
Total protein
Cholesterol
Triglycerides
Magnesium
Pancreatic amylase
C-reactive protein (CRP)</td></tr>
<tr><td colspan="3">All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as a serious adverse event (excluding studies of hepatic impairment or cirrhosis).

*: When albumin is lower than 4.0 g/dL, calcium corrected for albumin is calculated by the following formula:

• Calcium corrected for albumin (mg/dL) = calcium (mg/dL) + 0.8 × (4.0 – albumin [g/dL])</td></tr>
</table>

Laboratory Assessments	Parameters
Routine Urinalysis (Local Laboratory)	Dipstick (for qualitative urine, common kit provided by sponsor must be used): Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen
Other Screening Tests (Central Laboratory)	• Follicle-stimulating hormone (FSH) testing at screening for postmenopausal women only. • Pregnancy test for women of childbearing potential (WOCBP) only: β-hCG at only screening and Day 1, urine pregnancy test (urine pregnancy kit will be provided by the sponsor and should be assessed locally at timepoints described in SoA other than screening and Day 1). • HBsAg and HCV antibody tests at screening (these tests are not mandatory at screening when the participant has taken tests within 3 months prior to screening and the documentation could be provided). HIV test at screening (HIV test is not mandatory at screening when the participant has taken HIV test within 3 months prior to screening and the documentation could be provided).

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor; and signed and dated by the investigator. Protocol amendments must not be implemented without prior Institutional Ethics Committee (IEC)/Institutional Review Board (IRB) approval, or when the relevant competent authority has raised any grounds for nonacceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Protocol Supplementary Information, which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable

- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.3.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive for the treatment of his or her disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

In addition, when switching to an individualized treatment regimen, obtaining re-consent from participants is required.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

10.3.5. Long-term Retention of Samples for Additional Future Research

Not applicable.

10.3.6. Committees Structure

Independent Data Monitoring Committee

An IDMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study and to meet efficacy objectives. This committee will consist of at least one medical expert in the relevant therapeutic area, at least one medical expert in cardiology, and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review safety and efficacy data and results. After the review of the interim (futility) analysis results at Week 24, the IDMC will make recommendations regarding the continuation of the study.

Since the microbiological results are blinded up to Week 24, if the investigators consider the regimen change based on clinical worsening of the symptoms related to MAC-LD based on the result of chest CT scan and so on, the investigators can consult with IDMC.

This futility analysis is nonbinding and the IDMC will recommend the continuation or termination of the study based on the whole package of information, which also includes other efficacy and

safety assessments. Sponsor will decide the continuation or termination of the study based on the recommendation by IDMC.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding BDQ or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of BDQ, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will

be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed 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.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Quality tolerance limits (QTLs) will be defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

All participative measurements (eg, SGRQ and QOL-B NTM module) will be completed by the same individual who completed the initial baseline.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; study intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum
- Blood pressure and heart rate
- Height and weight
- Details of physical examination
- PROs

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first postinitiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions And Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or noninvestigational) product. An AE does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or noninvestigational) product. (Definition per ICH)

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, for time of last adverse event recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be

reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For BDQ, the expectedness of an AE will be determined by whether it is listed in the IB.

For rifamycin (RFP or RBT) and combination drugs (CAM and EB) with marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the Japanese package insert.

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the investigator. The following selection should be used to assess all AE. In case AMK is administered as individualized treatment for MAC-LD, the causal relationship to AMK should be assessed and determined by the investigator accordingly.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using Section 10.7, Appendix 7: A Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (November 2007). In case of the event is not listed in DMID table, the severity grade will be made accordingly.

Grade 1 (Mild): Transient or mild discomfort (<48 hours); no medical intervention/therapy required.

Grade 2 (Moderate): Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required.

Grade 3 (Severe): Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

Grade 4 (Life-threatening): Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study intervention
- Unexpected therapeutic or clinical benefit from use of a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions. If any change in seriousness or severity of a recorded AE is observed, the investigators must record it as new event in the eCRF.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)

- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the treatment period.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using an SAE reporting form, which must be completed and signed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Protocol Supplementary Information, which will be provided as a separate document.

10.5. Appendix 5: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the nonestrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of the study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*[a]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to medical cause) *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] –oral
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male condom with or without spermicide
• Diaphragm with spermicide
• A combination of male condom with either diaphragm with spermicide (double-barrier methods)
• Periodic abstinence (calendar, symptothermal, postovulation methods)
• Withdrawal (coitus-interruptus)
• Lactational amenorrhea method
[a] Typical use failure rates may differ from those when used consistently and correctly. [b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.

10.6. Appendix 6: Patient-reporting Questionnaires

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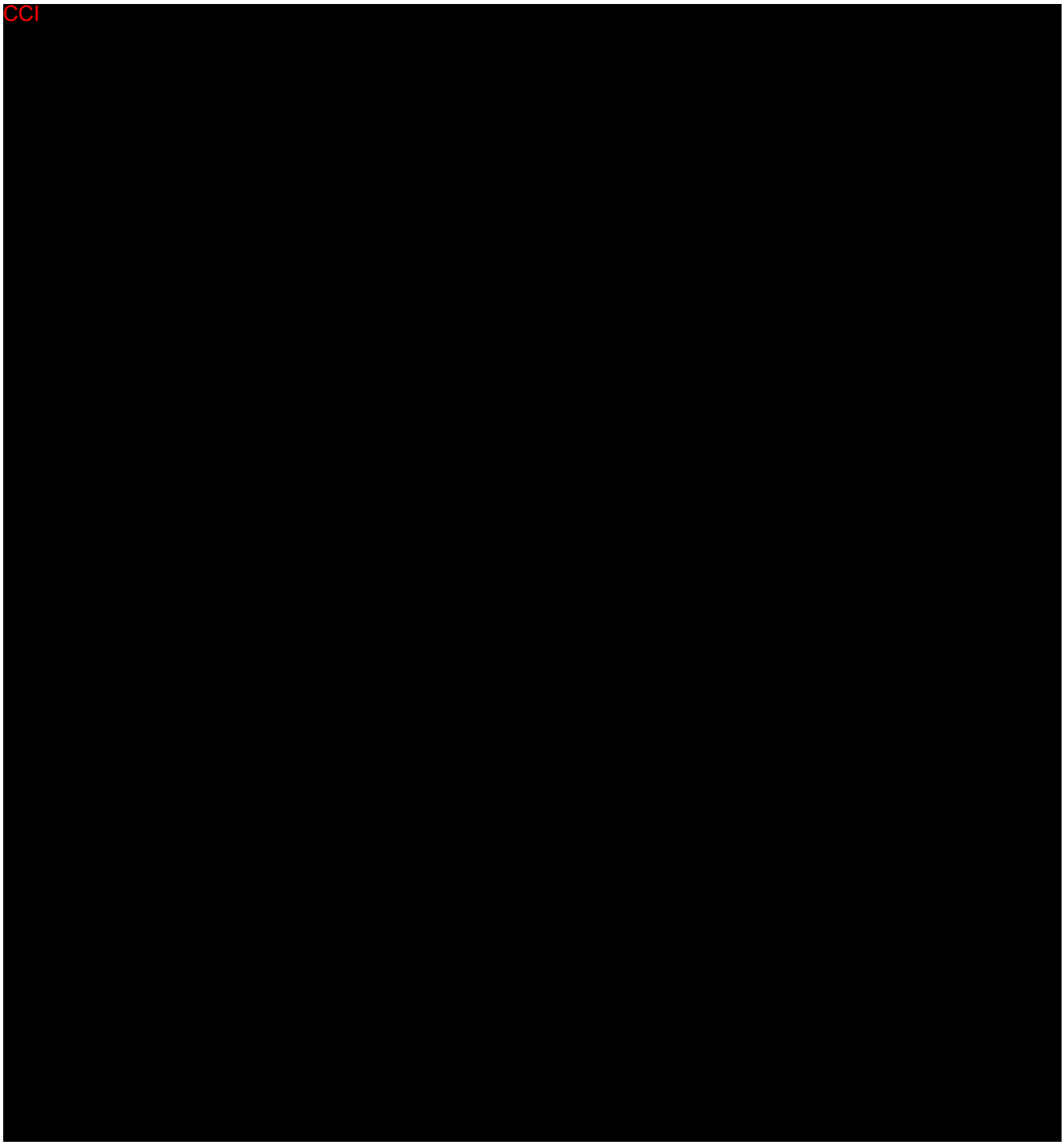

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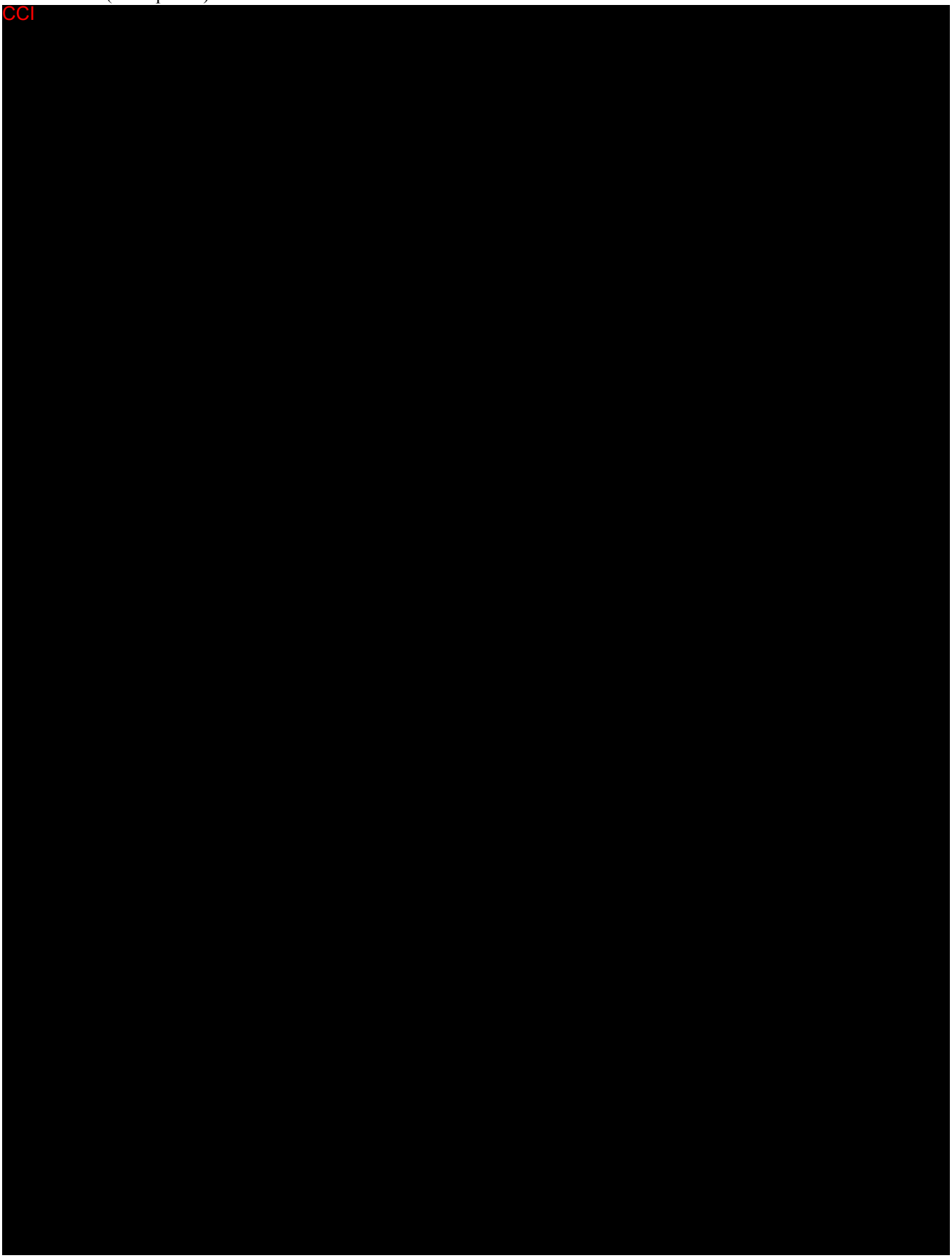

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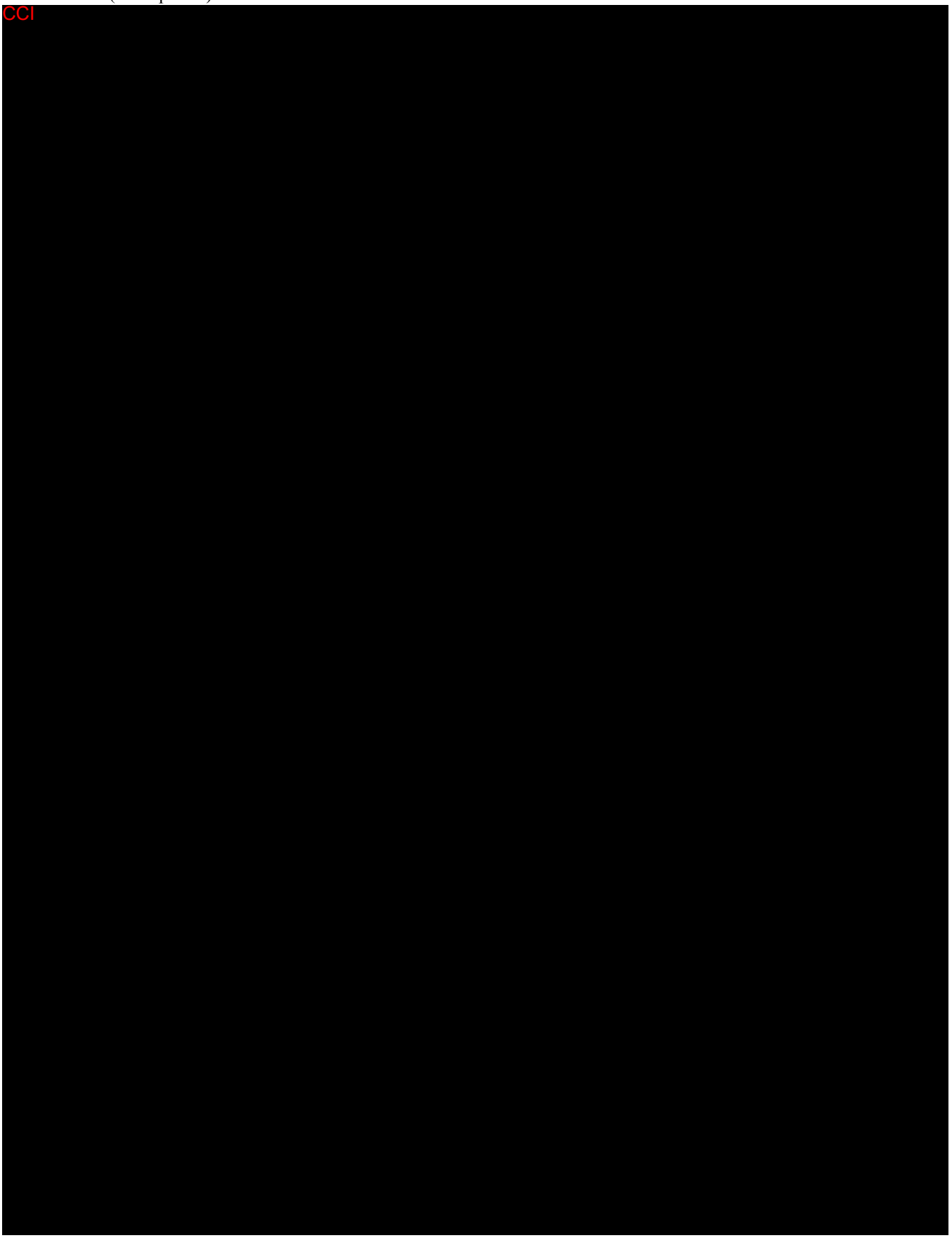

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QOL-B Questionnaire

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10.7. Appendix 7: A Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (November 2007)

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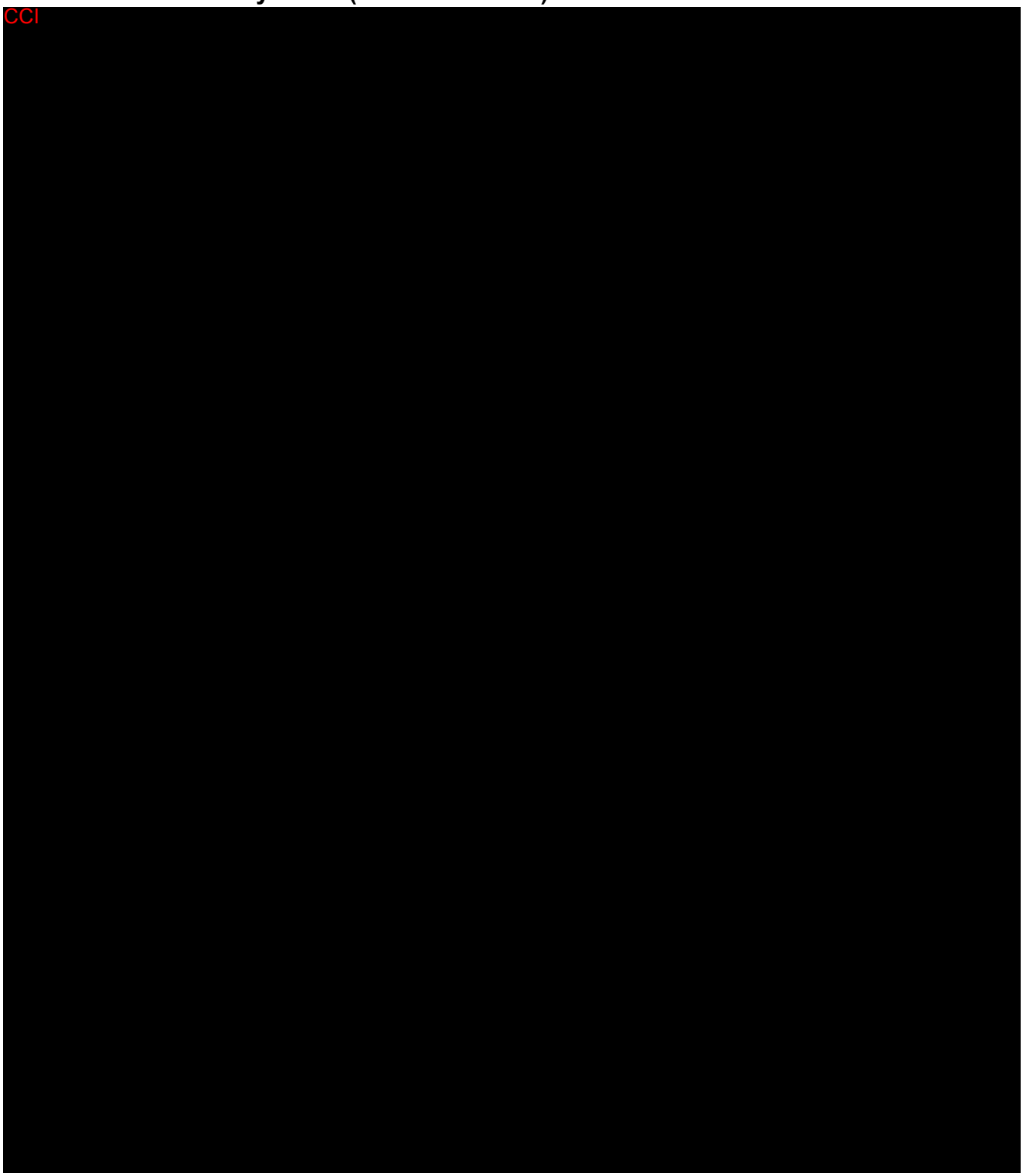

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10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 7 (30-Jun-2022)

Overall Rationale for the Amendment: To change text regarding extension of screening period and timing of visual examination and fundoscopy at Day 1.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) 1.3.1. Schedule of Activities (SoA) in the Optional Cohort	Updated to allow an extension of the screening period up to 14 weeks.	To specify the upper limit of allowable extended screening period.
1.3. Schedule of Activities (SoA) 1.3.1. Schedule of Activities (SoA) in the Optional Cohort 8.2.7. Other Safety Evaluations	Changed timing of visual examinations and fundoscopy at Day 1 within 4 weeks prior to Day 1 instead of 1 week prior to Day 1.	To revise the allowable time window for visual examination and fundoscopy.
Throughout the protocol	Minor changes were made.	Minor errors were noted.

Amendment 6 (20-Apr-2022)

Overall Rationale for the Amendment: To add actions to be taken when it takes time to obtain results of microbiology assessment of screening and Week 24, to indicate that site personnel involved in monitoring of the study sites and personnel involved in management operations of the central laboratory etc. are excluded from maintenance of blinding for microbiology assessment in order to confirm that switch to individualized treatment regimen and the optional cohort is carried out appropriately based on the protocol, to correct Japanese translation regarding exclusion criteria on ECG and text regarding ECG specifications, to clarify data used for OPD1, to clarify interval for early discontinuation visit, to add text regarding concomitant therapies to be recorded at screening, and to correct text on the QOL-B NTM module.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA) 1.3.1. Schedule of Activities (SoA) in the Optional Cohort	Changed applicable X notation of OPD1 to X on Schedule of Activities in the Optional Cohort. Note: (X)=If available, X=In principle, no additional test is required as OPD1 as data of Week 24 will be used as the baseline. Footnote a. Screening evaluations must be performed within 63 days (9 weeks) prior to baseline (Day 1). These 9 weeks include 14 days of rifamycin W/O for participants to whom it is applicable. If screening period exceeds 9 weeks for reasons such as time required to obtain the result of microbiology assessment of screening, the screening period may be extended.	Text was added for actions to be taken when it takes time to obtain results of microbiology assessment of screening and Week 24. Also, text was added to clarify the data used for OPD1 and interval for early discontinuation visit.

Section Number and Name	Description of Change	Brief Rationale
	Footnote f. Early discontinuation visit is to be scheduled within 7 days of the investigator's discretion to discontinue treatment with study intervention ~~after withdrawal from the study~~ (including the day of discontinuation ~~withdrawal~~, other than withdrawal of consent). Visit for switch to individualized treatment regimen is to be scheduled within 7 days after discontinuing the assigned treatment regimen (including the day of switch) and before the start of individualized treatment regimen. Footnote y. Including visual acuity, color discrimination, visual field. Audiology and visual examinations within 1 week prior to Day 1 and within 4 days prior or after each visit other than Day 1 will be acceptable. If screening period is extended for reasons such as time required to obtain the results of microbiology assessment of screening, audiology and visual examinations at Day 1 should be reassessed when the extended Day 1 is more than 28 days after the scheduled test date. Footnote z. After Week 24 assessment, all participants in the Group B who are nonconversion and well-tolerated, will be considered to receive the BDQ-containing regimen at the discretion of the investigators. When the investigator changes to BDQ-containing regimen, 2-week washout of treated rifamycin must be given before initiation of BDQ-containing regimen. The investigators can postpone the decision to transfer to the optional cohort for up to Week 32 in order to confirm a sputum culture positive at Week 24, if necessary. If decision to transfer to the optional cohort exceeds Week 32 for reasons such as time required to obtain the result of microbiology assessment of Week 24, the period may be extended. If necessary, consider study date of OPD1 by adding the number of days required to switch to the optional cohort to study date of Week 24. Footnote aa. OPD1 is Day 1 for participants who are transferred to optional cohort. Assessments planned on OPD1 must be performed prior to first dose of BDQ. The investigators can postpone the decision to switch to the optional cohort for up to Week 32 in order to confirm sputum culture	

Section Number and Name	Description of Change	Brief Rationale
	positive at Week 24. If decision to transfer to the optional cohort exceeds Week 32 for reasons such as time required to obtain the result of microbiology assessment of Week 24, the period may be extended. Footnote cc. In principle, testing data at Week 24 will be used as that of OPD1, so it is not necessary to perform another test as OPD1. If the transition period is extended due to confirmation of the result of sputum culture, the result of microbiology assessment of Week 24 will be used as that of OPD1, the latest data (Week 28, etc.) will be used when specified testing other than the microbiology assessment have been performed after Week 24 in Group B. Footnote dd. Fundoscopy within 1 week prior to Day 1 and within 4 days prior or after each visit other than Day 1 will be acceptable. If screening period is extended for reasons such as time required to obtain the results of microbiology assessment at screening, visual examinations at Day 1 should be reassessed when the extended Day 1 is more than 28 days after the scheduled test date.	
5.2. Exclusion Criteria	Japanese translation for Exclusion Criteria 8 has been corrected.	Corrected Japanese translation.
6.3. Measures to Minimize Bias: Randomization and Blinding	As this is an open-label study, blinding procedures are not applicable. However, the microbiological results from Week 2 to Week 24 will be blinded to the investigators, site staffs and, participants~~, and sponsor~~ until the completion of the other assessments at Week 24 by the investigators. In case the investigators need to know the microbiological result to decide if participants should be switched to an individualized treatment regimen or continue the study treatment regimen, due to clinical worsening, the investigators can access the microbiological result from the central laboratory (for the detailed procedure, refer to the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test). ~~In this case, s~~Sponsor except for specific personnel listed below must keep the blinding of all the microbiological assessment after Week 2 until ~~completion of~~ unblinding takes place for the primary analysis. In addition, sponsor personnel involved in monitoring of the study sites and personnel	Text was corrected to clearly describe the duration of blinding of microbiology assessment after Week 2 for the sponsor. In addition, since it is necessary to confirm that decision to switch individualized treatment regimen and the optional cohort is appropriately carried out based on the protocol, sponsor personnel involved in monitoring of the study sites and personnel involved in management operation of the central laboratory etc. are excluded from the scope of blinding for microbiology assessment.

Section Number and Name	Description of Change	Brief Rationale
	involved in management operation of the central laboratory etc. are excluded from maintenance of blinding for microbiology assessments, taking into account that sponsor needs to confirm that investigators and etc. comply with the protocol and the decision to switch to individualized treatment regimen and the optional cohort is made based on the appropriate process. Details will be provided in the statistical analysis plan (SAP).	
6.8. Concomitant Therapy	Concomitant therapies administered after signing informed consent (~~Prestudy therapies administered up to~~ 63 days before first dose of study intervention) and prestudy therapies for pulmonary MAC disease administered prior to signing informed consent must be recorded at screening.	Text was added to clarify the concomitant therapy to be recorded at screening.
7.1. Discontinuation of Study Intervention	The early discontinuation visit assessment will be performed within 7 days of the investigator's discretion to discontinue treatment with study intervention ~~after withdrawal from the study~~, unless the participant withdraws consent.	Text was modified to clarify interval for early discontinuation visit.
7.2. Participant Discontinuation/Withdrawal From the Study	Participants will be encouraged to complete the early discontinuation visit assessments, which is to be scheduled within 7 days of investigator's discretion to discontinue treatment with study intervention ~~after withdrawal from the study~~.	
8.1.2. Clinical Assessments in MAC-LD	The NTM module is developed specifically for NTM symptoms and consists mainly of NTM symptoms (7 items), body image (4 items), digestive symptoms (~~7~~6 items), and eating problems (3 items).	Corrected text.
8.2.3. Electrocardiograms	All tracings will be transmitted for blinded central analysis. Participants found to have a ~~QT or~~ QTcF ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms on ECG at any point during the treatment period will be further investigated.	Text on QT was removed to clarify that any participants with an QTcF ≥ 500 ms or an increase from baseline of > 60 ms while on study investigation should be further investigated, and is considered a notable event and should be reported immediately to the sponsor.
	Any ~~QT or~~ QTcF prolongation to ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms while on study intervention is considered a notable event and should be reported immediately to the sponsor.	

Amendment 5 (09-Dec-2021)

Overall Rationale for the Amendment: To reconsider transition period to the optional cohort (time to confirm the result of sputum culture), to clarify the reason for setting up the individualized treatment regimen, to clarify drug susceptibility test and genotyping, as well as to correct minor errors.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis	In addition, this study provides an option to receive BDQ -containing regimen for nonconverters in Group B based on the result of microbiological test up to ~~at~~ Week 24 as the optional cohort.	Text was corrected for clarification.
	A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) who reach the Week-24 time point or discontinued earlier or switched to individualized treatment regimen.	Text was added for clarification.
1.2. Schema	The following corrections were made to Figure 1: Schematic Overview of the Study. Footnote a. Prior to Week 24, participants who are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failures and can switch to an individualized treatment regimen (see Section 6.8.1), at the discretion of the investigator in consultation with IDMC. Footnote b. After Week 24 assessment, all participants who are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen (see Section 6.8.1) at the discretion of the investigator. Footnote e. All participants who are judged to have difficulty continuing their BDQ-containing regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen (see Section 6.8.1) at the discretion of the investigators.	Reference was added for clarification.
1.3. Schedule of Activities (SoA) 1.3.1. Schedule of Activities (SoA) in the Optional Cohort	Drug susceptibility testing after Week 2: The testing will be performed on positive isolates at Week 24 as well as ~~and at~~ the last ~~visit with~~ culture positive isolates ~~culture sample after Week 24, and also~~ in case of participants with nonconversion and recurrence (relapse/reinfection). ~~or~~ In addition, it will be performed on positive	Text was added and corrected for clarification.

Section Number and Name	Description of Change	Brief Rationale
	isolates at early discontinuation (if available). Drug susceptibility testing after OPW 2 in the optional cohort: The testing will be performed on ~~At~~ the last ~~visit with~~ culture positive isolates ~~culture sample and also~~ in case of participants with nonconversion and recurrence (relapse/reinfection). ~~or~~ In addition, it will be performed on positive isolates at early discontinuation (if available) VNTR or WGS after Week 2 and after OPW2 in the optional cohort: In case of recurrence (relapse/reinfection) ~~culture reversion~~, and if acquired resistance ~~or~~ (at least 4-fold increased MIC) to BDQ ~~any used drug~~, VNTR (and/or WGS~~)~~ will be performed on both baseline and postbaseline isolates. Fundoscopy in the optional cohort: footnote dd was added. Footnote f. Early discontinuation visit is to be scheduled within 7 days after withdrawal from the study (including the day of withdrawal, other than withdrawal of consent). ~~and or~~ Visit for switch to individualized treatment regimen is to be scheduled within 7 days after discontinuing the assigned treatment regimen (including the day of switch) and before the start of ~~switching to~~ individualized treatment regimen. Footnote p. Drug susceptibility testing (DST) will be done on culture positive isolates at screening, baseline, and at Week 24. ~~and at~~ The testing will be done on the last ~~visit with~~ culture positive isolates ~~culture sample and also~~ in case of participants with nonconversion and recurrence (relapse/reinfection). ~~or~~ In addition, the testing will be done on positive isolates at early discontinuation (if available). In the optional cohort, DST will be done on ~~at~~ the last ~~visit with~~ culture positive isolates ~~culture sample and also~~ in case of participants with nonconversion and recurrence (relapse/reinfection), ~~or~~ as well as positive isolates at early discontinuation (if available). Footnote q. In case of recurrence (relapse/reinfection ~~a positive culture~~	

Section Number and Name	Description of Change	Brief Rationale
	~~occurring after having been negative~~) or in case of acquired resistance ~~or~~ (at least 4-fold increased MIC) to BDQ is indicated by DST result ~~any used drug~~, baseline and postbaseline isolates will be identified ~~genotyped~~ using WGS or VNTR if necessary. ~~If WGS is available, it will be used to identify genetic markers of resistance and to compare baseline and postbaseline isolates.~~ If more than 1 postbaseline positive culture (isolate) showing resistant is available ~~and is resistant~~, ~~only~~ the last culture positive ~~culture~~ sample ~~(isolate)~~ will be tested for VNTR and/or WGS in addition to the baseline culture positive sample. ~~culture (isolate). If more than 1 positive culture (isolate) is available after having been negative, only the last positive culture (isolate) will be tested for VNTR or WGS in addition to the baseline positive culture (isolate).~~	
	Footnote z. After Week 24 assessment, all participants in the Group B who are nonconversion and well-tolerated, will be considered to receive the BDQ-containing regimen at the discretion of the investigators. When the investigator changes to BDQ-containing regimen, 2-week washout of treated rifamycin must be given before initiation of BDQ-containing regimen. The investigators can postpone the decision to transfer to the optional cohort for up to Week 32 ~~30~~ in order to confirm a sputum culture positive at Week 24, if necessary. If necessary, consider study date of OPD1 by adding the number of days required to switch to the optional cohort to study date of Week 24. Footnote aa. OPD1 is Day 1 for participants who are transferred to optional cohort. Assessments planned on OPD1 must be performed prior to first dose of BDQ. The investigators can postpone the decision to switch to the optional cohort for up to Week 32 ~~30~~ in order to confirm sputum culture positive at Week 24. Footnote cc. In principle, testing data at Week 24 will be used as that of OPD1. ~~Even~~ If ~~this duration~~ the transition period is extended ~~up to 6 weeks~~ due to confirmation of the result of sputum culture, the latest data will be used when specified testing	Text was corrected as the transition period (time to confirm the result of sputum culture) has been reconsidered and for clarification.

Section Number and Name	Description of Change	Brief Rationale
	have been performed after ~~on~~ Week 24 ~~or later~~ in Group B ~~will be used for these items~~.	
4.1. Overall Design	Participants requiring a treatment regimen change will be considered treatment failures for subsequent endpoints and will be followed up for safety only, but all assessments should be performed according to the protocol. In addition to the option to switch to the optional cohort in Group B and withdrawal from the study, individualized treatment regimen was set up to as a regimen that may be used when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by the results such as chest computed tomography [CT] scan) or the occurrence of AE. ~~All decisions on treatment regimen change should be made when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by the results such as chest computed tomography (CT) scan) or the occurrence of AE, except for switching to the optional cohort.~~ Since the microbiological results are blinded, if the investigators consider the regimen change based on the clinical worsening of symptoms related to MAC-LD supported by the result of chest CT scan and so on, the investigators can consult with IDMC before the change. Specific switching criteria, treatment options, visits and assessments before and after switching, and follow-up will be detailed in Section 6.8.1, Individualized Treatment Regimen.	The text was added and corrected to clarify the reason for setting up the individualized treatment regimen.
	In this optional cohort, during the 48-week treatment period (from Day 1 in optional cohort [OPD1] to Week 48 in optional cohort [OPW48]) of the study, participants may be changed to individualized treatment regimen ~~can have a change in their treatment regimen, in which MAC-LD treatment may continue in accordance with SOC of Japanese guidelines or medical practice at each study site~~.	Text was revised according to the clarification of individualized treatment regimen.
	The investigators can postpone the decision to transfer to the optional cohort for up to Week ~~30~~ 32 in order to confirm a sputum culture positive at Week 24, if necessary.	Text was corrected as the transition period (time to confirm the result of sputum culture) has been reconsidered

Section Number and Name	Description of Change	Brief Rationale
	Regardless of delay in the transition phase ~~up to 6 weeks~~, the treatment duration of the optional cohort will be for 48 weeks.	
4.2. Scientific Rationale for Study Design	In addition, participants who have not achieved culture conversion in Group A (BDQ-containing regimen) will continue their assigned regimen until Week 48, unless they have difficulty continuing due to failure to respond (see Section 6.8.1, based on nonconversion and clinical worsening) or the occurrence of AE related to the regimen. The participants in Group B (rifamycin-containing regimen) who do not achieve culture conversion up to Week 24 and continue the study, will have the option, at discretion of investigator, to (1) continue rifamycin-containing regimen, (2) switch to individualized treatment regimen (see Section 6.8.1, in principle, add on injectable SM, injectable or inhalation suspension of AMK), (3) switch to BDQ-containing regimen after 2-week washout of rifamycin. The latter option is called the "optional cohort" (see Section 6.8.2).	Reference was added for clarification.
4.4. End of Study Definition	A participant will be considered to have completed the study if he or she has completed assessments at Week 60 of the open label phase or at OPW48 of the optional cohort.~~, but~~ Following completion of the study, the participant may continue the SOC per Japanese guidelines or medical practice at each study site for at least 1 year after culture conversion, at the discretion of the investigator.	Text was revised to clarify that the action is to be taken after completion of the study.
6.3. Measures to Minimize Bias: Randomization and Blinding	As this is an open-label study, blinding procedures are not applicable. However, the microbiological results from Week 2 to Week 24 will be blinded to the investigator, participants, and sponsor until the completion of the other assessments at Week 24. In case the investigators need to know the microbiological result to decide if participants should be switched to an individualized treatment regimen or continue the study treatment regimen, due to clinical worsening, the investigators can access the microbiological result ~~directly~~ from the central laboratory (for the detailed procedure, refer to the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test).	Text was added and deleted for clarification.
6.8.1. Individualized Treatment Regimen	In addition to the option to switch to the optional cohort in Group B and withdrawal	Text was added and corrected to clarify the reason for setting up

Section Number and Name	Description of Change	Brief Rationale
	from the study, individualized treatment regimen was set up to as a regimen that may be used when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by the results such as chest computed tomography [CT] scan) or the occurrence of AE.	the individualized treatment regimen.
	Group A (Assigned treatment regimen: BDQ + CAM + EB) • BDQ + CAM + EB + aminoglycosides (add one of injectable SM, injectable or inhalation suspension) • BDQ + CAM + aminoglycosides (same as above) • BDQ + CAM (when difficult to continue treatment with EB and no clinical worsening) Group B (Assigned treatment regimen: Rifamycin + CAM + EB) • Rifamycin + CAM + EB + aminoglycoside (same as above) • Rifamycin + CAM + aminoglycoside (same as above) • Rifamycin + CAM (when difficult to continue treatment with EB and no clinical worsening) Note: From the viewpoint of preventing the development of CAM resistance, a regimen with EB discontinuation should be carefully considered.	Text was added for clarification. Also, a note regarding the regimen with EB discontinuation was added.
	Prior to switching to an individualized treatment regimen, visit and assessments for switch to individualized treatment regimen must be done as shown in Section 1.3, Schedule of Activities (SoA). After switching, a participants will continue their usual schedule for assigned treatment regimen. Note that participants in Group A who have switched to individualized treatment regimen can continue up to Week 48, participants in Group B can continue up to Week 60.	Text was added to clarify before and after switching to an individualized treatment regimen.
6.8.2. Optional cohort	The decision to switch to optional cohort can be made by Week 32~~30~~ (refer to Sections 1.2 and 4.1).	Text was corrected as the transition period (time to confirm the result of sputum culture) has been reconsidered

Section Number and Name	Description of Change	Brief Rationale
	• Participants are nonconverter based on the result of microbiological test (ie, positive) up to Week 24.	Text was added for clarification
	Switching to an individualized treatment regimen is permitted if the criteria described in Section 6.8.1 are met, even after switching to the optional cohort.	Text was added for clarification
8.1.1. Microbiology Assessment (MAC-LD Treatment Outcome)	Genotyping or Fingerprinting of Isolates This is to assess if baseline and postbaseline isolates are the same or different in case of resistance occurring at postbaseline and in case cultures become positive after having been negative, genotyping using variable number tandem repeat (VNTR) or whole genome sequencing (WGS) ~~(if available)~~ will be performed.	Text was deleted for clarification.
8.2.3. Electrocardiograms	In principle, 2 original ECG recordings will be provided. One original recording will be stored at the study site and another will be sent to a central cardiologist designated by the sponsor for review. Submission of ECG to a central cardiologist will be done by transmission or send a hardcopy ECG if transmission is not possible for any reasons (refer ECG manual for details).	Text was added for clarification.
9.5. Interim Analysis	A futility analysis will be implemented to evaluate early the benefit/risk balance by assessing safety and efficacy in the first 60 participants (about 30 participants from both groups) who reach the Week 24 time point or discontinued earlier or switched to individualized treatment regimen.	Text was added for clarification
10.2. Appendix 2: Clinical Laboratory Assessments	Hematology (Local laboratory) Note: A WBC evaluation may include any abnormal cells, which will then be reported by the local laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the local laboratory. In addition, any other abnormal cells in a blood smear will also be reported.	Text was added for clarification.

Amendment 4 (30-Sep-2021)

Overall Rationale for the Amendment: To revise the Inclusion Criteria 5 and 6, to partially revise a requirement for sputum collection, to add descriptions regarding individualized treatment regimen, as well as to correct unclear and inconsistent descriptions.

Section Number and Name	Description of Change	Brief Rationale
1.2. Schema	The following corrections were made to Figure 1: Schematic Overview of the Study. Footnote b was added to treatment Group B. Footnote a. Prior to Week 24, participants who are judged to have difficulty continuing their designated treatment regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failure and can switch to an individualized treatment regimen ~~based on clinical worsening supported by microbiology data, symptoms related to MAC-LD and/or the results of chest CT scan,~~ at the discretion of the investigator in consultation with IDMC ~~if needed~~. Footnote b. After Week 24 assessment, all participants who are judged to have difficulty continuing ~~failing~~ their designated treatment regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen at the discretion of the investigator. Footnote c. After completion of 48-week treatment, converters in the Group A will be followed for 12 weeks as drug-free period. Participants who failed to achieve sputum culture conversion (nonconverters) by Week 48 and continue chemotherapy will be discontinued from the study and ~~will be~~ switched to another ~~an individualized~~ treatment regimen. Footnote e. All participants who are judged to have difficulty continuing ~~failing~~ their BDQ containing regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE will be considered treatment failures and will be given the option to switch to an individualized treatment regimen at the discretion of the investigator.	A footnote associated with switching to individualized treatment regimen was added to treatment Group B. Also, footnote text was revised to ensure consistency with Section 6.8.1.
1.3. Schedule of Activities (SoA) 1.3.1. Schedule of Activities (SoA) in the Optional Cohort	Footnote m. ~~At least 2~~ Two sputum samples should be collected at each visit time point except for Week 2, 6, and 10. One should be collected in the early morning (at home or at the study site) and the other sample(s) at the study site. Samples collected at the study site can be spontaneous or induced. In case 2	To reduce the burden on participants and study sites, a requirement for handling sputum collection at W2, 6, and 10 was eased. Also, text was added to clarify that handling of

Section Number and Name	Description of Change	Brief Rationale
	sputum sample collection is not feasible at Week 2, 6, and 10, either no sample or 1 sample collection is allowed. Sputum samples will be shipped to the central microbiology laboratory where all cultures will be performed on solid and on liquid media. The same applies to sputum collections at OPW 2, 6 and 10 in the optional cohort.	sputum collections is the same in the optional cohort.
	Footnote t. Single sparse blood samples will be collected for measurement of plasma concentrations of BDQ (and M2 [optional]). These samples can be taken at any time after intake of BDQ on the day, but the date and time of the second to last and the last administration of BDQ and CAM, respectively, and the date and time of blood draw must be recorded.	Text was added for clarification.
2.3.1. Risks for Study Participation	The following text was added to Risks Due to Other Causes. Potential Risks of Clinical Significance: For an individualized treatment regimen in treatment Group A, aminoglycosides may be added to the BDQ-containing regimen. Summary of Data/Rationale for Risk: The antimicrobial activity of BDQ in combination with aminoglycosides against MAC has been confirmed from the results of a nonclinical study,[30] but its clinical efficacy has not been evaluated and its efficacy has not been demonstrated. In multidrug therapy approved for the treatment of pulmonary MDR-TB in Japan and overseas, aminoglycosides have been recommended as one of the agents to be used concomitantly with multidrug therapy including BDQ[48,49] and no safety issues have been observed. However, the clinical safety in patients with pulmonary MAC disease has not been evaluated and its safety has not been demonstrated. Mitigation Strategy: During the study, study svisits are scheduled at least once every 4 weeks to perform specified safety assessments.	Text was added to clarify the risks for study participation when aminoglycosides are added to BDQ-containing regimen in an individualized treatment regimen.
4.1. Overall Design	All decisions on treatment regimen change should be made when participants are judged to have difficulty continuing their designated treatment regimen due to failure to respond [based on nonconversion ~~clinical worsening~~ supported by microbiological results, and clinical worsening of symptoms related to MAC-LD supported by~~, and/or~~ the results	Text was revised to ensure consistency within the document.

Section Number and Name	Description of Change	Brief Rationale
	such as ~~of~~ chest computed tomography (CT) scan] or the occurrence of AE, except for switching to the optional cohort. Since the microbiological results are blinded, if the investigators consider the regimen change based on the clinical worsening of symptoms related to MAC-LD supported by ~~and/or~~ the result of chest CT scan and so on, the investigators can consult with IDMC before the change.	
	Nonconverters at Week 48 in Group A will be discontinued from the study and switched to another treatment regimen if they continue chemotherapy because the duration of BDQ treatment is 48 weeks ~~shifted to the individualized regimen and the study observations are continued up to Week 60~~.	Revised to be consistent with supply of interventional study in Group A after Week 48.
4.2. Scientific Rationale for Study Design	The present study will enroll patients with treatment-refractory MAC-LD defined as participants who are sputum culture positive for MAC despite at least 6 months and no more than 36 ~~24~~ months of MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within the last 12 months.	Text was revised according to the revision of Inclusion Criteria 5 and 6.
	In addition, participants who have not achieved culture conversion in Group A (BDQ-containing regimen) will continue their assigned regimen until Week 48, unless they have difficulty continuing due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of AE related to the regimen. If participants were judged to have difficulty continuing due to failure to respond to the regimen or the occurrence of the regimen related AE, at the discretion of investigators, there will be options to discontinue from the study or switch to an individualized treatment regimen (in principle, add on injectable SM, injectable or inhalation suspension of AMK). T~~t~~he participants in Group B (rifamycin-containing regimen) who do not achieve culture conversion up to Week 24 and continue the study, will have the option, at discretion of investigator, to (1) continue rifamycin-containing regimen, (2) switch to individualized treatment regimen (in principle, add on ~~which may include~~ injectable SM, ~~or~~ injectable or inhalation suspension of AMK ~~or SM~~), (3) switch to BDQ-containing regimen after 2-week washout of rifamycin.	Text was added to clarify regarding switching to an individualized treatment regimen in Group A. Also, text was revised for clarification.

Section Number and Name	Description of Change	Brief Rationale
4.2.1. Study-specific Ethical Design Considerations	Addition of aminoglycosides (injectable SM, injectable or inhalation suspension of AMK) is permitted as an individualized treatment regimen in either treatment group if participants are judged to have difficulty continuing the designated treatment regimen due to failure to respond (based on nonconversion and clinical worsening) or the occurrence of the regimen related AE, at the discretion of investigators. Addition of aminoglycosides in Group B is recommended by the Japanese guideline,[41] and is expected to be clinically efficacious in participants with clinical worsening. On the other hand, addition of aminoglycosides to the regimen in Group A has been confirmed to have antimicrobial activity based on nonclinical studies, but its clinical efficacy has not been confirmed at present. Regarding safety, in the Japanese and oversea guidelines on approved drug therapies for the treatment of pulmonary MDR-TB,[48,49] AMK and SM are recommended as agents to be used in combination with multiple drug therapies including BDQ, and there have been no reports of any problems concerning drug interactions and new adverse reactions associated with the combination use. However, experience in the treatment of pulmonary MAC disease is limited, and safety monitoring participants will be performed at least every 4 weeks until study completion or early discontinuation according to Section 1.3, Schedule of Activities (SoA). Since treatment options for participants who failed to respond are limited, addition of aminoglycosides, which is expected to convert and improve clinical symptoms, was selected as an individualized treatment regimen.	Explanation was added to clarify ethical consideration of individualized treatment regimen.
5.1. Inclusion Criteria	Inclusion Criteria 5. Criterion modified per Amendment 4. 5.1 Has at least 2 positive sputum cultures of MAC (sputum cultures to be taken at least 4 weeks apart): • one obtained within 12 months prior to screening, which was documented while being treated for MAC-LD for a total of at least 6 months and no longer than 36 ~~24~~ months. one at screening (by central microbiology laboratory).	The inclusion criterion was revised considering the feasibility of subject enrollment within the range considered to be a similar target population.
	Inclusion Criteria 6: Criterion modified per Amendment 4.	The inclusion criterion was revised considering the feasibility of subject enrollment

Section Number and Name	Description of Change	Brief Rationale
	6.1 Received at least 6 months and no more than 36 ~~24~~ months of consecutive MAC-LD treatment (at least 2 antibiotics for MAC, including a macrolide), that is either ongoing or has stopped within 12 months prior to screening.	within the range considered to be a similar target population.
6.1. Study Intervention Administered	The following corrections were made to Figure 1: Schematic Overview of the Study. Non-Investigational ~~Interventional~~ Medicinal Product	An error was corrected.
6.8. Concomitant Therapy	If contraindicated medication(s) listed in each package insert of comparator/combination drugs (RFP, RBT, CAM, or EB) are received during screening, the contraindicated medication(s) are prohibited from 7 days prior to Day 1 up to the last dose of the medications including study intervention. **NOTE:** The examples of potent CYP3A4 inhibitors and inducers do not form a complete list. The investigator should consult the prescribing information for study interventions and combination drugs (CAM and EB) ~~BDQ~~ and, if necessary, contact the appropriate sponsor representative. The following medications are prohibited because of their potential for QTc prolongation. These medications are not allowed from 7 days prior to Day 1 up to the last dose of study interventions and combination drugs (CAM and EB) (including individualized treatment regimens): The following medications are prohibited because of their potential for muscle damage (myopathy) from 7 days prior to Day 1 up to the last dose of study interventions and combination drugs (CAM and EB) (including individualized treatment regimens) (see note):	Text was revised in line with the modified definition of study drug in Amendment 3.
	Injectable SM, ~~or~~ injectable or inhalation suspension of ~~SM or~~ AMK is acceptable as part of an individualized treatment regimen. The use of injectable SM, injectable or inhalation suspension of ~~SM or~~ AMK for any purposes other than as part of an individualized treatment regimen is prohibited.	Text was revised for clarification.
	• moxifloxacin (prohibited from the initiation date ~~during administration~~ of	Text was revised for clarification.

Section Number and Name	Description of Change	Brief Rationale
	BDQ treatment ~~and~~ up to 1 month after the last dose of BDQ)	
6.8.1. Individualized Treatment Regimen	During the study, if deemed necessary by the investigator to ~~Participants can~~ switch to individualized treatment regimen (in principle, add on ~~which may include~~ injectable SM, injectable or inhalation suspension of AMK ~~or SM~~. Regimens that may be selected for each treatment group are listed below) and continue treatment, it can be done by obtaining re-consent from the participant ~~at the discretion of investigators~~ (refer to Sections 1.2 and 4.1). Participants should meet one of the following criteria to switch to individualized treatment regimen. (Note: Refer to Section 6.3 for blinding method of the microbiological assessment result). ~~Discontinuation of administration of BDQ in Group A or optional cohort is not considered as individualized treatment regimen in this study.~~ • Continuation of assigned treatment regimen is difficult because ~~P~~participants are nonconverters based on the result of microbiological test (ie, positive) and have clinical worsening of symptom associated with MAC-LD based on the ~~including~~ findings in chest CT scan and so on, at the discretion of investigators. • Continuation of assigned treatment regimen is difficult due to AE related to drug in assigned regimen, at the discretion of investigators. Individualized treatment regimens permitted in this study are described in below. Investigators should select the appropriate regimens for participants in each treatment group or if no regimen is considered appropriate the participants should be discontinued from the study. Group A (BDQ + CAM + EB) • BDQ + CAM + EB + aminoglycosides (add one of injectable SM, injectable or inhalation suspension) • BDQ + CAM + aminoglycosides (same as above) • BDQ + CAM (when difficult to continue treatment with EB and no clinical worsening)	Text was added and revised to clarify individualized treatment regimens permitted in the study.

Section Number and Name	Description of Change	Brief Rationale
	Group B (Rifamycin + CAM + EB) • Rifamycin + CAM + EB + aminoglycoside (same as above) • Rifamycin + CAM + aminoglycoside (same as above) • Rifamycin + CAM (when difficult to continue treatment with EB and no clinical worsening) If an investigator judges that it is necessary to use treatment regimens other than those listed above, such as discontinuation of study intervention, discontinuation of CAM or switching CAM to AZM (prohibited medication), the participant should be discontinued from the study and treatment regimens available at ~~T~~the study site will be provided ~~supply individualized treatment that will be obtained locally~~.	
6.8.2. Optional Cohort	Switching from an individualized treatment regimen to the optional cohort is not permitted.	Text was added to clarify that switching from an individualized treatment regimen to the optional cohort is not permitted.
8.2.3. Electrocardiograms	Participants found to have a QT or QTcF ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms on ECG at any point during the treatment period will be further investigated. Any QT or QTcF prolongation to ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms while on study intervention is considered a notable event and should be reported immediately to the sponsor.	Text was added for clarification.
	If a single ECG shows QTcF ≥500 ms or an increase from baseline (mean of triplicates on Day 1) of >60 ms, then complete additional triplicate ECGs, evaluate the mean QTcF, and record results on an unscheduled visit form.	Text was added to ensure consistency with the definition of QTcF prolongation (a QTcF value ≥500 ms, or an increase from baseline of >60 ms) described in Section 7.1.
10.3.3. Informed Consent Process	In addition, when switching to an individualized treatment regimen, obtaining re-consent from participants is required.	Text was added to clarify that obtaining re-consent from participants is required when switching to an individualized treatment regimen.
10.3.6. Committees Structure	Since the microbiological results are blinded up to Week 24, if the investigators consider the regimen change based on clinical worsening of the symptoms related to MAC-LD ~~and/or~~ based on the result of chest CT scan and so on, the investigators can consult with IDMC.	Text was revised to ensure consistency within the document.

Section Number and Name	Description of Change	Brief Rationale
11. REFERENCES	48. WHO [homepage on the Internet]. WHO consolidated guidelines on tuberculosis. Module 4: treatment drug-resistant tuberculosis treatment. Available at: https://www.who.int/publications/i/item/9789240007048 49. 日本結核 非結核性抗酸菌症学会治療委員会. 本邦での多剤耐性結核治療に対する考え方. Kekkaku. 2020, 95(2):79-84.	Added 2 references which was used in Section 4.2.1.

Amendment 3 (08-Jul-2021)

Overall Rationale for the Amendment: To describe that the comparator rifamycin (RFP or RBT) will be supplied by the sponsor and handled in an appropriate manner as a study intervention in accordance with GCP. Also, the term "study intervention" used throughout this protocol was clarified to refer to the study drug BDQ and the comparator rifamycin.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. OBJECTIVES AND ENDPOINTS	The term "study intervention" was replaced with "BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB" throughout the objectives.	Text was revised to clarify the objectives in line with the modified definition of study intervention.
	Microbiological assessment: To evaluate the efficacy of BDQ compared with rifamycin when administered as part of a treatment regimen with CAM and EB ~~the study intervention~~ in adult participants with treatment-refractory MAC-LD ~~at~~ up to Week 48.	Text was added to clarify the evaluation timepoint.
2. INTRODUCTION	The term "study intervention" throughout the protocol refers to BDQ~~,~~ and rifamycin (RFP or RBT)~~, CAM, and EB,~~ as defined in Section 6.1, Study Interventions Administered.	Definition of study intervention was modified.
	In Japan, CAM, RFP, RBT, EB,~~ and~~ SM, and AMK liposome inhalation suspension (ALIS) are approved for the treatment of MAC-LD. Kanamycin is listed in the Japanese guidelines, but KM is not approved for the treatment of MAC-LD.[41] Amikacin is not listed in the Japanese guidelines ~~and is not approved for the treatment of MAC-LD~~, but injectable AMK is reimbursed for the treatment of MAC-LD as from February 2019 and ALIS is approved for the treatment of MAC-LD in March 2021.[33]	Text was updated based on the approval of ALIS for the treatment of MAC-LD.
2.2.1. Comparator/Combination Therapy	For further information regarding above drugs, refer to each Japanese package insert.	Text was added for clarification.
2.3.1. Risks for Study Participation	Risks Due to Study Intervention (BDQ and~~, CAM,~~ RFP/RBT~~, EB~~) and Combination Drugs (CAM and EB)	Text was revised in line with the modified definition of study intervention.

Section Number and Name	Description of Change	Brief Rationale
	Discontinuation of study intervention and combination drugs will be required based on the result of ECG.	
	Investigator can switch to individual regimen based on the result of based on nonconversion and~~/or~~ clinical worsening.	Text was revised to keep consistency throughout the document.
4.2. Scientific Rationale for Study Design	Because rifamycin, which is included in the control regimen, is known to cause a reddish coloration of the urine, feces, sputum, sweat, serum, and discoloration of soft contact lenses, blinding of the study ~~intervention~~ drug/comparator is practically impossible due to the wide area of coloration effects.	Text was revised in line with the modified definition of study intervention.
	In addition, the participants in Group B (rifamycin-containing regimen) who do not achieve culture conversion up to Week 24, will have the option, at discretion of investigator, to (1) continue rifamycin-containing regimen, (2) switch to individualized treatment regimen (in principle, add on injectable or inhalation suspension of AMK or SM), (3) switch to BDQ-containing regimen after 2-week washout of rifamycin.	Text was added for clarification.
6.1 Study Interventions Administered	The study drug BDQ and the comparator rifamycin (RFP or RBT) will be provided as tablets for oral administration. ~~and~~ BDQ will be taken with food in the morning at approximately the same time each day, depending on visit and visit assessments. Rifamycin (RFP or RBT) will be taken according to the investigator's instructions as per Japanese package insert. ~~Comparator and~~ Combination drugs will not be provided by the sponsor and marketed product at study sites should be administered. BDQ will be manufactured and provided under the responsibility of the sponsor. Refer to the IB[40] for a list of excipients of BDQ. Rifamycin (RFP or RBT) will be provided under the responsibility of the sponsor. Refer to the respective Japanese package insert for a list of excipients of Rifamycin (RFP or RBT). Corrections were made to Table 2: Dosage and Administration Table for Study Interventions and Combination Drugs based on the above changes.	Text was added to clarify that the comparator will be provided by the sponsor. Also, text was revised in line with the modified definition of study intervention, and mistranslation of the term "study drug" was corrected in Japanese version of the document.
6.2. Preparation/Handling/ Storage/Accountability	All study intervention must be stored in the original blister sheet or container within the designated temperature range indicated by label of the kit in order to protect from light.	Text was added as comparator will be provided by the sponsor.

Section Number and Name	Description of Change	Brief Rationale
	Preparation, handling, and storage of combination drugs (CAM and EB) will be in accordance with procedures of the study sites.	Text was added to clarify the procedures for combination drugs.
6.3. Measures to Minimize Bias: randomization and Blinding 8. Study Assessments and Procedures 8.1.1. Microbiology Assessment (MAC-LD Treatment Outcome)	~~microbiology laboratory manual~~ Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test	Changed the name of procedure manual
6.4 Study Intervention Compliance	Study intervention compliance will be assessed by counting tablets and/or capsules returned and using participant diary during the site visits and documented in the source documents. The use of study intervention captured in participant diary will be recorded in the eCRF. Combination drug compliance will be assessed by participant diary during the site visits and documented in the source documents. The use of combination drug captured in participant diary will be recorded in the eCRF.	Text was added to clarify the assessment of study intervention and combination drug compliance.
6.7. Treatment of Overdose	Refer to the Japanese package insert of the comparator rifamycin (RFP or RBT) for advice on treatment of overdose.	Text was added to clarify the treatment of overdose of comparator.
6.8 Concomitant Therapy	Injectable or inhalation suspension of SM or AMK is acceptable as part of an individualized treatment regimen. The use of injectable or inhalation suspension of SM or AMK for any purposes other than as part of an individualized treatment regimen is prohibited.	Text was added for clarification.
6.8.1 Individualized Treatment Regimen	Participants can switch to individualized treatment regimen which may include injectable or inhalation suspension of AMK or SM at the discretion of investigators (refer to Sections 1.2 and 4.1).	Text was added for clarification.
7.1 Discontinuation of Study Intervention	• The participants discontinued administration of study intervention ~~BDQ~~ before Week 48 in Group A, Week 60 in Group B or OPW48 in ~~Group A or~~ optional cohort.	Text was revised in line with the modified definition of study intervention.
8. STUDY ASSESSMENTS AND PROCEDURES	Procedures for the collection, handling, and shipment of microbiological samples (sputum), as well as disclosure of blinded data are described in the Procedure for Confirmation and Reporting of Results of Blinded Sputum Culture Including Collection of Samples for Microbiology Test.	Text was added to clarify the procedures for handling of sputum samples and disclosure of unblinded data.

Section Number and Name	Description of Change	Brief Rationale
8.1.1. Microbiology Assessments (MAC-LD Treatment Outcome)	All sample collection and processing will be performed ~~by the staff at the clinical site,~~ according to the approved operating procedures	Text was revised to keep consistency throughout the document.
9.4.7. Other Analyses	Mean and median plasma BDQ, M2, CAM and 4-OH CAM concentration time profiles will be plotted after the first dose of BDQ ~~study intervention~~, and individual serum concentration time profiles may also be plotted.	Text was revised in line with the modified definition of study intervention.
10.1. Appendix 1: Abbreviations	Added amikacin liposome inhalation suspension (ALIS).	ALIS was added according to the text added.
10.4.1. Adverse Event Definitions And Classifications	For rifamycin (RFP or RBT) and combination drugs (CAM and EB) with marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the Japanese package insert.	Text was added to clarify how the expectedness of adverse events are determined for comparator and combination drugs.
Throughout the protocol	Minor changes were made.	Minor errors were noted.

Amendment 2 (14-Apr-2021)

Overall Rationale for the Amendment: The overall rationale for the amendment is to add the exclusion criterion of co-infected subject with NTM species other than MAC for clarifying adequate study population and clinical assessments, and add the methods of self-assessment of PROs (SGRQ, QOL-B and NTM module) according to each PRO author's advice.

Section Number and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Added the exclusion criterion of co-infected subject with NTM species other than MAC.	Clarification for adequate study population and clinical assessments.
8.1.2 Clinical Assessments in MAC-LD	Added the methods of self-assessment of PROs (SGRQ, QOL-B and NTM module).	According to each PRO author's advice.
Throughout the protocol	Minor corrections and clarifications were done throughout.	Minor errors were noted.

Amendment 1 (21-Oct-2020)

Overall Rationale for the Amendment: The overall rationale for the amendment is to change the duration of screening period, set the acceptable time window for lung function test, clarify data collection rule of PK blood samples and data handling rule of primary endpoint, correct inconsistencies and avoid misinterpretation by the investigators and site staffs.

Section Number and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 4.1 Overall Design 6.8 Concomitant Therapy	Changed screening period from maximum 8 weeks to maximum 9 weeks.	Re-estimated the required time for microbiology testing during screening period.
1.3 Schedule of Activities (SoA)	Acceptable time window was set for the lung function test on Day 1.	It was assumed that lung function test could not be performed on Day 1.

Section Number and Name	Description of Change	Brief Rationale
	Footnotes of drug susceptibility testing and optional cohort Day 1 were corrected.	Correction of inconsistency.
	Added how to collect the data for PK blood sampling.	Clarification of data collection rule for PK blood samples.
7.1 Discontinuation of Study Intervention	Corrected errors in referenced sections.	Mistakes in reference sections.
7.2 Participant Discontinuation/Withdrawal From the Study	Deleted duplicate text.	Correction of error.
8. STUDY ASSESSMENTS AND PROCEDURES	Added how to collect the data for unscheduled PK blood sampling.	Clarification of data collection rule for unscheduled PK blood samples.
9.4.2 Primary Estimand	Updated population and intercurrent events.	Modification and clarification of the primary estimand in line with ICH-E9 (R1).
9.4.3 Primary Endpoint	Added how to handle contaminated sputum culture and failed culture in the primary analysis.	Clarification of data handling rule for contaminated sputum culture and failed culture.
11 REFERENCES	Add 2 references.	Reviewed 2 references
Throughout the protocol	Minor corrections and clarifications were done throughout.	Minor errors were noted.

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD ; MD, PhD

Institution: Janssen Pharmaceutical K.K.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD [redacted]	08-Dec-2022 02:23:40 (GMT)	Document Approval

Janssen Pharmaceutical K.K. *

Clinical Protocol

COVID-19 Appendix Amendment 1

Protocol Title

A Phase 2/3, Multicenter, Randomized, Open-label, Active-controlled Study to Evaluate the Efficacy and Safety of Bedaquiline Administered as Part of a Treatment Regimen With Clarithromycin and Ethambutol in Adult Patients With Treatment-refractory Mycobacterium Avium Complex-lung Disease (MAC-LD)

Short Title

Bedaquiline/CAM/EB Study in Treatment-refractory MAC-LD Patients

Protocol TMC207NTM3002; Phase 2/3
AMENDMENT 2

TMC207 (Beadquiline)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the protocol to represent Janssen Pharmaceutical K.K.

Status: Approved
Date: 18 May 2021
Prepared by: Janssen Pharmaceutical K.K.
EDMS number: EDMS-RIM-289559, 2.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

IMPORTANT MATTERS RELATED TO COVID-19 AND COORDINATION OF STUDY CONDUCT

- During the course of COVID-19 pandemic, it may not be possible to visit the study site or perform tests as specified in the protocol. Temporary measures may therefore be taken if, in the judgment of the sponsor and the investigator (co-investigator), it is appropriate to continue the subject's study treatment and to maintain the integrity of the study. Specific measures may be required and should be implemented in accordance with applicable local laws, regulations, guidelines and procedures, including:. These deviations will be handled as "COVID-19 -related".
  - If a subject is unable to visit within the acceptable visit window, the subject may visit outside of the visit window.
  - If it becomes necessary to reduce the time spent for tests or if some tests are limited, etc. at the time of visit to the study site, the following actions are acceptable;
    - Sputum collection at the study site: If sputum collection at home is not possible, 2 collections are required at the study site. In such case, if good sputum specimen can be collected at the first time at the study site, no second collection will be acceptable
    - Sputum collection at home: If sputum collection including induced sputum specimen is not possible or limited at the study site, the submission of at least 1 spontaneous sputum specimen collected at home is acceptable without second collection at the study site. And, both sputum specimens at home and at the study site are not obtained and re-collection at home or at the study site is not possible, the submission of sputum specimens at this time point may be omitted
    - If two blood samplings for PK will be drawn at the study site, 2nd blood sampling may be drawn between 30 minutes to 4 hours after the intake. When the timing of 2nd blood sampling is changed, the timing of ECG measurement should be adjusted according to the protocol
    - Assessments of the SGRQ and QOL-B NTM module may be self-administered at home prior to the visit, provided the subject has an environment in place to receive the explanations to his/her queries to these questionnaires. If both assessments are performed after site visit, if only one assessment is feasible, the SGRQ assessment will take precedence and any missing QOL-B NTM module assessment will be allowed
    - Some or all of the lung function assessments, as well as CT scan, may be obtained on a different date from the visit if not available at the visit. Deviations due to missed tests are allowed in situations where the assessment themselves cannot be performed
    - Triplicate ECGs are required; however, if triplicate ECGs are difficult for any reason, duplicate ECGs or single ECG are acceptable
    - Visual and/or auditory examinations may be performed on different day(s) from the visit date. In addition, this examination(s) may be omitted only if the subject does not complain of any visual or auditory abnormalities
  - If any deviation other than the above may be occurred, the investigator or co-investigator will promptly report it to the sponsor and consider necessary measures.

- Unperformed tests, assessments, or visits will be recorded as a protocol deviation in the clinical trial management system. Discontinuation of investigational product treatment and withdrawal from the study must be documented on the case report form (CRF) preceded by the words "COVID-19 -related".
  - Other relevant study data affected by the pandemic will also be recorded/displayed as "COVID-19 -related" on the CRF and/or other study systems, as per sponsor guidance. This may include missing/late/visit modification/assessment/investigational product administration and temporary actions as described above.
- The sponsor will assess the overall impact of COVID-19 on the collection of critical study data and will provide details of the additional data analyses in the study SAP (Statistical Analysis Plan), if needed.
- Exclusion: Subjects with confirmed SARS-CoV-2 (COVID-19) infection (eg, positive PCR test) or strongly suspected SARS-CoV-2 infection (No test results recorded but clinical features present) within 4 weeks before informed consent are basically excluded from the study. However, patients who meet the following criteria 1 and 2 and in whom a validated SARS-CoV-2 test result has been recorded as negative can be enrolled in the study; however, the eligibility will be determined after carefully monitoring the conditions of candidate patients.

1. A negative test result was obtained at least 2 weeks after disappearance of the condition presumed to be due to SARS-CoV-2 infection (Key Clinical Features [eg, fever, cough, dyspnea, etc.])

   and

2. No SARS-CoV-2 infection or strongly suspected infection occurs during the screening period after a negative test result

- COVID-19 related exclusion considerations:

1. If a subject is excluded due to recent COVID-19 related circumstances, the reason for screen failure should be recorded on the CRF based on the exclusion criteria regarding a condition in which the subject's participation would not be in the subject's best interest or could interfere with the evaluation of the study.
2. Tests related to COVID-19 (Presence of SARS-CoV-2 virus in the body and items related to immunity to SARS-CoV-2 virus) are rapidly evolving. Additional tests may be performed at screening and/or during the study as deemed necessary by the Investigator (co-investigator) and as per regulation/regulatory guidance/standard of care.

COVID-19 APPENDIX AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Appendix Amendment 1	18-May-2021
Original Appendix	08-Jan-2021

Amendment 1 (18-May-2021)

Overall Rationale for the Amendment: The overall rationale for the amendment is to add the acceptance of the submission of at least 1 sputum specimen collected at home due to limited sputum collection at the study site.

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: Date:

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): _____

Institution: Janssen Pharmaceutical K.K.

[electronic signature appended at the end of the protocol]

Signature: Date:

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD [redacted]	18-May-2021 07:07:23 (GMT)	Document Approval