STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: PanACEA - DECODE – 01/LCB01-0371-20-2-02

A Phase IIb, Open-Label, Randomized Controlled Dose Ranging Multi-Center Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Exposure-Response Relationship of different doses of Delpazolid in combination with Bedaquiline Delamanid Moxifloxacin in Adult Subjects with Newly Diagnosed, Uncomplicated, Smear-Positive, Drug-sensitive Pulmonary Tuberculosis

[SAP VERSION 1.0]

DATE: 13/Feb/2023

SIGNATURE PAGE

Prepared by:	**Xue Gong**	**Statistician, University of California San Francisco**	DocuSigned by: Xue Gong 9BDD2BDC878F411... Feb/13/2023
Approved by:	**Patrick Phillips**	**Lead statistician, University of California San Francisco**	DocuSigned by: Patrick Phillips F39BACE644F44E6... 13/FEB/2023
	Suhyun Park	**Sponsor Delegated Person, LegoChem Biosciences, Inc.**	Suhyun Park Electronically signed by: Suhyun Park Reason: approval Date: 2023년 2월 14일 15:54 GMT+9
	Yunhee Lee	**Sponsor Delegated Person, LegoChem Biosciences, Inc.**	Electronically signed by: Yunhee Lee Reason: approved Date: 2023년 2월 15일 13:12 GMT+9
	Meekyung Lee	**Sponsor Delegated Person, LegoChem Biosciences, Inc.**	Meekyung Lee Electronically signed by: Meekyung Lee Reason: I attest to the accuracy and integrity of this document Date: 2023년 2월 15일 13:14 GMT+9

	Elin Svensson	**Pharmacometrician, Radboud University Medical Centre**	*Elin Svensson* Electronically signed by: Elin Svensson Reason: approval Date: 2023-02-14 08:10 GMT+1

Contents

List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
aPTT	Activated prolonged Thrombin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration Curve
AUC(0-t)	Area under the Plasma Concentration Curve from zero to t
BDM	Bedaquiline, Delamanid, Moxifloxacin
BDMD	Bedaquiline, Delamanid, Moxifloxacin, Delpazolid
BDQ	Bedaquiline
BID	Bis in die (twice daily)
BMI	Body Mass Index
C_{max}	Maximum Observed Plasma Concentration
CRF	Case Report Form
CRO	Contract Research Organization
Ct	Cycle threshold in GeneXpert MTB/RIF® test
CTCAE 4.0	Common Terminology Criteria for Adverse Events 4.0
DLM	Delamanid
DMP	Drug Management Plan
DSMB	Data Safety Monitoring Board
DS	Drug sensitive
DZD	Delpazolid

EBA	Early Bactericidal Activity
eCRF	electronic Case Report Form
EMB	Ethambutol
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
HED	Human Equivalent Dose
HIV	Human Immunodeficiency Virus
HRZE	Isoniazid, rifampicin, pyrazinamide, ethambutol
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
INH	Isoniazid
INR	International Normalized Ratio
IRB	Institutional Review Board
IWRS	Interactive Web Randomization System
kg	kilogram
LAM	Lipoarabinomannan
LCB	LegoChem Biosciences, Inc.
LZD	Linezolid
m	meter
MBLA	Molecular Bacterial Load Assay
MDR	Multidrug-Resistant
MGIT	Mycobacterium Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MOP	Manual of Procedures
MXF	Moxifloxacin
MTB	Mycobacterium tuberculosis
NIMR-MMRC	National Institute for Medical Research Mbeya- Medical Research Centre
NOAEL	No Observed Adverse Events Level
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PT	Prothrombin Time
PTM	Pretomanid
PZA	Pyrazinamide
QRS	Electrocardiographic QRS Interval
QTcF	QT-Interval corrected by Fridericia's formula
RIF	Rifampicin
SA	South Africa
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
TEAE	Treatment-Emergent Adverse Event
TB	Tuberculosis
T_{max}	Time to Reach C_{max}
TSC	Trial Steering Committee
TTP	Time to Positivity in Liquid Media
ULN	Upper limit of normal
WHO	World Health Organization

1. Document History

Version	Date	Reason for change	Protocol version	Dates of relevant trial activities (interim and final analyses)
1.0	13/Feb/2023		Version 2.1, 8/Sep/2021	First version.

2. Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods to be used during the analysis and reporting of baseline, efficacy safety and pharmacokinetic (PK) data collected for Protocol PanACEA - DECODE – 01. This SAP applies to the output produced for inclusion in the Clinical Study Report (CSR). All outputs required by ICH E9 statistical principles for clinical trials [1]will be produced.

This SAP should be read in conjunction with the Study Protocol, Case Report Forms (CRF), and Data Management Plan (DMP).

3. Objectives of the Study

3.1.Safety and Tolerability Objective

To describe the safety, tolerability and exposure-toxicity relationship of delpazolid (DZD) given over 16 weeks, in combination with standard-dose BDQ, DLM and MXF, compared to standard dose BDQ, DLM and MXF alone.

The aim is to identify the optimal dose of DZD to be used in subsequent studies that provides the best efficacy at acceptable safety of the drug when given daily over 4 months in patients with newly diagnosed, uncomplicated, smear-positive, drug-sensitive, pulmonary tuberculosis.

3.2.Efficacy Objectives

3.2.1. Primary Efficacy Objective:

To establish an exposure-response model for DZD, given over 16 weeks in combination with standard-dose BDQ, DLM and MXF, on the change in liquid culture MGIT time to positivity (TTP).

3.2.2. Secondary Efficacy Objectives:

- To assess dose and exposure-response relationships for DZD, based on secondary efficacy endpoints, including month-2 culture status in liquid media and on solid media, and time to culture conversion in liquid and on solid media.
- To assess the relative efficacy of increasing DZD doses compared to the background regimen without DZD, based on primary and secondary efficacy endpoints.
- To assess the proportion of patients who suffer relapse within 12 months post randomization, out of those patients completing 16 weeks of therapy and achieving sustained sputum culture conversion, defined as two successive negative liquid media cultures at or before WK08, with no positives to follow until the week 16 visit.

3.3.Pharmacokinetics Objectives

3.3.1. Primary Pharmacokinetics Objective

- To describe the pharmacokinetics (PK) of DZD through development of a population PK model.

3.3.2. Secondary Pharmacokinetics Objective

- To describe the PK of BDQ, DLM and MXF including their main metabolites.

3.4. Mycobacteriology Identification and Characterization Objectives

- To assess the minimum inhibitory concentrations (MIC) of BDQ, DLM, MXF, DZD of the infecting strain, at baseline and on representative isolate(s) grown at or after WK08.
- To investigate the frequency of acquired mutations in the infecting strain over treatment.
- In participants with recurrent disease: comparison of initial and recurrence isolate by whole genome sequencing to discriminate relapse from reinfection.

4. Trial Design

4.1. Overview

This will be an open label Phase IIb dose-finding, randomized, controlled study with a duration of 16 weeks of experimental therapy of DZD – Bedaquiline/Delamanid/Moxifloxacin (BDM) in adult participants with newly diagnosed, smear positive, uncomplicated, drug sensitive pulmonary tuberculosis (TB) to evaluate the safety, efficacy, tolerability, pharmacokinetics and exposure/response-relationship of different doses of delpazolid in combination with bedaquiline, delamanid and moxifloxacin.

Participants will be randomized to one of five arms containing BDM with different doses of DZD:

- Arm 1 (D0): 15 participants will receive 0 mg of DZD.
- Arm 2 (D400): 15 participants will receive 400 mg DZD orally once daily.
- Arm 3 (D800-OD): 15 participants will receive 800 mg DZD orally once daily.
- Arm 4 (D1200): 15 participants will receive 1200 mg DZD orally once daily.
- Arm 5 (D800-BD): 15 participants will receive 800 mg DZD orally twice daily.

Participants will visit the study clinic on a weekly basis for sputum collection, safety monitoring and receipt of study medication. After the completion of 16 weeks of experimental treatment, participants in the experimental arms, who did not achieve two successive negative liquid media cultures with the first at or before WK08, with no positives to follow by the week 16 visit, will be referred to their local health care facility to complete their course of anti-TB treatment according to the national TB program.

4.2.Randomization

Randomization will be implemented after all screening results are available for participants who have given informed consent and who have been found eligible for participation. Participants will be randomized by centralized allocation to a predefined list.

Participants will be allocated using the Internet-Based Randomization service system: RANDOMIZE.NET. Participant randomization will be stratified by bacterial load in sputum as measured by GeneXpert, cycle threshold (≥ 16, < 16), site (seven sites have been activated: The Aurum site, UCTLI, TASK Eden, Clinical HIV Research Unit (CHRU), KCRI/KIDH, the Ifakara site and the NIMR-MMRC site), and HIV status (positive, negative). Each site will have its own account and the allocation result will be generated by the web system immediately based on the minimization randomization algorithm. The minimization algorithm allocates the patient to the treatment arm with the lowest allocation proportion.

4.3. Sample Size Determination

15 participants per arm with a total of 75 participants, and a wide range of DZD doses (from 0mg to 800mg BID) has been determined as an adequate sample size for population PK modelling, and for exposure response modelling to detect a clinically meaningful dose-dependent relationship.

Furthermore, the planned sample size of 15 participants per treatment group is in keeping with other trials of this type and accounts for the possibility of up to 3 drop-outs per group, which based on previous studies of this type conducted at these sites, represents a conservative estimate of the expected drop-out rate.

Previous Phase IIA (EBA) studies indicate that the between patient standard deviation of logCFU can be approximately 0.2. Therefore, assuming similar variability in this trial the expected standard errors of group mean EBA and corresponding width of 95% confidence intervals are 0.052 and 0.101 respectively for a group size of 15 and 0.063 and 0.124 respectively for a group size of 10.

This level of precision with a group size of 15 is considered adequate.

4.4. Early Stopping Rules

An independent data safety monitoring board (DSMB) will be convened for the trial. The DSMB will review safety data at regular intervals as defined in the DSMB Charter, but will also perform expedited review if the following conditions are met:

- Three or more participants experience a grade 3 or higher AE (CTCAE 5.0) in the same organ system that are at least possibly related to one of the study drugs, and qualify as "unexpected" by being more severe than in previous experience with the drug in question.
- Two or more participants experience a grade 4 or higher AE (CTCAE 5.0) in the same organ system that are at least possibly related to one of the study drugs, and qualify as "unexpected" by being more severe than in previous experience with the drug in question.
- One patient experiences a grade 5 AE (death) that is at least possibly related to one of the study drugs.

Refer to DECODE Protocol and DSMB charter for more individual patient safety stopping criteria.

5. Trial Endpoints

5.1. Primary Endpoint:

5.1.1. Primary Safety Endpoint

Participants will be regularly assessed for AEs during treatment and follow-up phase, including assessments of vital signs, physical examination, weight, detailed neurological examination, colour vision and visual acuity tests, 12-lead ECGs and routine clinical laboratory tests (including chemistry, haematology and urinalysis data).

The safety of DZD will be investigated by evaluation of:

- Proportion of participants experiencing expected oxazolidinone class toxicities, defined as peripheral or optical neuropathy, or incident leukopenia, anemia or thrombocytopenia, or adverse events in line with tyramine pressor response, all of Grade 2 or higher, possibly, probably or definitely related to DZD.

5.1.2. Primary Efficacy Endpoint

The efficacy of DZD will be evaluated by measuring the change in mycobacterial load over time on treatment as quantified by time to positivity in BD MGIT 960® liquid culture described by nonlinear mixed-effects methodology (see section 10).

5.2. Secondary Endpoints:

See section 11 for fuller definitions of secondary endpoints.

5.2.1. Secondary Safety Endpoints

- All adverse events
- Adverse events of Grade 3 severity or higher
- Adverse events possibly, probably or definitely related to study drugs
- Treatment discontinuations or interruptions related to adverse events/serious adverse events
- Frequency, severity and type of ECG alterations
- Changes in ECG intervals of PR, RR, QRS, QT, Fridericia-corrected QT [QTcF]
- Proportion of participants with QTcF > 500ms in ECGs on treatment
- Proportion of participants with a prolongation of QTcF > 60ms in ECGs of grade 3 and above as defined in the protocol

5.2.2. Secondary Efficacy Endpoints

- Proportion of participants who suffer relapse, defined as recurrent disease caused by a strain indistinguishable to the baseline isolate (using whole genome sequencing), within 12 months post randomization, out of participants completing 16 weeks of therapy and achieving sustained sputum culture conversion defined as two successive negative liquid media cultures at or before WK08, with no positives to follow by the week 16 visit. Full definition of relapse in section 11.2.
- Time to recurrent TB, and to relapse, within 12 months post randomization.
- Time to culture conversion to negative on liquid media (defined as two negative cultures without an intervening positive culture).
- Proportion of participants converting to negative sputum culture in liquid media (defined as two negative cultures without an intervening positive culture) at each time point during treatment.
- Proportion of participants with negative sputum culture on solid media at WK 08 and other time-points.
- Proportion of participants developing drug resistance among those not converting to negative culture.

5.3. Pharmacokinetics Endpoints

A population PK model will be developed for DZD.

The following secondary parameters will be derived for DZD (model-based), for BDQ and main metabolite M2, DLM and main metabolite DM-6705, and for MXF (with NCA):

- Area under the plasma concentration curve from morning dosing to 24 hours (AUC 0-24) on day 14 (WK02)
- The observed maximum concentration (Cmax) on day 14
- Time to reach Cmax (Tmax) on day 14
- The minimum observed plasma concentration (Cmin) at day 14 (24 hours following the last dose for QD and 12 hours following the last dose for BID)

Analyses may be limited by available budget, which may lead to parameters for certain drugs not being reported.

5.4. Mycobacteriology Identification and Characterization Endpoint

Sputum cultures from various timepoints during the study will be assessed as follows:

- Minimum inhibitory concentrations (MIC) of BDQ, DLM, MXF, DZD of the infecting strain, at baseline and on representative isolate(s) grown at or after WK08, if any.
- Frequency of acquired mutations in the infecting strain over treatment by whole genome sequencing
- Comparison between bacterial strain causing recurrent disease, and the strain at baseline by whole genome sequencing, to discriminate relapse from re-infection.

These assessments will be performed dependent on the availability of lab capacity and budget, so may not be completed for all possible timepoints.

5.5. Exploratory Endpoints

Exploratory endpoints will be analysed depending on laboratory capacity and budget and may not be tested in all trial's sites equally. Refer to DECODE Protocol for more details.

6. Analysis Populations

The ITT analysis population will be primary for all analyses, apart from safety analyses where the safety population will be primary. The Adequate adherence (AA) population will be secondary.

6.1. Intent-to treat (ITT) population:

The ITT population will consist of all randomized participants in the groups to which they were randomly assigned, and who have taken at least one dose of study treatment.

6.2. Modified Intent-to treat (MITT) population:

The MITT population will be the same with ITT population but exclude participants that withdrew from study medications prior to PK sampling.

6.3. Adequate adherence (AA) population:

The AA population will be the same as the ITT population with the following participants excluded:

- Randomized participants not meeting the eligibility criteria

- Participants having missed one or more doses on 10 or more days of their allocated treatment.

6.4.Safety Population

The safety population will be defined as all participants who received any dose of study medication. This population will also be used for the PK and the exposure-response analysis.

7. Baseline Characteristics and Patient Disposition

7.1. Baseline patient characteristics

Baseline characteristics tables will be produced for both the ITT, AA, and safety analysis populations.

Demographic data will be summarized by dose group and overall. Summary statistics will be calculated by age, race and gender, height, weight, HIV status, body mass index (BMI) and bacterial load in sputum as measured by GeneExpert.

The results of the physical examination and vital signs (including systolic and diastolic blood pressure, heart rate, and body temperature), safety laboratory screening sample, chest radiography (X-ray) and ECG data will be tabulated by dose group.

Baseline characteristics, medical history, and analytical data will be summarized using descriptive statistical methods. Continuous data will be summarized using the median, the range (minimum and maximum value) and IQR. Categorical values will be summarized using frequency counts and percentages.

7.2. Patient recruitment

Total numbers of participants screened and randomized and reasons for participants not being randomized will be tabulated by site.

7.3.Patient withdrawal and follow-up

Timing of withdrawal and lost to follow up will be recorded and tabulated, the number and reasons of losses to follow up over the course of the trial will be summarized by treatment arms. The disposition of the participants who discontinue the treatment by meeting the stopping criteria as described in protocol section 13.10 ("Additional safety considerations: individual patient stopping criteria for Safety") will also be recorded and tabulated.

8. Delpazolid Pharmacokinetic Analysis

A population PK (popPK) model of delpazolid will be developed using nonlinear mixed-effects methodology. The analysis will be carried out and reported according to regulatory guidance documents from FDA and EMA: Population Pharmacokinetics Guidance for Industry and Guidance on Reporting the Results of Population Pharmacokinetic Analyses.[2,3] The model should serve the following purposes:

- Describe distributions for random inter-individual variability
- Identify and quantify sources of variability (covariates)
- Explore potential nonlinear kinetics
- Generate exposure metrics for the exposure-response analysis
- Provide a means to simulate exposures of alternative dosing scenarios and/or other populations

8.1.Software

Data management and post-processing of results will be performed in R,[4] with help of specialized packages as Xpose. The model will be developed in NONMEM 7.4 or later and parameters will be estimated using the First Order Conditional Estimation method with interaction (FOCE INTER).[5] If this estimation method turns out to generate unreliable results, alternative methods such as the SAEM method will be explored. Computations will be performed on the high-performance cluster managed by Radboudumc Applied Pharmacometrics. The development process will be documented using the Pirana run record system.[6]

8.2.Data Management

A NONMEM dataset will be generated through reproducible scripting in R. The raw PK data will be supplied from the Clinical Pharmacology lab, Radboudumc, in prespecified format (template to be agreed upon between lab and pharmacometrician before start of analysis). Patient characteristics and information about doses and sampling will be extracted from the main database provided from the responsible CRO (Tecro). Actual dosing and sampling dates and times will be used.

8.2.1. Handling of missing and erroneous data

The information on concentrations reported as below the lower limit of quantification (LLOQ) will be included in the popPK analysis. If dosing date or time is missing, the concentration records post the dose will be excluded. Concentration records with missing date or time will be excluded.

Missing values for a covariate at a particular time point will be replaced with an available measurement at the closest time point. For participants with no covariate information the following will be applied:

- Missing continuous covariates will be replaced with the median value in the population. Body weight would be sex-specific if replaced
- Missing categorical covariates will be replaced by the most common category

If a covariate is missing in more than 15% of the participants, more sophisticated methods will be used to impute the covariate based on regression models between covariates.

All imputed values will be flagged. Description of any missing data and the details related to any potential imputation will be recorded in the popPK model report (see 8.4).

8.2.2. Handling of Outliers

Outliers are defined as data points in the datasets that appear to be outside the norm for that dataset. Potential outliers in the popPK analysis will be identified based on inspection of graphical analysis and the output from initial satisfactory runs. The influence of the omitted data will be evaluated by running the final popPK model with all data and investigate the impact on parameter estimation. The reasons for omitting data will be carefully described in the popPK model report (see 8.4).

8.3.Model Components

The popPK model of delpazolid will be developed in steps, starting with the structural and stochastic models before the covariate model.

8.3.1. Structural model

One-, two- and three- compartmental disposition models will be considered for delpazolid. The absorption of delpazolid will be modeled with a first-order function without or with delay through transit compartments. Non-linear relations between dose and bioavailability will be explored, as well as non-linear clearance in relation to concentration (e.g. Michelis-Menten kinetics).

8.3.2. Stochastic model

The between-patient variability will be described using a log-normal distribution of structural model parameters:

$$P_i = \tilde{P}(\theta, z_i) \cdot e^{\eta_{Pi}}$$

or as a logit transformed distribution to constrain values between 0 and 1 (e.g. for absolute bioavailability):

$$P_i = \frac{e^{(\varphi + \eta_{Pi})}}{1 + e^{(\varphi + \eta_{Pi})}} \text{ where } \varphi = \log\left(\frac{\tilde{P}(\theta, z_i)}{1 - \tilde{P}(\theta, z_i)}\right)$$

P_i represents the value of the PK parameter P for the ith subject, while $\tilde{P}(\theta, z_i)$ is the typical population value of parameter P in the structural model given the vector of fixed effects parameters θ and the covariate vector z_i of subject i. η_{Pi} is a normally distributed random effect with mean zero and an estimated variance ω^2 ($\eta_{Pi} \sim N[0, \omega^2]$). η_{Pi} describes the deviation of P_i from and $\tilde{P}(z_i)$. Other models will be considered if indicated by the data.

Additive (homoscedastic), proportional (heteroscedastic) and combined additive and proportional models will be tested on untransformed or log-transformed data (other transformations may be used if applicable). The combined additive and proportional residual error model for drugx for untransformed data follows:

$$C_{ij} = \hat{C}_{ij} \cdot (1 + \varepsilon_{pij}) + \varepsilon_{aij}$$

C_{ij} is the j^{th} measured observation of drugx in the ith individual

8.3.3. Covariate model

When the basic popPK model is established the covariate model will be developed. Initially, allometric scaled body weight will be applied for all volume terms and all clearance terms. Thereafter, further covariates will be evaluated using a stepwise search based on both statistical significance test and clinical significance i.e. the magnitude of the effect of the covariate on the parameter examined.

Allometric scaled body weight will be applied for all volume terms and all clearance terms as follows:

$$\text{Typical}\frac{\text{CL}}{\text{F}} = \theta_1 \cdot \left(\frac{\text{WT}_i}{70}\right)^{\frac{3}{4}}$$

$$\text{Typical}\frac{\text{V}}{\text{F}} = \theta_2 \cdot \left(\frac{\text{WT}_i}{70}\right)^{1}$$

WT_i denotes individual body weight; q_1 and q_2 are the typical oral clearance and volume of distribution, respectively, in a patient weighing 70 kg. Other body size metrics, such as fat-free mass, could be evaluated instead of total bodyweight.

The effect of categorical covariates will be evaluated as exemplified here for the effect of SEX on a particular PK parameter P, where P is the typical value for this parameter:

$$P=\theta_1 \times (1+\theta_2 \times SEX)$$

SEX is an indicator variable, which is equal to 0 for male and 1 for female. Accordingly, q_1 is the typical estimate of the PK parameter for male participants and q_2 is the fractional increase/decrease in the typical parameter value for females (SEX=1) compared to males. The lower limit of q_2 was set to –1 to restrict the typical value to take on a negative value.

The effects of continuous covariates will be evaluated initially with a linear function as exemplified here for the effect of AGE on a particular PK parameter P, where P is the typical value for this parameter:

$$P=\theta_1*(1+\theta_2\times(AGE-AGE_{median}))$$

AGE_{median} is the observed median AGE, q_1 is the typical estimate of the PK parameter at the median age and q_2 is the fractional change in the parameter different from the median age.

The specific parameters-covariate to minimally be tested in the delpazolid popPK model are listed in Table 2 below. When a relation is found statistically significant further investigation determining potential effect of influential individuals will be conducted and an assessment of scientific plausibility and clinical relevance (i.e. resulting in >20% difference in drug exposure) will be made before final decision on inclusion in the model.

Table 2: Covariate relations to be tested

Parameter	Covariates
Clearance	Body size metrics, Age, Race, HIV-status
Volume of distribution	Body size metrics, Sex
Bioavailability	Sex, Race, HIV-status, Dose

8.4.Model Selection, evaluation and documentation

Model comparisons will be based on the objective function value (OFV), goodness-of-fit plots, precision in parameter estimates and scientific plausibility. A difference in OFV between two nested models is approximately χ^2-distributed. A difference in OFV ≥3.84 and 6.63 (one degree of freedom) is thus significant at the 5% and 1% level, respectively.

The final model will be evaluated according to best practice using primarily visual predictive checks (VPCs) and comparison of individual concentration observations and predictions[7]. The model development process will be documented with a run-record exported from Pirana including all key decision points. The popPK dataset, model development process and final model will be described in the popPK model report.

9. Pharmacokinetic analysis companion TB drugs

Non-compartmental PK analysis will be conducted for all the companion drugs (bedaquiline plus metabolite M2, delamanid and moxifloxacin). The following PK parameters will be estimated for day 14 from each participants' individual plasma concentrations by applying a noncompartmental approach using PK software WinNonlin Phoenix or R packages with the same functionality.

Cmax	Maximum observed drug concentration
Cmin	Minimum observed drug concentration (not including predose observation)
Tmax	Time of the maximum drug concentration (obtained without interpolation)
AUC(0-24H)	Area under the drug concentration-time curve calculated using Log linear trapezoidal summation from time zero to time 24 h post dose

In addition, for moxifloxacin the following parameters will be reported:

Kel	Terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration vs. time curve
T½	Elimination half-life calculated as ln(2)/Kel
CL/F	Apparent oral clearance [Dose/AUC(0-24H)]
Vd/F	Apparent volume of distribution following oral administration [Vd/F = (CL/F)/Kel]

The actual elapsed time will be calculated from actual dosing and sampling times and used in the parameter estimation.

The rate constant of the elimination phase (λ_z) will be calculated by log-linear regression of the terminal portion of the concentration-time profile where there are sufficient data (i.e. at least 3 time points and the correlation coefficients for the terminal slope [R^2] is greater than or equal to 0.9). If these criteria are not fulfilled, λ_z and $t_{1/2}$ will not be reported.

During the derivation of individual subject PK parameters plasma concentrations:

- Any values below the LLOQ that occur before the first quantifiable concentration will be replaced with zero.
- Any values that fall below the LLOQ between 2 measurable values will be treated as missing.

Deviations from this convention may be considered on a case-by-case basis as deemed appropriate. These will be documented fully with the rationale for the deviation.

If the concentrations at x h post dose (all after the last measurable concentration) are below the LLOQ they will be calculated using the formula $Cx = C_{last} * e^{-Kel*(x-Tlast)}$, in which Clast is the last measurable concentration and Tlast is the time to reach Clast. These extrapolated concentrations will be used together with other measured concentrations to assess the Area under the drug concentration - time curves using Log linear trapezoidal summation from time zero to time 24 h post dose.

In summary plots of mean concentration-time profiles, statistics will be calculated having set concentrations to missing if either of the following cases is true:

- A concentration has been collected as ND (i.e. not done) or NS (i.e. no sample),
- A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous. This will be documented fully with the rationale for the decision.

Plasma concentrations that are below the lower limit of quantification (<LLOQ) will be set to zero in the computation of mean concentration values.

Descriptive statistics including mean, standard deviation, geometric mean, coefficient of variation, median, minimum and maximum will be computed for each PK parameter by dose group. In addition, mean and median concentration-versus-time graphs will be provided (with error bars as appropriate).

10. Primary Efficacy Analysis: Exposure-response modelling

To establish an exposure-response model for delpazolid, the change in liquid culture MGIT time to positivity (TTP) will be modeled and linked to derived PK metrics. Software and data management will be as described in section 8 (popPK model). The TTP data will be transferred from the responsible CRO (Tecro) in a consistent format. There are two TTP observations from each sampling point and those will be included separately as individual observations (no averaging). In the primary analysis, the MITT analysis population will be used. For patients discontinuing study medications prematurely (before 16 weeks), TTP data collected after the discontinuation will be excluded. Contaminated culture results will be ignored.

10.1. Base model of TTP

Time to positivity (TTP) in the MGIT system will be analysed to evaluate efficacy. The model for TTP will be based on previously developed and published models.
Option 1: Semi-mechanistic model linking a latent variable describing the decline in bacterial load to a model of probability of detection in MGIT (handling negative samples) and a time-to-event model for TTP.[8] The TTP value measured at baseline will be used to individualize the starting point for each patient. Only TTP values measured after start of treatment will be included in the fit of the model. Inter-individual variability with long-normal distributions will be included for parameters describing the bacterial load at baseline and the decline in bacterial load.

Option 2: Bi-linear models with estimated inflexion-point and negative cultures handled by the M3 method (estimating a probability of negative sample at the given time)[9,10]

Option 3: Shifted logistic model and negative cultures handled by the M3 method[911].

The models may be adjusted as needed to achieve a satisfactory fit of the observed data. The fit will be evaluated primarily with two types of goodness of fit plots: visual predictive checks of the proportion of negative samples over time on treatment and Kaplan-Meier visual predictive checks of TTP per treatment week (for option 1) and visual predictive checks of quantitative TTP over time on treatment (for option 2 and 3). The choice of model to use for the exposure-response evaluation will be based on the mentioned goodness-of-fit plots, the objective function value, precision in estimated model parameters and estimation stability (successful convergence of estimation algorithm).

10.2. Exposure-response model

The following PK parameters (derived from the popPK model) will be considered in the exposure response analysis: delpazolidAUC0-24h, Cmax and Cmin from day 14 morning dose. The PK parameters will be evaluated as predictors for the decline in bacterial load and the following relations will be tested: linear, Emax and sigmoid Emax. Likelihood ratio tests and a 5%-significance level will be used for testing the statistical significance of inclusion of PK effects.

10.3. Other covariates

Patient characteristics may influence the TTP dynamics, like the severity of disease at start of treatment (degree of cavitation, baseline bacterial load), co-infection with HIV, sex, adherence to treatment, etc. Those factors will be evaluated as predictors for the decline in bacterial load. Likelihood ratio tests and a 5%-significance level will be used for testing the statistical significance of inclusion of covariate effects.

Parameter estimates with corresponding uncertainty for the final model will be reported.

11. Outcome Definitions

11.1. Culture results

Two sputum specimens at each visit for culture. The culture results are reported as:

- Positive for MTB Complex
- Positive for MTB Complex with contamination
- Negative
- Contaminated

- No result

With the potential for results from two sputum samples at each time-point(visit) a rule is required to define a negative or a positive time-point for determination of sputum-culture conversion. For this trial the definitions are:

- **Positive timepoint** – Any timepoint with one or more culture result of Positive for MTB Complex or Positive for MTB Complex with contamination
- **Negative timepoint** – Any timepoint with one or more culture result of Negative and no cultures with a result of Positive for MTB Complex or Positive for MTB Complex with contamination
- **Contaminated timepoint** – Any timepoint with one or more culture result of Contaminated and no cultures with a result of Positive for MTB Complex or Positive for MTB Complex with contamination or Negative
- **No result timepoint** – Any timepoints with no positive, negative, or contaminated results reported for any specimen submitted for analysis

11.2. Relapse

An important secondary outcome is the proportion of participants who suffer relapse among those completing 16 weeks of therapy, achieve early culture conversion to negative in liquid media if there is a culture negative timepoint at two consecutive visits, the first of which is at or before week 08, without an intervening culture positive timepoint, and terminating therapy.

All participants will be classified as follows:

- Not achieved culture conversion to negative before or at week 8 after randomization (based on the analysis visit window). These participants will not end treatment at week 16 according to the protocol and therefore are not included in the relapse analysis.
- Relapse – defined as having two consecutive culture positive timepoints without an intervening culture negative timepoint where the first occurs after Week 16 after randomization (based on the analysis visit window) and the recurrence strain of MTb is shown to be the same as that at baseline. If strain typing results are missing or inconclusive, a recurrence will be considered a relapse (rather than a reinfection).
- Reinfection – defined as having two consecutive culture positive timepoints without an intervening culture negative timepoint where the first occurs after Week 16 after randomization (based on the analysis visit window) and the recurrence strain of MTb is shown to be different from that at baseline.
- Died at any point during the study
- Culture positive timepoint when last seen (not meeting criteria for other outcomes above)
- Culture negative timepoint when last seen (not meeting criteria for other outcomes above)

Outcomes will be tabulated by treatment arm among all in the ITT analysis population and among those in the AA analysis population.

A sensitivity analysis will be conducted repeating this relapse analysis using the second definition of time to culture conversion described below under the latter part of section 11.4.

11.3. Time to recurrent TB and relapse

Time to recurrent TB will be defined as time from randomization to first culture positive timepoint that leads to a classification of relapse or reinfection. Participants without reinfection or relapse will be censored at time of last culture result. Time to relapse will be defined in the same way, except considering only relapses (and not reinfections) as events.

11.4. Time to culture conversion to negative on liquid media

Participants will be classified as having culture conversion to negative in liquid media if there are two consecutive culture negative timepoints without an intervening culture positive timepoint. Any other results will be ignored for the calculation of time to culture conversion. Culture timepoints will be classified as negative or positive according to the trial definition under 11.1.

Time will be taken from the date of randomization to the first occurrence of two consecutive negative culture timepoints.

Culture positive timepoints that occur after culture conversion has been achieved do not affect time to culture conversion.

This will be the primary definition of time to culture conversion. Primary analysis will be performed based on the primary definition. We will, in addition, perform two sensitivity analyses with alternative definitions of time to culture conversion:

1) The definition will be as above, with the exception that culture conversion can only be achieved if the two consecutive visits assessed as culture negative timepoints without an intervening culture positive timepoint are at least 28 days apart.

2) The definition will be as above, with the exception that culture conversion is only achieved provided no further culture positive timepoints occur after 'culture conversion', in the period up to and including the week 16 visits (a subsequent culture positive timepoint effectively 'cancels' out culture conversion).

12. Analysis Method

12.1. Analysis of time to culture conversion by dose group.

Descriptive summary statistics, such as mean/median of the time to culture conversion will be tabulated. Proportion of participants achieving culture conversion at each time point during treatment will be summarized using the Kaplan-Meier estimator with 95% confidence intervals.

A Cox regression model will be used to compare each arm with different DZD doses to the background regimen without DZD, in time to culture conversion. The analysis will be adjusted for the baseline cultures using time to positivity (TTP) at the time of screening and enrolment. Demographic and clinical characters, such as gender, age, race, BMI, HIV status, smoking, alcohol usage, will also be adjusted in sensitivity analyses. To check the Proportional Hazard (PH) assumption, we will do statistical tests and graphical diagnostics based on the Schoenfeld residuals.[12] If the PH assumption is violated, cox regression models will be presented but interpretation will take into account this violation and alternative methods will be added including restricted mean survival time[13].

12.2. Analysis of negative sputum culture on solid media

LJ solid media will be performed at the following visits only: WK00, WK08, WK12, WK16, and FU1-FU4. The proportion of participants with culture negative timepoint at each visit will be calculated by treatment arm for each of the ITT and AA analysis populations. Participants will be classified as culture negative, culture positive, contaminated, culture result missing, participant died, or participant lost to follow-up (if lost to follow-up prior to that time point).

12.3. Development of drug resistance

Any changes in drug resistance profile from baseline will be listed including baseline and any follow-up drug resistance data, culture results, and treatment arm.

12.4. Analysis of Experimental Efficacy Endpoints

The molecular bacterial load assay (MBLA) and the sputum Lipoarabinomannan (LAM) assay will be evaluated against the conventional drug development endpoints, bacterial load measured in the BD MGIT™ liquid media culture system. Comparisons between methods will be performed on a per-sample, per-patient, and per-treatment arm basis.

12.5. Handling of missing data

No missing data will be replaced, unless otherwise specified above, and will be shown in any summaries as missing.

12.5.1. Missing Dates

Imputation rules for missing or partial medication start/stop dates for concomitant medications and date of onset for AEs are defined below:

1) Missing or partial start date:
   a) If only DAY is missing, use the first day of the month. UK(missing)-MMM-YYYY: impute to 01-MMM-YYYY;
   b) If DAY and Month are both missing, use the first day of the year. UK-UKN-YYYY: impute to 01-JAN-YYYY;
   c) If DAY, Month and Year are all missing, use the date of initial screening.
2) Missing or partial stop date:
   a) If only DAY is missing, use the last day of the month.
   b) If DAY and Month are both missing, use the last day of the year.
   c) If DAY, Month and year are all missing, assign 'continuing' status to stop date.

12.6. Visit Windows

For timing of data items, the time is based on actual visit dates where data was collected (e.g. blood sample, sputum sample, data recorded) rather than scheduled visit name or date. The time from randomization is calculated as the difference between visit date and randomization date + 1 (so that data collected on the day of randomization is on day = 1).

Any visit, scheduled or unscheduled, that falls into the analysis window below will be assigned to that visit for the purpose of analysis. If two visits fall within the same interval, the one closet to the target date will be used for the analyses by visit, so that there is only one unique visit for each patient and analysis time-point. These visit windows relate to analyses of tabulations of data by visit.

Visit	Target Date: Days after Treatment Allocation (wk*7+1)	Analysis Window
Baseline	1	Date of screening consent-3
Week 01	7	4-10
Week 02	14	11-17
Week 03	21	18-24
Week 04	28	25-31
Week 05	35	32-38
Week 06	42	39-45
Week 07	49	46-52
Week 08	56	53-59

Week 09	63	60-66
Week 10	70	67-73
Week 11	77	74-80
Week 12	84	81-87
Week 13	91	88-94
Week 14	98	95-101
Week 15	105	102-108
Week 16	112	109-121
Week 18	126	122-154
Week 26	182	155-210
Week 38	266	211-313
Week 52	364	314-no upper bound

13. Safety Analysis

13.1. Safety Variables

13.1.1. ECG Analysis

QT and QTcF (Friderica's correction) data will be analyzed categorically based on the number and percentage of participants classified in each category by treatment group, in addition to summarizing mean QT/QTcF over time by dose group.

Post-baseline QT and QTcF intervals will be classified into following categories:

- QT/QTcF < 450 ms
- 450 ms <QT/QTcF <480 ms
- 480 ms < QT/QTcF < 500 ms
- QT/QTcF > 500 ms

QTcF changes from baseline will be classified into the following categories:

- Decrease (an increase < 0 ms)
- Increase < 30 ms
- >30 ms and < 60 ms
- increase >60 ms

QT and QTcF will be categorized (<450, 450-479, 480-499, ≥500) and tabulated by visit and treatment arm, and highest post-randomization value overall by treatment arm. Change from baseline of QT and QTcF will also be categorized (<30, 30-59, ≥60) and tabulated by treatment arm, and highest post-randomization value overall by treatment arm. These tables will be done for the whole study period and repeated for the treatment phase only.

Frequency, severity and type of ECG alterations will be tabulated and described.

Both mean (and SE) QT, QTcF, PR, RR, QRS, and heart rate (HR) by visit and treatment arm, and mean (and SE) QT, QTcF, PR, RR, QRS, and HR change from baseline by visit (within visit window) and treatment arm will be tabulated.

13.1.2. Adverse Events (AE)

The incidence of treatment-emergent adverse events, defined as all AEs that occur after the administration of IMP, and their relatedness to experimental treatment will be summarized by treatment group, by system organ class and preferred term, maximum severity, and potential relationship to IMP, SAE, as well as TEAEs with an outcome of death, serious TEAEs, and discontinuations due to TEAEs. These summary tables will be restricted to AEs with date of onset during or up to 14 days after treatment. Separate summary tables will be created for the incidence of AEs over the whole study period.

Adverse events will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

13.1.3. Prior and Concomitant Medication

Prior and concomitant medications will be summarized and listed on a per-participant basis, if a patient reported the same medication repeatedly, the medication will be counted only once in tables; counts (N) and percentages (%) will be presented by treatment arm. Concomitant medication will also be listed with one row for each occurrence of each medication per participant. If a medication has a completely missing or partially missing start/stop date, the date will be imputed as described above and then it will be classified as prior, concomitant, or post-treatment medication.

Imputation rules for missing or partial medication start/stop dates are defined above.

13.2. Method for safety analysis

Binary and categorical variables will be tabulated by treatment arm. Continuous variables will be summarized with location (such as mean or median) and precision (such as standard error or interquartile range) summary estimates.

Participants with worsening condition from baseline on any variable will be described and tabulated.

The following variables will be analyzed:

Participants with worsening condition from baseline on any variable will be described and tabulated. The following variables will be analyzed:

- Laboratory Parameters: a list of safety laboratory parameters collected in the trial is described under 'Safety Laboratory' in Protocol.
- Ophthalmologic Variables: Visual Acuity (Snellen) and Colour Vision (Ishihara) tests
- Physical Examination incl. neurological examination; esp. presence of Hunter score criteria
- Vital signs Timings of Analyses
- Extent of exposure to all drugs

13.3. Interim Analyses for Data Safety Management Board (DSMB)

An independent data safety monitoring board (DSMB) will be convened for the trial. The DSMB will review safety data at regular intervals as defined in the DSMB Charter, DSMBs report will be provided including safety data. The sponsor and the medical monitor will remain blind to results, only the DSMB committee members and unblinded statistician(s) will see aggregate data by study arm.

13.4. Interim 16-week analysis

Analysis for the primary endpoints, and secondary endpoints unrelated to disease recurrence or relapse, will be performed after data are available (allowing for time for culture growth) after the last patient completed their WK16 (or otherwise last treatment) visit. This will be considered the primary analysis data extract for presentation and publications. Secondary outcomes including data after 16 weeks will be presented based on available data, recognizing that full data on these endpoints will not be available until the final analysis.

The sponsor and study staff will not remain blinded once this interim analysis has been undertaken.

A partial database lock will be performed for this purpose, with a final database lock at the end of study after all long-term outcome data are available.

13.5. Final Analysis

Analysis for the secondary and additional endpoints that include any data available after 16 weeks will be performed when the final database lock at the end of study after all long-term outcome data are available and all participant visits have been completed.

14. Further Analysis Details

14.1. Statistical Software

For popPK analysis, output will be generated using NONMEM in Unix environment, all other output will be generated using R, Stata (latest versions) or WinNonlin running in a Windows 10 environment.

15. Table of Responsibilities

- Study Statistician (all other analyses): Xue Gong, University of California San Francisco
- Senior Statistician: Patrick Phillips, University of California San Francisco
- Lead data management: Cornea Venter, TECRO.
- Lead pharmacometrician (PK and exposure-response modelling): Dr. Elin Svensson, Radboud University Medical Centre
    - Analyses led by pharmacometrician are described above in sections 8-10. All other analyses will be led by study statistician.
- Sponsor Delegated Person: MeeKyung Lee, Legochem Biosciences, Inc.

  Yunhee Lee, LegoChem Biosciences, Inc.

  Suhyun Park, LegoChem Biosciences, Inc.
- Sponsor Medical Expert: Norbert Heinrich, LMU Munich

- Sponsor Monitor: Erina Pretorius, TCD Global

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Appendix: Shells of tables and listings

This section presents the shells for the planned Tables and Listings to be programmed in support of the planned analyses identified in the SAP. This section is intended to support the SAP and provides guidance on the programming specifications (shells) for the planned outputs and may be updated, with any updates appropriately documented, reviewed, and approved.

1. Demographic and Baseline

Table 1.1 Participant Disposition – All Participants Screened

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Screened for Eligibility						x
Randomized	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Screen Failure [1]						x
Reason 1						x
Reason 2						x
Reason 3						x
Others						x

[1] Participants who have not met eligibility criteria, or otherwise chose not to participate in the study.

Table 1.2 Participant Disposition – All Participants Randomized

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Randomized	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Intent-To-Treat Population [2]	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Adequate adherence (AA) population	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Safety Population	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Completed Study	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Discontinued Early	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Adverse Event	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Subject Withdrawal of Consent	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

[2] The ITT population will consist of all randomized participants in the groups to which they were randomly assigned, and who have taken at least one dose of study treatment.

Table 1.3 Major Protocol Deviations Intent-To-Treat Population

Major Protocol Deviation Category	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Participants with any Major Deviation	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Deviation 1>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Deviation 2>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Deviation 3>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Table 1.4 Demographic and Baseline Characteristics by Treatment Arm*

	Arm 1 D0 (N=x) n (%)	Arm 2 D400 (N=x) n (%)	Arm 3 D800-OD (N=x) n (%)	Arm 4 D1200 (N=x) n (%)	Arm 5 D800-BD (N=x) n (%)	Total (N=x) n (%)
Sex, n (%)						
Female	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Male	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Age (years)						
Mean (SD)	xx	xx	xx	xx	xx	xx
Median	xx	xx	xx	xx	xx	xx
Min – Max	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)
Race, n (%)						
Black	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
White	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Asian	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
American Indian or Alaska Native	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unknown	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Ethnicity, n (%)						
Hispanic or Latino	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Not Hispanic or Latino	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unknown	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Height (cm)						
Mean (SD)	xx	xx	xx	xx	xx	xx
Median	xx	xx	xx	xx	xx	xx
Min – Max	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)
Weigh (kg)						
Mean (SD)	xx	xx	xx	xx	xx	xx

Median	xx	xx	xx	xx	xx	xx
Min – Max	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)
BMI (kg/m²)						
Mean (SD)	xx	xx	xx	xx	xx	xx
Median	xx	xx	xx	xx	xx	xx
Min – Max	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)
HIV Status						
Positive	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Negative	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
TTP at baseline (Median)						
Smear Grade baseline	xx	xx	xx	xx	xx	xx
Bacterial Load in Sputum (GeneExpert)						
≥ 16	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
< 16	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Tobacco Use	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Number of Products Consumed	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Frequency	xx	xx	xx	xx	xx	xx
Alcohol Use	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Number of Products Consumed	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Frequency	xx	xx	xx	xx	xx	xx
Recreational drug use	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Number of Products Consumed	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Frequency	xx	xx	xx	xx	xx	xx

* This table will be repeated for the mITT, AA, and safety population.

Table 1.5 Summary of Prior Medications by Treatment Arm

Prior Medications	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
<Medication 1>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Medication 2>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

<Medication 3>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Medication 4>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Listing 1.1 Summary of Medical History by Subject

Subject ID	Condition	Start Date	End Date	Severity	Ongoing	Pattern of Condition
xxxxxxx	x	x		x	x	x
xxxxxxx	x	x		x	x	x
xxxxxxx	x	x		x	x	x

Table 1.6 Summary of Baseline Culture Results by Randomized Treatment.

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Positive for MTB Complex	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Positive for MTB Complex with contamination	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Negative	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Contaminated	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No Results	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

2. Analysis of Efficacy

<Describe the efficacy analysis and results>

Table 2.1 Summary of Culture Results by Randomized Treatment of Week 00.

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Positive for MTB Complex	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Positive for MTB Complex with contamination	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Negative	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Contaminated	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No Results	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Table 2.2 Summary of Culture Results by Randomized Treatment of Week 02.

{Similar shell table as Table 2.1}

Table 2.3 Summary of Culture Results by Randomized Treatment of Week 08.

{Similar shell table as Table 2.1}

Table 2.4 Summary of Culture Results by Randomized Treatment of Week 12.

{Similar shell table as Table 2.1}

Table 2.5 Summary of Culture Results by Randomized Treatment of Week 14.

{Similar shell table as Table 2.1}

Table 2.6 Summary of Culture Results by Randomized Treatment of Week 16.

{Similar shell table as Table 2.1}

Table 2.7 Summary of Time to Positivity (TTP) by Treatment Arm of Week 00*.

TTP	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Mean (SD)	xx	xx	xx	xx	xx	xx
Median	xx	xx	xx	xx	xx	xx
Min – Max	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)	(xx, xx)

*Same tables will be applied to each week (from week 00 to week 16).

Table 2.8 Analysis of Time to Culture Conversion on Liquid Media.

TTP	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**
25th centile, weeks	xx	xx	xx	xx	xx
Median (50th centile), weeks	xx	xx	xx	xx	xx
75th centile, weeks	xx	xx	xx	xx	xx
Mean	xx	xx	xx	xx	xx

% With culture conversion at 0 week					
% With culture conversion at 2 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 4 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 6 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 8 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 12 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 14 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 16 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
Unadjusted Hazard Ratio (95% CI)	/	xx(xx, xx)	xx(xx, xx)	xx(xx, xx)	xx(xx, xx)
Adjusted Hazard Ratio (95% CI)*	/	xx(xx, xx)	xx(xx, xx)	xx(xx, xx)	xx(xx, xx)

* Analysis has been adjusted for: gender, age, race, BMI, HIV status, baseline culture (using time to positivity)

Table 2.9 Analysis of Time to Culture Conversion on Solid Media.

TTP	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**
25th centile	xx	xx	xx	xx	xx
Median (50th centile)	xx	xx	xx	xx	xx
75th centile	xx	xx	xx	xx	xx
% With culture conversion at 0 week	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 8 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 12 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%

% With culture conversion at 14 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
% With culture conversion at 16 weeks	xx.x%	xx.x%	xx.x%	xx.x%	xx.x%
Hazard Ratio (95% CI)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

Figure 2.1: Kaplan – Meier plot of time to first of two negative culture conversions.

{including Kaplan – Meier plot comparing 4 arms with number at risk/control below}

Table 2.10 Summary of Relapse by Treatment Arm

TTP	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Total in ITT analysis population	xx	xx	xx	xx	xx	xx
Not achieved time to stable culture conversion	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Relapse	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Time to relapse (mean +- SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Reinfection	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Time to Reinfection (mean +- SD)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)	xx (xx)
Death	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Culture positive when last seen	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Culture negative when last seen	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Table 2.11 Summary of Drug resistance by Treatment and Visit:

	Arm 1 D0 (N=x)	**Arm 2 D400 (N=x)**	**Arm 3 D800-OD (N=x)**	**Arm 4 D1200 (N=x)**	**Arm 5 D800-BD (N=x)**	**Total (N=x)**

Number of Participants						
Drug Name of Resistance						
Proportion of Participants developing drug resistance among those not converting to negative culture.						

Listing 2.1 Listing of all Drug Resistance

{This section will list a record of all drug resistance, including drug name, visit number, participant ID etc. F}

{Additional sensitivity analysis will be performed with alternative definitions of time to culture conversion, tables 2.8 and 2.9 will be repeated for each sensitivity definition of time to culture conversion.}

3. Safety Evaluation

3.1 ECG

These tables will be produced for QTcF,QT, PR, RR, QRS.

QTcF:

Table 3.1.1 Summary of QTcF by Treatment Arm

QTcF (Friderica's correction)	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
QTcF < 450 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
450 ms ≤ QTcF <480 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
480 ms ≤ QTcF < 500 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
QTcF ≥ 500 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Table 3.1.2 Participants Proportion of QTcF Changes from Baseline by Treatment Arm

QTcF Changes from Baseline	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Decrease (an increase < 0 ms)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
0 ≤ Increase < 30 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
30 ms ≤ Increase < 60 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Increase ≥ 60 ms	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Table 3.1.3 Summary of QTcF Actual Value by Visit

Visit	**Arm 1 D0 Mean (SE) /N***	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**
Baseline	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

* Number of Participants be analyzed.

Table 3.1.4 Summary of QTcF Changes from Baseline Value by Treatment Arm

Visit	**Arm 1 D0 Mean (SE) /N***	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**

Baseline	0	0	0	0	0
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

QT

Table 3.1.5 Summary of QT Actual Value by Visit

{Similar shell table as Table 3.1.1}

Table 3.1.6 Participants Proportion of QT Changes from Baseline by Treatment Arm

{Similar shell table as Table 3.1.2}

Table 3.1.7 Summary of QT Actual Value by Visit

{Similar shell table as Table 3.1.3}

Table 3.1.8 Summary of QT Changes from Baseline Value by Treatment Arm

{Similar shell table as Table 3.1.4}

PR:

Table 3.1.9 Summary of PR Actual Value by Visit

{Similar shell table as Table 3.1.1}

Table 3.1.10 Participants Proportion of PR Changes from Baseline by Treatment Arm

{Similar shell table as Table 3.1.2}

Table 3.1.11 Summary of PR Actual Value by Visit

{Similar shell table as Table 3.1.3}

Table 3.1.12 Summary of PR Changes from Baseline Value by Treatment Arm

{Similar shell table as Table 3.1.4}

RR

Table 3.1.13 Summary of RR Actual Value by Visit

{Similar shell table as Table 3.1.1}

Table 3.1.14 Participants Proportion of RR Changes from Baseline by Treatment Arm

{Similar shell table as Table 3.1.2}

Table 3.1.15 Summary of RR Actual Value by Visit

{Similar shell table as Table 3.1.3

Table 3.1.16 Summary of RR Changes from Baseline Value by Treatment Arm

{Similar shell table as Table 3.1.4}

QRS

Table 3.1.17 Summary of QRS Actual Value by Visit

{Similar shell table as Table 3.1.1}

Table 3.1.18 Participants Proportion of QRS Changes from Baseline by Treatment Arm

{Similar shell table as Table 3.1.2}

Table 3.1.19 Summary of QRS Actual Value by Visit

{Similar shell table as Table 3.1.3}

Table 3.1.20 Summary of QRS Changes from Baseline Value by Treatment Arm

{Similar shell table as Table 3.1.4}

Heart Rate (HR)
Table 3.1.21 Summary of HR Actual Value by Visit

{Similar shell table as Table 3.1.1}

Table 3.1.22 Participants Proportion of HR Changes from Baseline by Treatment Arm

{Similar shell table as Table 3.1.2}

Table 3.1.23 Summary of HR Actual Value by Visit

{Similar shell table as Table 3.1.3}

Table 3.1.24 Summary of HR Changes from Baseline Value by Treatment Arm

{Similar shell table as Table 3.1.4}

3.2 Safety Laboratory

Serum Chemistry
These tables will be produced for ALT, AST, Total Bilirubin, Gamma-Glutamyl Transferase, Potassium, Alkaline Phosphatase (ALP), Creatinine.

ALT

Table 3.2.1 Summary of Group Mean ALT (x ULN) Changes over time

Visit	**Arm 1 D0 Mean (SE) /N**	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**
Baseline	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

Table 3.2.2 Summary of Absolute value ALT (IU/L) Changes over time

Visit	**Arm 1 D0 Mean (SE) /N**	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**
Baseline	0	0	0	0	0
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

AST

Table 3.2.3 Summary of Group Mean AST (x ULN) Changes over time

{Similar shell table as Table 3.2.1}

Table 3.2.4 Summary of Absolute value AST (IU/L) Changes over time

{Similar shell table as Table 3.2.2}

Total Bilirubin

Table 3.2.5 Summary of Group Mean Total Bilirubin (x ULN) Changes over time

{Similar shell table as Table 3.2.1}

Table 3.2.6 Summary of Absolute value Total Bilirubin (UMOL/L) Changes over time

{Similar shell table as Table 3.2.2}

Gamma-Glutamyl Transferase

Table 3.2.7 Summary of Group Mean Gamma-Glutamyl Transferase (x ULN) Changes over time

{Similar shell table as Table 3.2.1}

Table 3.2.8 Summary of Absolute value Gamma-Glutamyl Transferase (UMOL/L) Changes over time

{Similar shell table as Table 3.2.2}

Alkaline Phosphatase (ALP)

Table 3.2.9 Summary of Group Mean Alkaline Phosphatase (ALP) (x ULN) Changes over time

{Similar shell table as Table 3.2.1}

Table 3.2.10 Summary of Absolute value Alkaline Phosphatase (ALP) (IU/L) Changes over time

{Similar shell table as Table 3.2.2}

Potassium

Table 3.2.11 Summary of Group Mean Potassium (x ULN) Changes over time*

{Similar shell table as Table 3.2.1}

Table 3.2.12 Summary of Absolute value Potassium (mmol/L) Changes over time*

{Similar shell table as Table 3.2.2}

*Tables will be repeated as a sensitivity analysis excluding outliers.

Sodium

Table 3.2.13 Summary of Group Mean Sodium (x ULN) Changes over time*

{Similar shell table as Table 3.2.1}

Table 3.2.14 Summary of Absolute value Sodium (mmol/L) Changes over time*

{Similar shell table as Table 3.2.2}

*Tables will be repeated as a sensitivity analysis excluding outliers.

Creatinine

Table 3.2.15 Summary of Group Mean Potassium (x ULN) Changes over time

{Similar shell table as Table 3.2.1}

Table 3.2.16 Summary of Absolute value Potassium (umol/L) Changes over time

{Similar shell table as Table 3.2.2}

Haematology and Coagulation Results

Platelet Count

Table 3.2.17 Summary of Group Mean Platelet Count Changes over time

{Similar shell table as Table 3.2.1}

Haemoglobin

Table 3.2.18 Summary of Group Mean Platelet Count Changes over time

{Similar shell table as Table 3.2.1}

3.3 Vital Signs

Body Temperature

Table 3.3.1 Summary of Group Mean of Actual Body Temperature Changes over time.

Visit	**Arm 1 D0 Mean (SE) /N**	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**
Baseline	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

Table 3.3.2 Group Mean of Body Temperature Changes from Baseline over time.

Visit	**Arm 1 D0 Mean (SE) /N**	**Arm 2 D400 Mean (SE) /N**	**Arm 3 D800-OD Mean (SE) /N**	**Arm 4 D1200 Mean (SE) /N**	**Arm 5 D800-BD Mean (SE) /N**
Baseline	0	0	0	0	0
Week 01	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 02	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 03	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 04	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 05	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 06	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 07	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 08	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 09	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 10	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 11	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 12	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 13	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 14	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 15	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 16	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 18	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 26	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 38	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N
Week 52	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N	xx (xx.x) / N

Pulse Rate

Table 3.3.3 Summary of Group Mean of Pulse Rate Changes over time.

{Similar shell table as Table 3.3.1}

Table 3.3.4 Group Mean of Pulse Rate Changes from Baseline over time.

{Similar shell table as Table 3.3.2}

Respiration Rate

Table 3.3.5 Summary of Group Mean of Respiration Rate Changes over time.

{Similar shell table as Table 3.3.1}

Table 3.3.6 Group Mean of Respiration Rate Changes from Baseline over time.

{Similar shell table as Table 3.3.2}

Blood Pressure

Systolic Blood Pressure:

Table 3.3.7 Summary of Group Mean of Actual Systolic Blood Pressure Changes over time.

{Similar shell table as Table 3.3.1}

Table 3.3.8 Group Mean of Actual Systolic Blood Pressure Changes from Baseline over time.

{Similar shell table as Table 3.3.2}

Diastolic Blood Pressure

Table 3.3.9 Summary of Group Mean of Actual Diastolic Blood Pressure Changes over time.

{Similar shell table as Table 3.3.1}

Table 3.3.10 Group Mean of Actual Diastolic Blood Pressure Changes from Baseline over time.

{Similar shell table as Table 3.3.2}

3.4 Adverse Events

3.4.1 All Adverse Events

Table 3.4.1: Summary of All adverse Events for Enrolled Participants:

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Total randomized	x	x	x	x	x	x
Number of AEs reported	x	x	x	x	x	x
Number of Participants with AEs	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number of SAEs reported	x	x	x	x	x	x
Number of Participants with SAEs	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number of AEs by Severity	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Grade 1: Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 2: Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 3: Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 4: Life Threatening	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 5: Death	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Participants with AEs by Severity	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Grade 1: Mild	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 2: Moderate	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 3: Severe	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 4: Life Threatening	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Grade 5: Death	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number of AEs by Relatedness to Treatment	**Arm 1 D0 (N=x)**	**Arm 2 D400 (N=x)**	**Arm 3 D800-OD (N=x)**	**Arm 4 D1200 (N=x)**	**Arm 5 D800-BD (N=x)**	**Total (N=x) n (%)**

	n (%)	n (%)	n (%)	n (%)	n (%)	
Unrelated	x	x	x	x	x	x
Unlikely	x	x	x	x	x	x
Possible	x	x	x	x	x	x
Probable	x	x	x	x	x	x
Definitely related	x	x	x	x	x	x
Participants with AEs by Relatedness to Treatment	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Unrelated	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Unlikely	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Possible	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Probable	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Definitely related	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

Table 3.4.2: Summary of All adverse Events for Enrolled Participants by Primary SOCs and PT:

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
All SOCS	x	x	x	x	x	x
Primary SOC 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Primary SOC 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

Table 3.4.3: Summary of All adverse Reactions for Enrolled Participants by Primary SOCs and PT:

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
All SOCS	x	x	x	x	x	x
Primary SOC 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Primary SOC 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

3.4.2 Serious Adverse Events

Table 3.4.4: Summary of All Serious Adverse Events for Enrolled Participants

	Arm 1 D0	**Arm 2 D400**	**Arm 3 D800-OD**	**Arm 4 D1200**	**Arm 5 D800-BD**	**Total (N=x)**

	(N=x) n (%)	(N=x) n (%)	(N=x) n (%)	(N=x) n (%)	(N=x) n (%)	n (%)
Number of SAEs reported	x	x	x	x	x	x
Number of Participants with SAEs	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Number of AEs by Relatedness to Treatment	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Unrelated	x	x	x	x	x	x
Unlikely	x	x	x	x	x	x
Possible	x	x	x	x	x	x
Probable	x	x	x	x	x	x
Definitely related	x	x	x	x	x	x
Participants with AEs by Relatedness to Treatment	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
Unrelated	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Unlikely	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Possible	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Probable	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Definitely related	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

Table 3.4.5: Summary of Serious adverse Events for Enrolled Participants by Primary SOCs and PT:

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
All SOCS	x	x	x	x	x	x
Primary SOC 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Primary SOC 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

Table 3.4.6: Summary of Serious adverse Reactions for Enrolled Participants by Primary SOCs and PT:

	Arm 1 D0 (N=x) n (%)	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
All SOCS	x	x	x	x	x	x
Primary SOC 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
Primary SOC 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 1	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)
PT 2	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)	x (xx.x%)

Listing 3.1. Listing of All Serious Adverse Events for Enrolled Participants:

ID	DIAGNOSIS	START DATE	END DATE	OTHER DIAGNOSIS	SEVERITY	CAUSALITY TO IMP	DATE OF TREATMENT ASSIGNMENT	ARM
XXXXX	xxx	DD/MM/YYYY	DD/MM/YYYY	xxx	Grade 1/2/3/4	xxx	DD/MM/YYYY	Arm 1/2/3/4/5
XXXXX	xxx	DD/MM/YYYY	DD/MM/YYYY	xxx	Grade 1/2/3/4	xxx	DD/MM/YYYY	Arm 1/2/3/4/5
XXXXX	xxx	DD/MM/YYYY	DD/MM/YYYY	xxx	Grade 1/2/3/4	xxx	DD/MM/YYYY	Arm 1/2/3/4/5

3.5 Concomitant Medication

Table 3.5.1 Summary of Concomitant Medications by Randomized Treatment

Concomitant Medications	**Arm 1 D0 (N=x) n (%)**	**Arm 2 D400 (N=x) n (%)**	**Arm 3 D800-OD (N=x) n (%)**	**Arm 4 D1200 (N=x) n (%)**	**Arm 5 D800-BD (N=x) n (%)**	**Total (N=x) n (%)**
<Medication 1>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Medication 2>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Medication 3>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
<Medication 4>	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)