Reporting and Analysis Plan

Study ID: 201214

Official Title of Study: Reporting and Analysis Plan for a Phase IIa open-label trial to investigate the early bactericidal activity, safety and tolerability of GSK3036656 in participants with drug sensitive pulmonary tuberculosis.

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Compound Number	:	GSK3036656
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Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol TMF-13331420.

- This RAP is intended to describe analysis requirements during the study to support the dose escalation analyses and the final analyses required for the study in terms of conveying the content of the Statistical Analysis Complete (SAC) deliverable.

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1.   INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Protocol Revision Chronology:		
2017N332005_00	09-FEB-2018	Original
2017N332005_01	20-FEB-2018	Protocol Amendment 1: CCI
2017N332005_02	24-SEP-2018	Protocol Amendment 2: The primary motivation for this amendment was to update the eligibility criteria to impose a minimum renal function (as defined by creatinine clearance) in light of the first-in-human data that showed the main route of clearance for GSK3036656 is through the kidneys. As a result of the long half-life of GSK3036656, an updated dosing strategy has also been implemented incorporating the use of loading doses.
2017N332005_03	24-JUL-2019	Protocol Amendment 3: To document the increase in exposure limits and change in eligibility criteria following the availability of new non-clinical data.
TMF-11820616	17-FEB-2021	Protocol Amendment 4: To allow for standard of care medication administered in the study to be either Rifafour e-275 or an equivalent generic alternative and to allow for analysis of the primary endpoint data to be performed on additional cohorts.
TMF-13331420	12-MAY-2021	Protocol Amendment 5: Variability in the rate of change of log10CFU observed in the trial to-date is lower than anticipated. Due to this, and slower than anticipated recruitment, the study sample size has been re-calculated. The potential to modify the haemoglobin exclusion and stopping criteria in subsequent cohorts investigating lower doses of GSK3036656 has been added.

1.1. RAP Amendments

RAP Version	Approval Date	Protocol Version (Date) on Which RAP is Based	Change	Rationale
Reporting and Analysis Plan 201214 Final V1	11-DEC-2018	Protocol Amendment 2 (24-SEP-2018)	N/A	Original Version
Reporting and Analysis Plan 201214 Amendment1 V0.1	Refer to document date	Protocol Amendment 5 (12-MAY-2021)	1. Section 2.3: Study Design – The number of participants per treatment arm has been changed from 20 to 12-20. 2. Section 7.1.5.1: Statistical Methodology Specification – For the analysis of the primary endpoint a mixed model with repeated measures analysis has been added as the primary analysis. Dose has been replaced by treatment, with data for participants receiving standard-of-care included, and BMI has been added as a covariate. 3. Section 10: Additional Analyses Due to the COVID-19 Pandemic – Additional study population and safety displays have been added. 4. Section 12.4.1.2: Phases of COVID-19 Pandemic measures – details have been added as to how to	1. The required number of participants for the later cohorts was reduced in protocol amendment 5. 2. A repeated measures analysis, including day as a covariate is more appropriate for measuring the rate of change over the entire 14 day treatment period. It is important to understand the effect of SoC on the endpoint. BMI has a potential influence on the EBA endpoints. 3. In order to understand the impact of the COVID-19 pandemic on the study conduct and the results, additional summaries are required. 4. The COVID-19 pandemic began at different times in

			determine when the pandemic began for the categorisation of AEs. 5. Minor clarifications and corrections.	different countries with multiple waves. Guidance is therefore required for determining timings. 5. Minor clarifications and corrections have been made where wording was ambiguous/vague or errors were identified to improve the accuracy and comprehensiveness of the RAP.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

The change or deviation to the originally planned statistical analysis specified in the protocol amendment 5 [(Dated: 12/MAY/2021)] is mentioned below.

Protocol	RAP	Rational
Section 10.3.1: Activity/ Pharmacokinetic Analyses	Section 7.1.5.1: Model 2: Bi-linear Bayesian regression model	The model 2 Bi-linear regression analysis has been added as an additional supportive analysis. This is recommended for the analysis of EBA endpoints in TB due to them sometimes following a bi-linear rate of change.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To determine the early bactericidal activity of GSK3036656 over 14 days of once daily repeat dosing.	• Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period baseline to Day 14 (EBA CFU$_{0-14}$).
Secondary Objectives	**Secondary Endpoints**
• To assess the safety & tolerability of GSK3036656 administered once daily over 14 days to patients with tuberculosis.	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG) parameters.
• To characterise the pharmacokinetics of 14-day once daily dosing of GSK3036656 in tuberculosis patients	• Derived pharmacokinetic parameters for GSK3036656 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC (0-24)), maximum observed plasma drug concentration (Cmax), and time to maximum observed plasma drug concentration (tmax), as appropriate.
• To determine the early bactericidal activity of GSK3036656 over the first 2 days and the last 12 days with 14 days of once daily repeat dosing.	• Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period baseline to Day 2 (EBA CFU$_{0-2}$). • Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period Day 2 to Day 14 (EBA CFU$_{2-14}$). • Rate of change in time to sputum culture

Objectives	Endpoints
	positivity (TTP) over the time period baseline to Day 14 (EBA TTP_{0-14}) • Rate of change in time to sputum culture positivity over the time period baseline to Day 2 (EBA TTP_{0-2}) • Rate of change in time to sputum culture positivity over the time period Day 2 to Day 14 (EBA TTP_{2-14})
Exploratory Objectives	**Exploratory Endpoints**
CCI	

For the purpose of assessment of bacterial CCI endpoints, the pre-treatment baseline will be defined as the mean of Day −2 and Day −1; if data is available at only Day −2 or Day −1 then that value will be used as baseline. For ECG endpoints, baseline is screening. CCI

2.3. Study Design

Overview of Study Design and Key Features	
This is not part of the study but is the post-study definitive treatment of TB.	
Design Features	• A single-centre, open-label trial in up to five sequential cohorts. • Each cohort will involve participants being randomised to one of two possible treatments: either GSK3036656 or Standard-of-Care (SoC) regimen (e.g. Rifafour®e-275) for rifampicin-susceptible (drug sensitive) tuberculosis (DS-TB). • Screening will be performed on days -9 to -1, followed by 14 days of once daily dosing and a follow-up visit 28 days after the first dose. • All laboratory staff involved in analysing and reporting the primary and secondary change in CFU counts and TTP endpoint results will be blinded to treatment allocation.
Dosing	• Once daily repeat dosing for 14 days. • The starting dose for the GSK3036656 arm is a 15mg loading dose on Day 1 and 5mg maintenance dose on Days 2-14, given orally. The study will employ dose escalation, where the GSK3036656 dose for each cohort will be decided based on reviews of preliminary safety, tolerability and pharmacokinetic data; in addition, efficacy data will be considered if available.
Time & Events	• See Appendix 2: Schedule of Activities
Treatment Assignment	• 12-20 participants in each cohort (excluding possible replacements), randomised 3:1 to GSK3036656 or Standard of Care respectively. • GSK RandAll NG will be used to generate the randomisation schedule.
Dose Escalation Analysis	• No formal interim analysis is planned. • Safety, tolerability and pharmacokinetic data will be reviewed before each dose escalation. • The primary endpoint may be analysed (including data from all available cohorts) as part of the dose escalation analyses. The earliest this can occur is after the final visit of the last subject on the second consecutive cohort that reaches or exceeds the target PK plasma exposure for efficacy..

2.4. Statistical Analyses

The primary endpoint, EBA CFU_{0-14}, will be analysed using a mixed effects model including treatment, day, BMI and treatment-by-day as covariates. Secondary endpoints of EBA CFU_{0-2}, CFU_{2-14}, TTP_{0-2}, TTP_{0-14} and TTP_{2-14} will be analysed similarly to the primary endpoint. See Section 7: Efficacy Analyses for further details.

Plasma concentration-time data will be analysed by non-compartmental methods, the following pharmacokinetic parameters will be determined: Maximum observed plasma drug concentration (Cmax), Time to maximum observed plasma drug concentration (tmax), Area under the concentration-time curve from time of dosing to last quantified concentration, regardless of time (AUC(0-t)), Area under the concentration-time curve from time of dosing extrapolated to 24 hours (AUC(0-24)) and Trough Concentration (Cτ). AUC(0-t) or AUC(0-24) and Cmax may be used for assessment of dose proportionality. Trough concentration (Cτ) samples will be used to assess attainment of steady state. See Section 9 for further details.

Safety data, including AEs, clinical laboratory values, vital signs and ECG, will be summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. See Section 8: Safety Analyses for further details.

3.   PLANNED ANALYSES

3.1.   Interim Analyses

No formal interim analyses are planned for this study. However, safety, tolerability and pharmacokinetic data will be reviewed before each dose escalation. In addition, the primary endpoint may be analysed, including data from all available cohorts, after the final visit of the last subject on the second consecutive cohort that reaches or exceeds the target PK plasma exposure for efficacy.

Dose Escalation

Pharmacokinetic (PK) Analysis

Dose escalation will primarily be based on population PK modelling.

The population PK model will be a fit for purpose model. Candidate model selection will be primarily based on a significant reduction in the objective function value (≥ 3.32, $\chi 2$ <0.05) and improvement in the fits of diagnostic scatter plots. Inter-individual variability will be modelled using an exponential error model and residual error will be described by a proportional, proportional plus additive, or additive error model, depending on the data. Model performance will be evaluated using a visual predictive check. Simulations for dose recommendations will be conducted to determine the probability of an individual participant exceeding the defined exposure margins for AUC_{0-24} (4.9 µg.h/mL) and Cmax (0.443 ug/mL).

Alternatively, if a population PK model is not feasible, dose escalation will be based on a dose-exposure model of the form:

$\log(AUC) = a + b*\log(DOSE) + c*\log(BWT/70)$

$\log(CMAX) = d + e*\log(DOSE) + f*\log(BWT/70)$

where a and d are AUC and Cmax values, respectively; c = -0.75 and f = -1.00 are set values for allometric scaling; and b and e are scaling factors for dose proportionality.

Efficacy Analysis

In addition to the PK modelling, the primary endpoint may be analysed including data from all available cohorts, after the final visit of the last subject from the second consecutive cohort that reaches or exceeds the target PK plasma exposure for efficacy. The purpose of this efficacy analysis is to optimise dosing for subsequent cohorts (e.g. to help estimate the dose response curve) as well as to aid internal decision making. If this cohort is the fifth (final) cohort then the efficacy analysis will be performed as part of the final SAC deliverable. The primary endpoint will be analysed as planned for the final analysis, see Section 7: Efficacy Analyses.

The efficacy analyses will be performed after the completion of the following sequential steps:

1. All participants in the current cohort have completed their Day 15 study visit as defined in the protocol.

2. Data have been made available by Data Management (no specific data cleaning requirements for the efficacy analysis).

3. All criteria for unblinding the randomization codes have been met.

4. Randomization codes have been distributed according to RandAll NG procedures.

3.2.   Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.

2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

3. All criteria for unblinding the randomization codes have been met.

4. Randomization codes have been distributed according to RandAll NG procedures.

4.   ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility	• Study Population
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to. • Any participant who receives a treatment randomization number will be considered to have been randomized.	• Study Population
Enrolled	• All participants who passed screening and entered the study. Included are run-in failures and randomized participants. • Note: screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• All randomized participants who received at least one dose of study treatment.	• Safety

Population	Definition / Criteria	Analyses Evaluated
	• Participants will be analysed according to the treatment they actually received. • Note: Participants who were not randomized but received at least one dose of study treatment should be listed.	
Efficacy	• All participants in the safety population who provided at least two evaluable overnight sputum samples. • This population will be based on the treatment the participant was randomized to.	• Efficacy
Pharmacokinetic (PK)	• Participants in the safety population who received at least one dose of GSK3036656 and have at least one evaluable PK sample. • Participants will be analysed according to the treatment actually received.	• PK

For participants who receive the incorrect treatment (i.e. a different treatment to what they were randomised to), the participants will be assigned to the actual treatment groups if they received that treatment for more than 50% of their doses.

4.1.   Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the latest Protocol Deviation Management Plan (PDMP).

- o Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- o This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		**Data Displays for Reporting**	
Code	**Description**	**Description[1]**	**Order in Tables, Figures and Listings**
SOC	Standard of Care (Rifafour)	Rifafour	1
D1	GSK3036656 Dose 1	GSK3036656 5 mg	2
D2	GSK3036656 Dose 2	GSK3036656 15 mg	3
D3	GSK3036656 Dose 3	GSK3036656 30 mg	4
D4	GSK3036656 Dose 4	GSK3036656 X mg	5
D5	GSK3036656 Dose 5	GSK3036656 X mg	6

Note:
- The decision to proceed to each subsequent dose level will be made by the dose escalation committee.
- In tables, figures and listings, treatments should be presented with standard of care (Rifafour) first, then in order of increasing dose.
- [1] 'X mg' is to be replaced by actual maintenance dose.

5.2. Baseline Definitions

For all endpoints, except those noted below, the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits (e.g. if Day 1 (pre-dose) is missing, Day -1 will be used). If there are no pre-dose data, then no derivation will be performed, and baseline will be set to missing.

For bacterial endpoints, baseline will be calculated as the mean of Day -2 and Day -1; if data are available at only one of these timepoints then that value will be used as baseline (i.e. data prior to Day -2 will not be used for calculation of baseline, even in the event there is missing data for both Day -2 and Day -1).

Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that timepoint.

If time is missing, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

5.3.   Examination of Covariates

For the analysis of CFU and TTP, the demographic variable of Body Mass Index (BMI) will be included as a covariate in the model, see Section 7: Efficacy Analyses for further details.

Additional covariates of age (continuous), creatinine clearance (continuous), HIV status (yes/no), diabetes status (yes/no), smoking status (<20 or >=20/day) and baseline cavities (yes/no) will be investigated in an exploratory manner to assess their importance in future possible analyses.

5.4.   Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety population, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

Data from the standard of care arm will be pooled for the analysis, except for the display of Summary of Participant Disposition at Each Study Epoch, which will be displayed by cohort.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

Rate of change in $\log_{10}$ colony forming units ($\log_{10}$CFU) per ml direct respiratory sputum samples over the period baseline to Day 14 (EBA CFU_{0-14}).

7.1.2. Summary Measure

Mean daily rate of change in $\log_{10}$CFU for each treatment group.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the efficacy population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The primary treatment effect to be estimated will be the while on treatment effect of initial randomised treatment.

All recorded data up to the time of study withdrawal will be included in the analysis, regardless of discontinuation of study medication.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1.　Statistical Methodology Specification

Endpoint
• Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period baseline to Day 14.

Model Specification

Model 1:
- Mixed model repeated measures analysis. Terms in the model:
  - **Response**: $\log_{10}$CFU
  - **Categorical**: treatment
  - **Continuous**: time, BMI
  - **Interaction**: treatment*time
  - **Random**: Subject

Model 2:

In addition, to characterize any bi-linear characteristics a bi- linear Bayesian regression model of the following form will also be fitted:

$$y_i = \begin{cases} normal\,(\alpha + \beta_1(t_i - cp), \sigma^2) & if\ t_i < cp \\ normal\,(\alpha + \beta_2(t_i - cp), \sigma^2) & if\ t_i \geq cp \end{cases}$$

- Where cp=change (node) point as determined by the data (separate nodes for each treatment group), and t=time.
- The model will include terms for intercept, BMI, treatment, treatment*day before node, treatment*day after node, subject.
- This model would utilize uninformative uniform priors for cp and σ^2 (discrete uniform(2,13) and uniform(0,5) respectively) and uninformative normal priors for the intercept, treatment, baseline $\log_{10}$CFU and BMI (normal(0,var=1000000)). Subject will be a random effect with an uninformative prior (normal(0,var), where var=uniform(0,5).
- The efficacy population will be used for both models.
- Data from the standard of care arm will be pooled for the analysis.
- Where CFU plate counts are Too Numerous To Count (TNTC) a value of 2500 should be imputed for both models.

Model Checking & Diagnostics

Model 1: Mixed model repeated measures analysis:
- An autoregressive 1 covariance structure will be used. In the event this fails to converge alternative covariance structures may be considered such as VC.
- The Kenward and Roger method for approximating the denominator degrees of freedom will be used.
- Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumptions and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data (e.g. square root).

Model 2: Bi-linear Bayesian regression model:

- The convergence will be examined using trace plots: All chains' trace plots will be inspected visually, to assess the mixing of each chain. Convergence is indicated when all chains appear to be mixing well and overlapping each other randomly (no chain's convergence is indicated until the chains of all model parameters appear well-mixed).
- Additional convergence diagnostics, such as Monte Carlo Standard Error divided by the standard deviation of the posterior distribution (MCSE/SD), Gelman-Rubin statistic, effective sample size (ESS) and autocorrelation plots may also be reviewed.
- The modelling will be subject to independent quality control. The final parameter estimates for the mean slopes and the mean node point should be within two times the Monte Carlo Standard Error (2xMCSE).

Model Results Presentation

- Model 1: Summary of the mean daily rate of change, standard deviation and associated 95% confidence interval will be presented for each treatment arm.
- Model 2: The mean and 95% highest posterior density (HDP) interval of the node, slope parameter before node and slope parameter after node, will be presented for each treatment arm.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- A sensitivity analysis will be performed (Model 1 only) excluding participants who withdraw from the study before Day 10 and/or who were replaced during the study.
- Additional covariates (see Section 5.3) will be investigated in an exploratory manner using a mixed model repeated measures analysis. Each covariate will be investigated separately utilizing the model described for the primary endpoint. First the primary endpoint model will be fitted but including the covariate of interest and then the primary endpoint model will be fitted including both the covariate and treatment-by-covariate interaction.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

- Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period baseline to Day 2 (EBA CFU_{0-2}).

- Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period Day 2 to Day 14 (EBA CFU_{2-14}).

- Rate of change in time to sputum culture positivity (TTP) over the time period baseline to Day 14 (EBA TTP_{0-14})

- Rate of change in time to sputum culture positivity (TTP) over the time period baseline to Day 2 (EBA TTP_{0-2})

- Rate of change in time to sputum culture positivity (TTP) over the time period Day 2 to Day 14 (EBA TTP_{2-14})

7.2.2. Summary Measure

Mean daily rate of change in $\log_{10}CFU$ or TTP for each treatment group.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the efficacy population, unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

The treatment effect to be estimated will be the while on treatment effect of initial randomised treatment.

All applicable recorded data up to the time of study withdrawal will be included in the analysis, regardless of discontinuation of study medication.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.5.1. Statistical Methodology Specification

Endpoint
• Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period baseline to Day 2.   • Rate of change in time to sputum culture positivity (TTP) over the time period baseline to Day 2 (EBA TTP_{0-2})
Model Specification

• Mixed models repeated measures analysis.
 • Terms in the model:
     • **Response**: $\log_{10}$CFU or TTP as appropriate
     • **Categorical**: treatment
     • **Continuous**: time, BMI
     • **Interaction:** treatment*time.
     • **Random**: Subject
 • Efficacy population
 • Data from the standard of care arm will be pooled for the analysis.

Model Checking & Diagnostics
• Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumptions and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.   • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data (e.g. log transformation (to base 10 for TTP), square root).
Model Results Presentation
• Summary of the mean, standard deviation, standard error and associated 95% confidence interval for each treatment arm.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity or supportive analyses are planned for this endpoint.

Endpoint
- Rate of change in $\log_{10}$CFU per ml direct respiratory sputum samples over the period Day 2 to Day 14.   - Rate of change in time to sputum culture positivity (TTP) over the time period baseline to Day 14 (EBA TTP_{0-14})   - Rate of change in time to sputum culture positivity (TTP) over the time period Day 2 to Day 14 (EBA TTP_{2-14})
Model Specification
- As described for the primary endpoint, see Section 7.1.5, except: - For the models for Days 2-14, baseline $\log_{10}$CFU (or baseline TTP for TTP (2-14) should be included as a continuous covariate.   - For the TTP endpoints, the data may be log transformed using base 10 if the residuals do not follow a normal distribution.
Model Checking & Diagnostics
As described for the primary endpoint, see Section 7.1.5.
Model Results Presentation
As described for the primary endpoint, see Section 7.1.5.
Subgroup Analyses
No subgroup analyses are planned for these endpoints.
Sensitivity and Supportive Analyses
No sensitivity or supportive analyses are planned for these endpoints.

7.3. Exploratory Efficacy Analyses

7.3.1. Endpoint / Variables

CCI

These exploratory endpoints will be analysed and reported separately.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards.

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

Listings of the troponin data and mycobacterial data will be produced.

9. PHARMACOKINETIC ANALYSES

9.1. Secondary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

Derived PK parameters: AUC(0-t) or AUC(0-24), Cmax, tmax and Cτ.

9.1.2. Summary Measure

- Dose proportionality of AUC(0-t) or AUC(0-24)
- Dose proportionality of Cmax
- Achievement of Steady State (Cτ)
- Summary statistics for tmax

9.1.3. Population of Interest

The PK analyses will be based on the PK population, unless otherwise specified.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

- The treatment effect to be estimated will be the while on treatment effect of actual received treatment.
- All applicable recorded data up to the time of the intercurrent event will be included in the analysis.

9.1.5. Statistical Analyses / Methods

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

For each of the parameters Cmax, tmax, AUC(0-t), AUC(0-24), Cτ the following summary statistics will be calculated and tabulated by dose group:

- Untransformed data: N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum

The following additional summary statistics will be calculated and tabulated by dose group, for the parameters Cmax, AUC(0-t), AUC(0-24) and Cτ.

- Log-transformed data: Geometric mean, 95% CI for the geometric mean, SD, between participant coefficient of variation (%CVb)

%CVb will be calculated as: CVb (%) = $\sqrt{(\exp(SD^2) - 1)} * 100$

Where SD = SD of $\log_e$ transformed data

9.1.5.1.   Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data are available (i.e. if participants have well-defined plasma profiles).

Endpoint
• Dose proportionality of AUC(0-t) or AUC(0-24)   • Dose proportionality of Cmax
Model Specification
• This will be analysed using a power model: $y = \alpha * dose^{\beta}$ where y = PK parameter being analysed (i.e. AUC or Cmax) and α = participant.   • Log_e transformed data will be analysed by fitting the following terms in the mixed effect model: Fixed, continuous effect: $\log_e(dose)$ Random effect: Participant   • The Kenward Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.   • An unstructured (UN) covariance structure for the G matrix will be used.   • For AUC, AUC(0-24) will be analysed where calculable; where doses do not have quantifiable concentrations at 24 hours, AUC(0-t) will be analysed.   • PK population   • Data from at least three doses must be available to perform the dose proportionality analysis.   • A slope ≈ 1 implies dose proportionality
Model Checking & Diagnostics
• If the model does not converge, the random participant effect will be removed from the model.
Model Results Presentation
• Estimates of the mean slopes of $\log_e(dose)$ will be reported along with corresponding 90% confidence intervals.   • A figure of log(dose) vs log(AUC) will be presented in the form of a scatterplot of all individual participant values, along with a regression line and associated 95% confidence interval. A similar plot will be produced for log(dose) vs log(Cmax).

Endpoint
• Achievement of Steady State (Cτ)
Model Specification
• This will be analysed using a mixed model:

Fixed effects: $\log_e$(dose), day, $\log_e$(dose)*day

Random effect: participant

Day will be treated as a continuous variable, dose as a categorical variable.

- The dose-by-day interaction will be tested for its significance at the 5% level, if the interaction is not significant then a single point estimate for all dose levels pooled will be calculated in addition to the individual dose levels.

- The Kenward Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

- An unstructured (UN) covariance structure for the G matrix will be used.

    - In the event that this model fails to converge, alternative covariance structures may be considered such as variance components (VC) or compound symmetry (CS).

    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.

Model Checking & Diagnostics

- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively).

- If there are any departures from the distributional assumptions, alternative transformations, such as data squared or square root of data, will be explored.

- Non-parametric analyses will be conducted if the normality assumption does not hold.

Model Results Presentation

- The coefficients of the slopes for the day effect for each dose, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved.

- If the interaction is not significant, then a single point estimate and corresponding 90% confidence interval for all dose levels pooled will be presented.

- Trough concentration levels collected pre-morning dose will be plotted by collection day and dose.

10. ADDITIONAL ANALYSES DUE TO THE COVID-19 PANDEMIC

10.1. Study Population

10.1.1. Subject Disposition

The 'Summary of Subject Status and Subject Disposition for the Study Conclusion Record' and the 'Summary of Treatment Status and Reasons for Discontinuation of Study Treatment' will include the reason withdrawal/discontinuation due to issues related to the COVID-19 pandemic. In addition, these two summaries will be repeated, with the reason for withdrawal/discontinuation categorised as related to COVID-19 pandemic, or non-related to COVID-19 pandemic. The summaries will be based on GSK Core Data Standards, and details are provided in Appendix 10: List of Data Displays.

10.1.2. Protocol Deviations

In addition to the overall summary of important protocol deviations, separate summaries will be produced of important protocol deviations related to COVID-19, and important protocol deviations not related to COVID-19. A listing of non-important protocol deviations related to COVID-19 will also be produced.

10.2. Safety

10.2.1. Assessment of COVID-19 AEs

A standardised MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

The incidence of AEs and SAEs (Fatal and Non-Fatal) of COVID-19, COVID-19 AEs leading to study drug discontinuation and COVID-19 AEs leading to study withdrawal will be obtained from standard AE and SAE summaries.

10.2.2. Impact of COVID-19 Pandemic on Safety Results

The following tables will be produced, showing the incidence rates for events occurring before or after the start of the COVID-19 pandemic. The phases (before and after the start of the COVID-19 pandemic) are defined in Section 12.4.1.2:

- Summary of exposure adjusted incidence rates of adverse events
- Summary of exposure adjusted incidence rates by age

- Summary of COVID-19 assessments for subjects with COVID-19 Adverse events

The above displays will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

11. REFERENCES

Burger D, Schall R. A Bayesian nonlinear mixed-effects regression model for the characterisation of early bactericidal activity of tuberculosis drugs. *Journal of Biopharmaceutical Statistics, 25: 1247-1271 (2015).*

GlaxoSmithKline Document Number 2017N332005_02 (Amendment 2 – 24-SEP-2018): A Phase IIa open-label trial to investigate the early bactericidal activity, safety and tolerability of GSK3036656 in participants with drug-sensitive pulmonary tuberculosis.

GlaxoSmithKline Document Number 2018N381501_00: Data Analysis and Reporting Plan (DAP) for Population pharmacokinetic studies.

GUI_137354, Information for Authors: Reporting and Analysis Plan (RAP), Global

GUI_51487, Non-Compartmental Analysis of Pharmacokinetic Data, CPMS Global

SOP_54838, Development, Review & Approval of Reporting & Analysis Plan (RAP), Global

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management and Definitions for PK and Efficacy Population

There are no pre-defined categories leading to exclusion from the PK population, but all protocol deviations will be reviewed on a case-by-case basis.
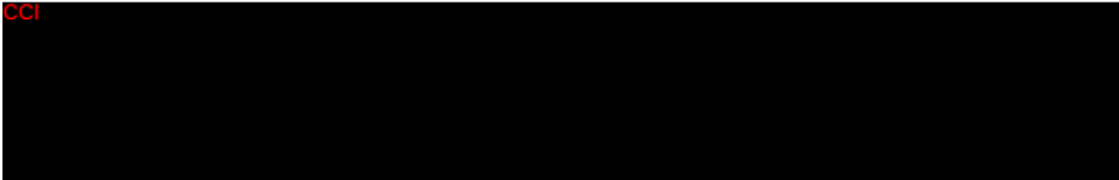
Any participant in the safety population who does not provide at least two evaluable overnight sputum samples will be excluded from the efficacy population. All other protocol deviations will be reviewed on a case-by-case basis.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Period	Screening			Dosing						Follow-up	
Visit	1	2	3	4	5 to 10	11	12 to 16	17	18	Early Withdrawal	19
Day	(-9 to -3) A	-2 B	-1	1	2 to 7 C	8	9 to 13 C	14	15		28 (± 7)
Documentation of Positive GeneXpert and/or TB smear (TB clinic/site of initial diagnosis)	X										
Written Informed Consent	X										
Demography (including smoking history)	X										
Medical & Treatment History	X										
Inclusion/Exclusion/Eligibility Assessment		X									
Chest X-ray		X									
Physical Examination D	X			X	X	X	X	X	X	X	X
Vital Signs E	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X								X	X	X
Randomisation M		X									
Echocardiogram (may be conducted at any of the screening visits)		X								X5	X5
Blood PK F							XF	X	X	X	
Spot Sputum (confirm TB & adequate bacterial load) G	X										
Rifampicin Resistance Test (rapid)G (microscopy and GeneXpert tests may be repeated on an overnight sputum sample if needed)	X										
Haematology, Clinical Chemistry, Urinalysis H	X			X	X	X		X		X	X
Cardiac safety biomarkers T		X		X	X			X			
Urine Drug Screen I	X	XI									
HIV Test (and CD4 Count if HIV confirmed)	X										
CCI				X	X			X		X	
				X	X			X		X	
			X						X		
Hospital Admission	XB	XB									

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Period	Screening			Dosing						Follow-up	
Visit	1	2	3	4	5 to 10	11	12 to 16	17	18	Early Withdrawal	19
Day	(-9 to -3) A	-2 B	-1	1	2 to 7 C	8	9 to 13 C	14	15		28 (± 7)
Overnight Sputum L	X	X	X	X	X	X	X	X			
IP Administration and Compliance Check N				X	X	X	X	X			
Mycobacteriology Assessments O		X	X					X			
Hospital Discharge									X	X	
Concomitant Medication		X	X	X	X	X	X	X	X	X	X
Adverse Events P				X	X	X	X	X	X	X	X
Point of Care Blood Glucose or HbA1c Q			X					X			

a. The Visit 1 (day -9 to -3) time period will be up to a maximum of 7 days but will be kept as short as possible.

b. Participants can proceed with the Visit 2 (day -2) assessments as soon as their Visit 1 (day -9 to -3) assessments have been completed i.e. Visits 1 and 2 may occur on the same day as long as the screening results are available in time for randomisation. Participants may be hospitalised during the entire pre-treatment period if the Investigator considers it advisable for reasons of safety or compliance.

c. All events listed as occurring on Visit 5 (day 2) to Visit 10 (day 7) and Visit 12 (day 9) to Visit 16 (day 13) will be conducted each day during these visits.

d. Height (m) will only be collected once at Visit 1 (day -9 to -3). A full physical examination will be performed at Visit 1 (day -9 to -3), with symptom-directed physical examinations at Visit 17 (day 14), Visit 19 (day 28) and Early Withdrawal Visit (EWV). Symptom directed physical examinations may be conducted as required during the study (visits 4 to 16). Requirements for the physical examination are specified in the SRM.

e. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg), heart rate (beats per minute [bpm]), body temperature (°C), respiratory rate (breathes per minute) and weight (kg). To be performed within 4 hours prior to the first daily dosing on Visit 4 (day 1) through to Visit 17 (day 14) and within 4 hours before the time dosing would have occurred on Visit 18 (day 15). On days where the following assessments are done the order should be: vital signs before blood draws for PK or safety assessments.

f. PKs will be performed as noted in the PK table. A single pre-dose PK sample will be collected on each of Days 12 & 13, and serial PK blood sampling will occur on Day 14 (see PK table below). At EWV a PK sample will be taken before the time of the planned daily dosing. If this is not possible, a spontaneous PK sample will be taken.

g. Sputum smear microscopy and molecular rapid test for confirmation of Mycobacterium tuberculosis and rifampicin susceptibility (GeneXpert). If the first spot sputum or overnight sputum sample shows an unfavourable result, the tests may be repeated on a freshly collected spot sputum or overnight sputum sample and that result used instead.

h. Refer to Appendix 3 for details.

i. Urine drug screen: cocaine, amphetamines and opiates. Urine drug screen can be repeated at Visit 2 (day -2) for participants who were not hospitalized at Visit 1 (day -9 to -3).

j. CCI

k.

l. Overnight sputum sampling may start at Screening visit (day -9 to -3) or on Visit 2 (day –2) and will continue daily until Visit 7 (day 4). Additional sampling will be conducted at visit 9 (day 6), Visit 11 (day 8), Visit 13 (day 10), Visit

15 (day 12) and Visit 17 (day 14). Sputum sampling will stop on the morning of Visit 18 (day 15). Sputum collection will start in the afternoons at 15:00 hours (±1 hour) and continue for 16 hours overnight. The 16-hour sputum sampling for each of the sampling days must be finished prior to the administration of the next day's IP. Overnight sputum collection may be collected as many times as required over the screening period until an eligible sample is obtained. Of the pre-treatment period samples collected, only the Visit 2 (day-2) and Visit 3(day -1) overnight sputum samples will be used for the efficacy endpoint tests.

The day sputum collection starts reflects the day to which that sample applies. e.g. a sample whose collection starts on day 1 and ends on day 2, is designated as the day 1 overnight sputum sample (and results).

m. Randomization may occur once all the screening results are available and the Investigator has determined that the participant is eligible for the trial.

n. After the first dose of IP, subsequent doses of IP will be administered 23 to 25 hours after the previous dose.

o. Minimum inhibitory concentration (MIC) and speciation of the infecting organism by polymerase chain reaction (PCR) will be estimated from a culture collected on a pre-treatment day (day-1 or day-2) and from the last available culture on a treatment day (day 14 or earlier, but not earlier than day 8). Drug susceptibility testing of *M. tuberculosis* for sensitivity to rifampicin with a molecular method will be tested at Visit 1. Susceptibility to INH, Rif, EMB and PZA will be tested on a culture grown from a baseline sample (day -2 or day -1). The analysis of any bacterial isolates sent to GSK, Spain for further characterisation in the event of MIC change will not be reported in the clinical study report and will be reported separately.

p. Adverse events (AE) will be collected by the Investigator from the time a participant receives his/her first dose of IP through to the Visit 19 (day 28) Follow up Visit.

q. CCI

r. *[not used]*

s. Only to be performed on participants as determined by the dose escalation committee (DEC) or on participants with changes in clinical status warranting a follow-up echo in the opinion of the investigator. The DEC may decide to perform this assessment in additional cohorts within this study.

t. Samples will be assayed for: Troponin I. The first two samples at least 24 hours apart, one during the screening phase and one prior to the first dose of study treatment. Day 14 sample window is ±24 hours. Third sample to be taken on Day 3.

PK sampling time and events table

STUDY VISIT	Visit 15	Visit 16	Visit 17										Visit 18
STUDY DAY	Day 12	Day 13	Day 14										Day 15
STUDY HOUR[B]			0	0.5	1	1.5	2	3	4	6	8	12	24
Pharmacokinetic sampling[C]	X[A]	X[A]	X[D]	X	X	X	X	X	X	X	X	X	X

A. Sample to be taken within 30 minutes pre-dose.

B. All values are relative to the time of day that the study treatment is administered on Day 14.

C. PK sampling is only to be performed on participants receiving GSK3036656. PK samples will not be taken from participants receiving Rifafour e-275 (or equivalent generic alternative).

D. Sample to be taken within 10 minutes pre-dose

PK Sample timing window allowances

Sample timepoint	Sample collection window allowed
Pre dose	Not applicable (see footnotes above)
0h - 4h post	± 5 min
> 4h – 12h post	± 15 min
> 12h – 24h post	± 1 h

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint
			Beginning Timepoint	Ending Timepoint	
Safety, Efficacy	All	Day -3	Day -9	Day -3	Screening
Safety, Efficacy	All	Day -2	Day -2	Day -2	Day -2, Screening
Safety, Efficacy	All	Day -1	Day -1	Day -1	Day -1, Screening
Safety, Efficacy	All	Day 1	Day 1	Day 1	Day 1
Safety, Efficacy	All	Day 2	Day 2	Day 2	Day 2
Safety, Efficacy	All	Day 3	Day 3	Day 3	Day 3
Safety, Efficacy	All	Day 4	Day 4	Day 4	Day 4
Safety	All	Day 5	Day 5	Day 5	Day 5
Safety, Efficacy	All	Day 6	Day 6	Day 6	Day 6
Safety	All	Day 7	Day 7	Day 7	Day 7
Safety, Efficacy	All	Day 8	Day 8	Day 8	Day 8
Safety	All	Day 9	Day 9	Day 9	Day 9
Safety, Efficacy	All	Day 10	Day 10	Day 10	Day 10
Safety	All	Day 11	Day 11	Day 11	Day 11
Safety, Efficacy, PK	All	Day 12	Day 12	Day 12	Day 12
Safety, PK	All	Day 13	Day 13	Day 13	Day 13
Safety, Efficacy, PK	All	Day 14	Day 14	Day 14	Day 14
Safety, PK	All	Day 15	Day 15	Day 15	Day 15
Safety	All	Day 28	Day 21	Day 35	Day 28

NOTES:
- For data summarised by visit, the nominal visit description will be used. Unscheduled and withdrawal visit data will be slotted into a scheduled visit window, if no competing visit exists within the window. If there are multiple assessments within the same window which are not unscheduled visits, the earliest results will be used in the summaries.

12.4.   Appendix 4: Study Phases and Treatment Emergent Adverse Events

12.4.1.   Study Phases

Adverse events will be classified according to the time of occurrence relative to the start of study treatment.

Study Phase	Definition
Pre-Treatment	Date and Time ≤ Study Treatment Start Date and Time
On-Treatment	Study Treatment Start Date and Time < Date and Time ≤ Study Treatment Stop Date and Time + 48 hours
Post-Treatment	Date and Time > Study Treatment Stop Date and Time + 48 hours

12.4.1.1.   Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date and time is not missing and is before start of study treatment
Concomitant	Any medication that is not a prior medication

NOTES:
- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.4.1.2.   Phases of COVID-19 Pandemic Measures

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), and available within the HARP reporting environment (arcomn folder), will be used to determine the start date of pandemic measures within each country. A copy of this dataset will be taken at the time of database freeze (DBF).

Adverse events will be summarised according to whether the onset date was before or after the start of the COVID-19 pandemic measures.

Pandemic Measures Phase	Definition
Before	AE onset date < pandemic measures start date
After	Pandemic measures start date ≤ AE onset date

12.4.2.   Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date and time is after treatment start date and time and before treatment stop date and time + 48 hours, i.e.: Study Treatment Start Date and Time $\leq$ AE Start Date and Time $\leq$ Study Treatment Stop Date and Time + 48 hours.

NOTES:
• If the study treatment stop date is missing, then the AE will be considered to be Treatment-Emergent.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: arenv/arprod/GSK3036656/mid201214
Analysis Datasets	
• Analysis datasets will be created according to legacy GSK Analysis and Reporting dataset standards.	
Generation of RTF Files	
• RTF files will be generated for SAC.	

12.5.2. Reporting Standards

General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: • 4.03 to 4.23: General Principles • 5.01 to 5.08: Principles Related to Data Listings • 6.01 to 6.11: Principles Related to Summary Tables • 7.01 to 7.13: Principles Related to Graphics
Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DPs) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DPs.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses: • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables or figures, unless the data has been slotted to a visit (Section 12.3).
• All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays
• Refer to IDSL Statistical Principals 7.01 to 7.13.

12.5.3. Reporting Standards for Pharmacokinetics

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in the Data Analysis Plan (DAP) (GSK Document Number: 2018N381501_00).
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by Programmer	All necessary PK parameters as defined in Section 9.1.5 (Cmax, tmax, AUC(0-t), AUC(0-24), Cτ) will be derived by the Clinical Pharmacology Modelling and Simulation function.
Pharmacokinetic Parameter Data	
Is non-quantifiable (NQ) impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 12.3.1) the earliest value in that window will be used. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Dose Date:
  • Ref Date = Missing   → Study Day = Missing
  • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date
  • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

12.6.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.
Demographics
• Body mass index (BMI) will be calculated as: Weight (kg) at screening / [Height (m)]^2

12.6.3. Efficacy

Efficacy
CFU
• Baseline CFU will be calculated as: Mean (log10(CFU Day -1), log10(CFU Day -2)) • Log(CFU) will be calculated as: Log(CFU/ml) = log10(mean(Total count 1:Total Count 2)*2*5*10^Dilution)

Efficacy
where: • Total count 1 and total count 2 are the bacterial counts from plates 1 and 2 respectively. Where plate counts are reported at be Too Numerous To Count (TNTC), a value of 2500 will be imputed. If a count is only available for 1 plate, then that count will be used instead of the mean. • Dilution is the dilution factor for that plate. • In the calculation, the *2 represents the 1:1 dilution of the original specimen and the *5 represents the 0.2 ml (200 µl) inoculation of the specimen. • For bacteria counts with a comment of "Half of plate X was contaminated so only half the plate was counted", the count for that plate will be doubled for the analysis.
TTP
• The mean of the time to positivity for both plates (plate 1 and plate 2) at each timepoint will be calculated and used in any derivation of summary statistics and analyses. If a result is only available for 1 plate, then that value will be used instead of the mean. Where listed, all data will be presented.

12.6.4.   Safety

Laboratory Parameters

• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than or greater than x in the comment field) is present, the number of decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
   • Example 1: 2 decimal places = '< x' becomes x – 0.01
   • Example 2: 1 decimal place = '> x' becomes x + 0.1
   • Example 3: 0 decimal places = '< x' becomes x – 1
• For values '<=x' or '>=x' the value itself ('x') should be imputed as the numeric value.

• Mean arterial blood pressure (BP) will be calculated as: Mean arterial BP (mmHg) = 1/3 (systolic BP (mmHg)) + 2/3 (diastolic BP (mmHg))

12.6.5.   Pharmacokinetic

Pharmacokinetic Parameters
Derived Pharmacokinetic Parameters
• Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin 5.2 or higher. • All calculations of non-compartmental parameters will be based on actual sampling times recorded during the study.

Pharmacokinetic Parameters

- The following pharmacokinetic parameters will be determined and summarised, as data permit.:

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time of dosing to last quantified concentration, regardless of time.
AUC(0-24)	Area under the concentration-time curve from time of dosing extrapolated to 24 hours
Cmax	Maximum observed plasma drug concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the plasma drug concentration-time data
Cτ	Trough concentration

- Additional parameters may be calculated.
- All calculated parameters will be listed.
- For graphical displays, IDSL Statistical Principles 7.01 to 7.13 and the standards for the transfer and reporting of PK data using HARP will be followed.

12.7.   Appendix 7: Reporting Standards for Missing Data

12.7.1.   Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion is defined as a participant who has completed all phases of the study including the last visit (the follow-up visit). • Withdrawn participants may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

12.7.2.   Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data are excluded from the listing. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

12.7.2.1.   Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. o Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study

Element	Reporting Detail
	treatment stop date will be used.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
	• AEs with entirely missing or unknown start dates will be assumed to be on-treatment for reporting.
	• AEs with missing end dates are not anticipated to affect reporting.
	• AEs with missing start or end times which started on the same day as study treatment or ended on the same day as study treatment plus 2 days will be assumed to be on-treatment for reporting and classed as treatment emergent for adverse events.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Change from Baseline	Decrease of 0.075	
Haemoglobin	g/L	Male	75	180
		Female	75	180
		Change from Baseline	Decrease of 25	
Lymphocytes	x10^9/ L		0.8	
Neutrophil Count	x10^9/ L		0.5	
Platelet Count	x10^9/ L		100	550
While Blood Cell Count (WBC)	x10^9/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		20	
Calcium	mmol/L		2	2.75
Creatinine	%	Change from Baseline		Increase of 30%
Glucose	mmol/L		3	11
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT / SGPT	IU/L	High	≥ 3x ULN
AST / SGOT	IU/L	High	≥ 3x ULN
AlkPhos	IU/L	High	≥ 2x ULN
T Bilirubin	μmol/L	High	≥ 1.5x ULN
T. Bilirubin + ALT	μmol/L	High	1.5x ULN T. Bilirubin

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
			+
	U/L		$\geq$ 2x ULN ALT

ULN = Upper Limit of Normal; ALT=Alanine Aminotransferase; AST=Aspartate Aminotransferase; SGPT=Serum Glutamic Pyruvic Transaminase; SGOT=Serum Glutamic Oxaloacetic Transaminase; T. Bilirubin=Total Bilirubin

12.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTcF Interval	msec		>450
Absolute PR Interval	msec	< 110	>220
Absolute QRS Interval	msec	< 75	>110
Change from Baseline			
Increase from Baseline QTcF	msec		>60

QTcF=QT Interval corrected for heart rate (Fridericia); PR=Electrocardiographic PR Interval

12.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 85	>160
Diastolic Blood Pressure	mmHg	< 45	>100
Heart Rate	bpm	< 40	>110
Respiratory Rate	Breaths/min	10	28
Temperature	Degrees C	35.0	37.9

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
%CVb	Between participant geometric coefficient of variation
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC(0-t)	Area under the concentration-time curve from time of dosing to last quantified concentration, regardless of time.
AUC(0-24)	Area under the concentration-time curve from time of dosing extrapolated to 24 hours
BMI	Body Mass Index
BP	Blood Pressure
Cτ	Trough Concentration
CFU	Colony Forming Units
Cmax	Maximum observed plasma drug concentration
CS	Compound Symmetry
CSR	Clinical Study Report
CPMS	Clinical Pharmacology Modelling & Simulation
CPSSO	Clinical Pharmacology Science and Study Operations
DAP	Data Analysis Plan
DBF	Database Freeze
DBR	Database Release
DS	Drug sensitive (i.e. Rifampicin-Susceptible)
EBA	Early Bactericidal Activity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDG	Fluorodeoxyglucose
FPD	Future Pipelines Discovery
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HPD	Highest Posterior Density
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
MedDRA	Medical Dictionary for Regulatory Activities
Mtb	Mycobacterium tuberculosis
PCI	Potential Clinical Importance
PDMP	Protocol Deviation Management Plan
CCI	
PK	Pharmacokinetic

Abbreviation	Description
QD	Once Daily
QTc	QT Interval Corrected for Heart Rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting and Analysis Plan
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SERM	Safety Evaluation and Risk Management
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxaloacetic Transaminase
SoC	Standard-of-Care
SOP	Standard Operating Procedure
SRT	Safety Review Team
TB	Tuberculosis
tmax	Time to maximum observed plasma drug concentration
TNTC	Too Numerous To Count
TTP	Time to Sputum Culture Positivity
ULN	Upper Limit of Normal
UN	Unstructured
VC	Variance Components
WBC	White Blood Cell Count

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonlin

12.10.   Appendix 10: List of Data Displays

12.10.1.   Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.18	None
Efficacy	2.1 to 2.10	2.1 to 2.5
Safety	3.1 to 3.23	3.1 to 3.5
Pharmacokinetic	4.1 to 4.5	4.1 to 4.7
Section	**Listings**	
ICH Listings	1 to 31	
Other Listings	32 to 39	

12.10.2.   Mock Example Shell Referencing

Non-integrated data standards library (IDSL) specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:
- Non-Standard displays are indicated in the 'IDSL / Example Shell' column as '[Non-Standard] + Reference.'

12.10.3.   Deliverables

Delivery	Description
DE	Dose Escalation Efficacy Analysis
SAC	Final Statistical Analysis Complete

Note, all displays (Tables, Figures and Listings) will use the term 'subjects', in place of participants.

12.10.4. Study Population Tables

Study Population Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Subject Disposition					
1.1.	Safety	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT Add footnote: "5mg=15mg loading dose and 5mg maintenance dose, Xmg=…"	DE, SAC
1.2.	Safety	ES1	Summary of Subject Status and Subject Disposition for the Study Conclusion Record by Relationship to COVID-19 Pandemic	Page by COVID-19 relationship Yes/No.	SAC
1.3.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.4.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic		SAC
1.5.	Safety	ES4	Summary of Subject Disposition at Each Study Epoch	ICH E3 Display by cohort (i.e. epoch=cohort).	SAC
1.6.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.7.	Enrolled	NS1	Summary of Number of Participants by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.8.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
1.9.	Safety	DV1	Summary of Important COVID-19 Related Protocol Deviations		SAC
1.10.	Safety	DV1	Summary of Important Non COVID-19 Related Protocol Deviations		SAC
Population Analysed					

			Study Population Tables		
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.11.	Screened	SP1	Summary of Study Populations	IDSL Include all columns in the IDSL template.	DE, SAC
1.12.	Safety	SP2A	Summary of Exclusions from the Efficacy Population	IDSL	DE, SAC
1.13.	Safety	SP2A	Summary of Exclusions from the PK Population	IDSL	SAC
Demographic and Baseline Characteristics					
1.14.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include BMI and smoking status.	SAC
1.15.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.16.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
Prior and Concomitant Medications					
1.17.	Safety	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.18.	Safety	MH1	Summary of Current Medical Conditions	ICH E3	SAC

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
CFU					
2.1.	Efficacy	Non-standard EFF_T1	Summary Table of $\log_{10}$CFU Counts Over Time		DE, SAC
2.2.	Efficacy	Non-standard EFF_T1	Summary Table of Change from Baseline in $\log_{10}$CFU Counts Over Time	Include baseline row similar to LB1 template.	DE, SAC
2.3.	Efficacy	Non-standard EFF_T2	Rate of Change in $\log_{10}$CFU by Treatment – Mixed Model Analysis	For dose escalation analysis, calculate EBA CFU(0-14) only. Supportive SAS output to be produced and archived	DE, SAC
2.4.	Efficacy	Non-standard EFF_T3	Node and Slope Parameter Estimates for log10CFU by Treatment – Bi-linear Bayesian Model Analysis	For dose escalation analysis, calculate EBA CFU(0-14) only. Supportive SAS output to be produced and archived	DE, SAC
2.5.	Efficacy	Non-standard EFF_T2	Rate of Change in $\log_{10}$CFU by Treatment – Mixed Model Analysis – Withdrawn/Replaced Participants Excluded	For endpoints CFU(0-14) and CFU(2-14) only. Supportive SAS output to be produced and archived	SAC
2.6.	Efficacy	Non-standard EFF_T4	Summary of Covariate and Treatment*Covariate Interaction Significance For $\log_{10}$CFU(0-14) Mixed Model Analysis	. Supportive SAS output to be produced and archived	SAC
TTP					
2.7.	Efficacy	Non-standard EFF_T1	Summary Table of TTP Counts Over Time		SAC

2.8.	Efficacy	Non-standard EFF_T1	Summary Table of Change from Baseline in TTP Counts Over Time	Include baseline row similar to LB1 template.	SAC
2.9.	Efficacy	Non-standard EFF_T2	Rate of Change in TTP –Mixed Model Analysis	Supportive SAS output to be produced and archived	SAC
2.10.	Efficacy	Non-standard EFF_T3	Node and Slope Parameter Estimates for TTP by Treatment –Bi-linear Bayesian Model Analysis	For endpoint TTP(0-14) only. Supportive SAS output to be produced and archived	

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Efficacy					
2.1.	Efficacy	Non-standard EFF_F1	Line Graph of $\log_{10}$CFU Over Time by Treatment	Include separate lines for each dose/treatment group.	DE, SAC
2.2.	Efficacy	Non-standard EFF_F1	Line Graph of Change from Baseline in $\log_{10}$CFU Over Time by Treatment	Include separate lines for each dose/treatment group.	DE, SAC
2.3.	Efficacy	Non-standard EFF_F2	Individual Subject Profile Plots of log10(CFU) Count Over Time by Treatment	Include CFU(0-14) regression line and 95% CI. Separate figure for each treatment group.	SAC
2.4.	Efficacy	Non-standard EFF_F3	Line Graph of Dose vs $\log_{10}$CFU (0-14) Slope	Include regression line and 95% CI	DE, SAC
2.5.	Efficacy	Non-standard EFF_F1	Line Graph of TTP Over Time by Treatment	Include separate lines for each dose/treatment group.	SAC

12.10.7. Safety Tables

Safety: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Adverse Events (AEs)					
3.1.	Safety	AE5B	Summary of All Adverse Events by System Organ Class, Preferred Term and Maximum Grade	ICH E3	SAC
3.2.	Safety	AE5B	Summary of All Drug-Related Adverse Events by System Organ Class, Preferred Term and Maximum Grade	ICH E3	SAC
3.3.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
Serious and Other Significant Adverse Events					
3.4.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
3.5.	Safety	AE5B	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class, Preferred Term and Maximum Grade	IDSL	SAC
3.6.	Safety	AE5B	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class, Preferred Term and Maximum Grade	IDSL	SAC
3.7.	Safety	AE20	Summary of Serious Fatal and Non-Fatal Drug-Related Adverse Events by Overall Frequency	Plain Language Summary requirements (PLS).	SAC
3.8.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time Relative to COVID-19 Pandemic Measures		SAC
3.9.	Safety	PAN10	Summary of Exposure Adjusted Incidence Rates of Adverse Events Over Time By Age Relative to COVID-19 Pandemic Measures		SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory: Chemistry					
3.10.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC
3.11.	Safety	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Haematology					
3.12.	Safety	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC
3.13.	Safety	LB17	Summary of Worst Case Haematology by PCI Criteria Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Urinalysis					
3.14.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.15.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC
3.16.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC
ECG					
3.17.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.18.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
3.19.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
3.20.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
Vital Signs					
3.21.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
3.22.	Safety	VS7	Summary of Worst Case Vital Signs Results by PCI Criteria Post-Baseline Relative to Baseline	IDSL	SAC
COVID-19 Assessments					
3.23.	Safety	PAN1	Summary of COVID-19 Assessments for Subjects with COVID-19 Adverse Events		SAC

12.10.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Laboratory					
3.1.	Safety	LIVER9	Scatterplot of ALT vs Total Bilirubin by Treatment	Separate plots for each treatment group. Include all timepoints.	SAC
3.2.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin by Treatment	IDSL Separate plots for each treatment group.	SAC
3.3.	Safety	LB11	ALT Profile Plots by Treatment	Separate plots for each treatment group, with individual lines for each subject	SAC
3.4.	Safety	LB11	Haematology Profile Plots by Treatment	Separate plots for each treatment group, with individual lines for each subject.	SAC
Vital Signs					
3.5.	Safety	LB11	Vital Signs Profile Plots by Treatment	Separate plots for each treatment group and vital signs parameter (DBP, SBP, mean BP, heart rate). Display individual lines for each subject, within a treatment, for each plot.	SAC

12.10.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Pharmacokinetic Concentration Data					
4.1.	PK	PK01	Summary of Plasma GSK3036656 Pharmacokinetic Concentration-Time Data		SAC
Derived Pharmacokinetic Parameters					
4.2.	PK	PK03	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (Untransformed Data)	AUC(0-t), AUC(0-24), Cmax, tmax, Cт	SAC
4.3.	PK	PK05	Summary of Derived Plasma GSK3036656 Pharmacokinetic Parameters (Log-transformed Data)	AUC(0-t), AUC(0-24), Cmax, tmax, Cт	SAC
4.4.	PK	Non-standard PK_T1	Statistical Analysis of Log Transformed Plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose Proportionality (Power Model)	AUC(0-t) or AUC(0-24), Cmax Supportive SAS output to be produced and archived.	SAC
4.5.	PK	Non-standard PK_T2	Statistical Analysis of Log Transformed Plasma GSK3036656 Trough Concentration Assessing Steady-State	Cт Supportive SAS output to be produced and archived.	SAC

12.10.10. Pharmacokinetic Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Pharmacokinetic: Figures					
Pharmacokinetic Concentration Data					
4.1.	PK	PK16a	Individual Plasma GSK3036656 Concentration-Time Plot (Linear and Semi-Log) by Subject		SAC
4.2.	PK	PK24	Individual Plasma GSK3036656 Concentration-Time Plot (Linear and Semi-Log) by Treatment	Include Day 14 and 15 data only.	SAC
4.3.	PK	PK17	Mean Plasma GSK3036656 Concentration-Time Plots (Linear and Semi-Log)	Include Day 14 and 15 data only.	SAC
4.4.	PK	PK18	Median Plasma GSK3036656 Concentration-Time Plots (Linear and Semi-Log)	Include Day 14 and 15 data only.	SAC
Derived Pharmacokinetic Parameters					
4.5.	PK	PK25	Comparative Plot of Individual Subject Plasma GSK3036656 Pharmacokinetic Parameter By Treatment	C_T	SAC
4.6.	PK	Non-standard PK_F1	Scatterplot of log(dose) vs log(AUC)	Add footnote: Doses displayed on the log scale are Xmg, Xmg, Xmg and Xmg.	SAC
4.7.	PK	Non-standard PK_F1	Scatterplot of log(dose) vs log(Cmax)	Add footnote: Doses displayed on the log scale are Xmg, Xmg, Xmg and Xmg.	SAC

12.10.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	Randomised	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
5.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
6.	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
7.	Safety	SP3	Listing of Subjects Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
8.	Safety	DM2	Listing of Demographic Characteristics	ICH E3 Include BMI and smoking status.	SAC
9.	Safety	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
10.	Safety	CP_CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
11.	Safety	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
12.	Safety	AE8CP	Listing of All Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
13.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
14.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
15.	Safety	AE8CP	Listing of Serious Adverse Events	ICH E3	SAC
16.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
17.	Safety	AECP8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
Hepatobiliary (Liver)					
18.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC
19.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC
All Laboratory					
20.	Safety	LB5	Listing of All Clinical Chemistry Data for Subjects with Any Value of Potential Clinical Importance	ICH E3 Display ALL chemistry data for a subject who experienced a value of potential clinical importance.	SAC
21.	Safety	LB5	Listing of Clinical Chemistry Values of Potential Clinical Importance		SAC
22.	Safety	LB5	Listing of All Hematology Data for Subjects with Any Value of Potential Clinical Importance	Display ALL hematology data for a subject who experienced a value of potential clinical importance.	SAC
23.	Safety	LB5	Listing of Hematology Values of Potential Clinical Importance		SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
24.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
25.	Safety	UR2A	Listing of All Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3 Display ALL urinalysis data for a subject who experienced a value of potential clinical importance	SAC
ECG					
26.	Safety	EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	IDSL Display ALL ECG data for a subject who experienced a value of potential clinical importance.	SAC
27.	Safety	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
28.	Safety	EG5	Listing of All ECG Findings for Subjects with an Abnormal ECG Finding	IDSL	SAC
29.	Safety	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
30.	Safety	VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL Display ALL vital signs data for a subject who experienced a value of potential clinical importance.	SAC
31.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

12.10.12. Non-ICH Listings

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable
Non-ICH: Listings					
Protocol Deviation					
32.	Safety	DV2	Listing of All Non-Important COVID-19 Related Protocol Deviations		SAC
Adverse Events					
33.	Safety	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events		SAC
Pharmacokinetic					
34.	PK	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data		SAC
35.	PK	PK13	Listing of Derived Plasma Pharmacokinetic Parameters		SAC
Efficacy					
36.	Efficacy	Non-standard EFF_L1	Listing of Sputum Counts	Include CFU, log_{10}CFU and TTP	SAC
37.	Safety	Non-standard EFF_L2	Listing of Mycobacterial Data		SAC
38.	Safety	Non-standard EFF_L3	Listing of Drug Susceptibility Data at Screening		SAC
All Laboratory					
39.	Safety	Non-standard SAFE_L1	Listing of Troponin Data		SAC

12.11.   Appendix 11: Example Mock Shells for Data Displays

```
Example     : EFF_T1
Population  : Efficacy
```

Table EFF_T1
Summary Table of $\log_{10}$CFU Counts Over Time

Treatment	N	Planned Time	n	Mean	SD	Median	Min.	Max.
\<Rifafour\>	xx	Baseline	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 1	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 2	xx	x.xx	x.xxx	x.xx	x.x	x.x
		…	…	…	…	…	…	…
		Day 14	xx	x.xx	x.xxx	x.xx	x.x	x.x
\<656 Dose 1\>	xx	Baseline	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 1	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 2	xx	x.xx	x.xxx	x.xx	x.x	x.x
		…	…	…	…	…	…	…
		Day 14	xx	x.xx	x.xxx	x.xx	x.x	x.x
...								
\<656 Dose 5\>	xx	Baseline	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 1	xx	x.xx	x.xxx	x.xx	x.x	x.x
		Day 2	xx	x.xx	x.xxx	x.xx	x.x	x.x
		…	…	…	…	…	…	…
		Day 14	xx	x.xx	x.xxx	x.xx	x.x	x.x

Baseline (Day 0) is defined as the mean of Day -2 and Day -1; if data was available at only one of these timepoints then that value was used as baseline. Where plate counts were Too Numerous To Count (TNTC), a value of 2500 was imputed for the analysis.

Example   : EFF_T2
Population : Efficacy

Table EFF_T2
Rate of Change in $\log_{10}$CFU by Treatment – Mixed Model Analysis

Endpoint (units)	Treatment	N	n	Mean	SE	95% Confidence Interval
EBA CFU$_{0-14}$ ($\log_{10}$CFU/mL)	\<Rifafour\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 1\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 2\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 3\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 4\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 5\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
EBA CFU$_{0-2}$ ($\log_{10}$CFU/mL)	\<Rifafour\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 1\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 2\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 3\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 4\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
EBA CFU$_{2-14}$ ($\log_{10}$CFU/mL)	\<Rifafour\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 1\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 2\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 3\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 4\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)
	\<656 Dose 5\>	xx	xx	x.xx	x.xx	(x.xxx, x.xxx)

Mixed model including treatment, day,, BMI and treatment-by-day as covariates. The Day 2-14 model
also includes log baseline CFU as a covariate.
Baseline (Day 0) is defined as the mean of Day -2 and Day -1; if data was available at only one of
these timepoints then that value was used as baseline.

Example   : EFF_T3
Population : Efficacy

Table EFF_T3
Node and Slope Parameter Estimates for $\log_{10}$CFU by Treatment – Bi-linear Bayesian Model Analysis

Endpoint (units)	Treatment	N	n	Mean (95% HPD Interval) Node	Slope Before Node	Slope After Node
EBA CFU$_{0-14}$ ($\log_{10}$CFU/mL)	\<Rifafour>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 1>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 2>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose …>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 5>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
EBA CFU$_{2-14}$ ($\log_{10}$CFU/mL)	\<Rifafour>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 1>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 2>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose …>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
	\<656 Dose 5>	xx	xx	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)

Bi-linear model including treatment, day, BMI and treatment-by-day before node and treatment-by-day after node as covariates. The Day 2-14 model also includes log baseline CFU as a covariate. Baseline (Day 0) is defined as the mean of Day -2 and Day -1; if data was available at only one of these timepoints then that value was used as baseline.

Example   : EFF_T4
Population : Efficacy

Table EFF_T4
Summary of Covariate and Treatment*Covariate Interaction Significance For log_{10}CFU (0-14) Mixed Model
Analysis

Terms in the Model	Numerator Degrees of Freedom	Denominator Degrees of Freedom	F-test	p-value
Age [1]	xx	xx	x.xx	0.xxx
Treatment*Age [1]	xx	xx	x.xx	0.xxx
Creatinine clearance [2]	xx	xx	x.xx	0.xxx
Treatment*creatinine clearance [2]	xx	xx	x.xx	0.xxx
...				

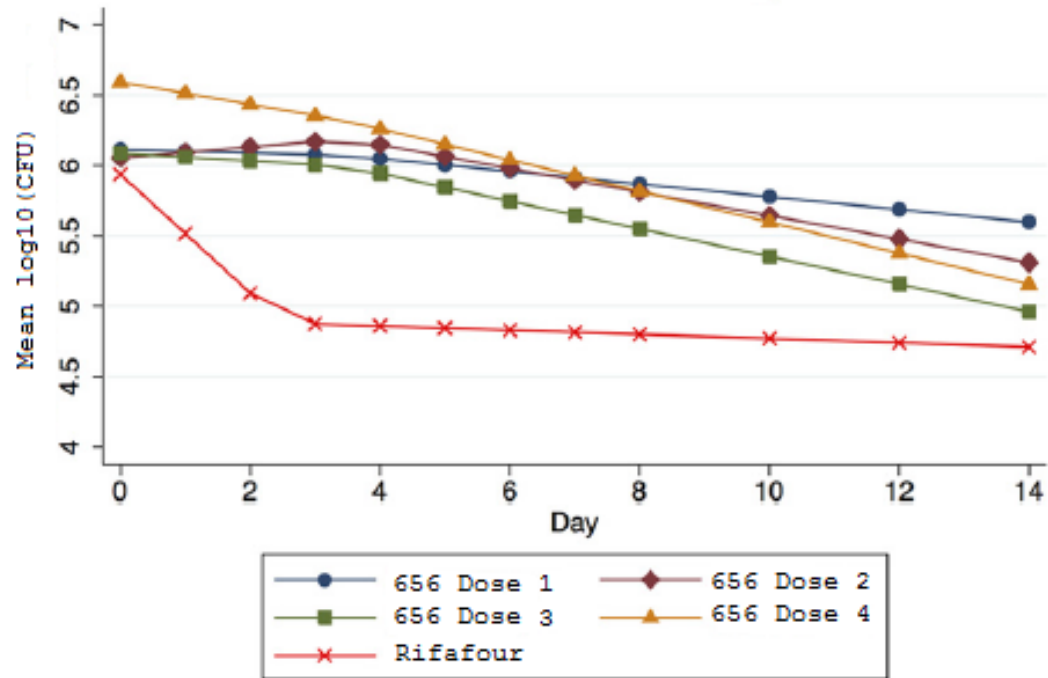Primary model includes treatment, day, BMI and treatment-by-day as covariates.
[1] Primary model fitted first with age, then with age + age*treatment
[2] Primary model fitted first with creatinine clearance, then with creatinine clearance creatinine clearance*treatment
…

Example   : EFF_F1
Population : Efficacy

Table EFF_F1
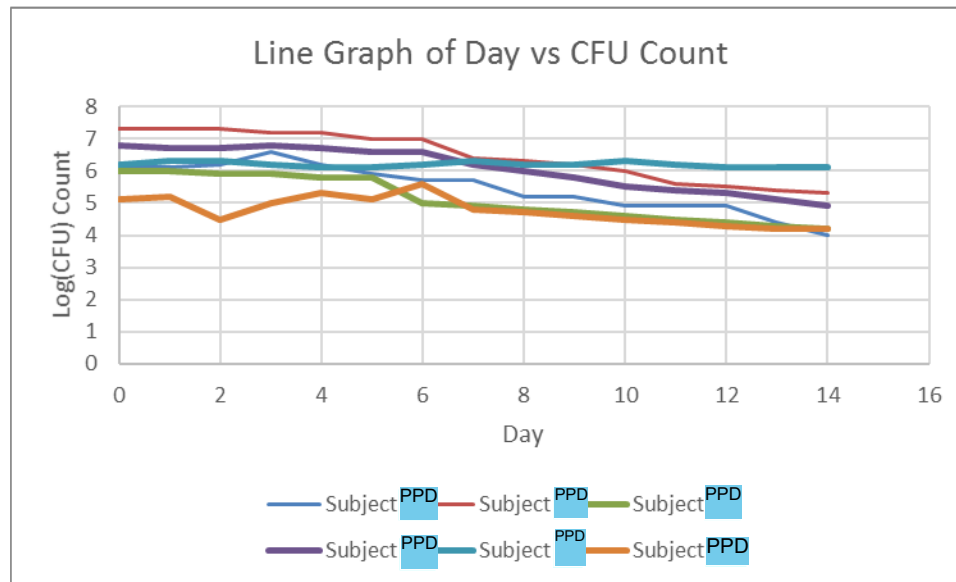Line Graph of Mean $\log_{10}$CFU Over Time by Treatment

Programming note: Include 95% confidence intervals of the slopes.

Example   : EFF_F2
Population : Efficacy
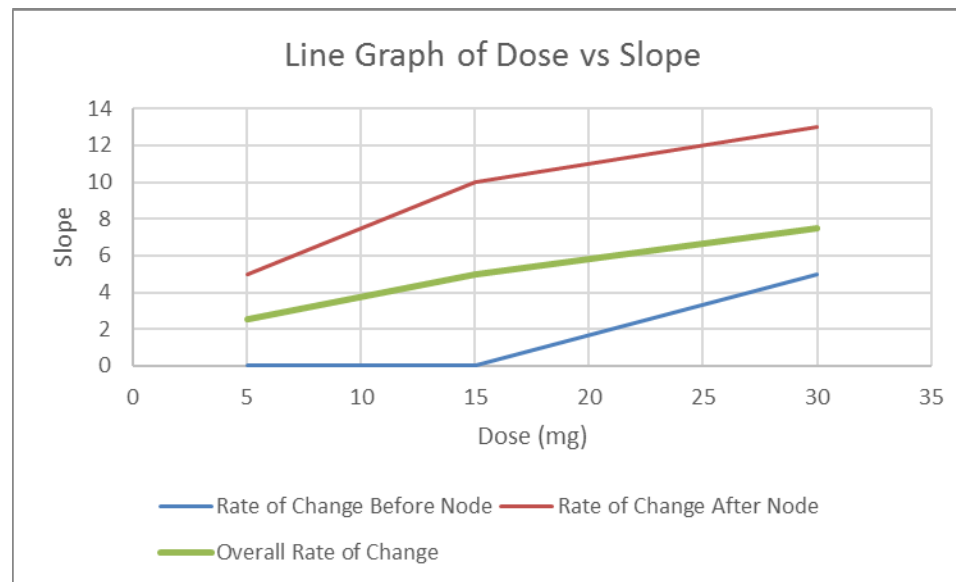

Table EFF_F2
Individual Subject Profile Plots of log10(CFU) Count Over Time by Treatment

Programming notes: Produce separate figure per treatment group.

Example   : EFF_F3
Population : Efficacy

Table EFF_F3
Line Graph of Dose vs $\log_{10}CFU(0-14)$ Slope

Programming note: Include 95% HPD interval of the slopes.

Example   : PK_T1
Population : Pharmacokinetic

Table PK_T1
Statistical Analysis of Log Transformed Plasma GSK3036656 Pharmacokinetic Parameters Assessing Dose
Proportionality (Power Model)

Parameter (Units)	Timepoint	Slope Log Parameter vs Log Dose	90% CI of the Slope
<AUC(0-t) (μg.h/mL)>	Day 14	x.xx	(x.xx, x.xx)
Cmax (μg/mL)	Day 14	x.xx	(x.xx, x.xx)

Log(dose) is fitted as a fixed effect.
A slope of 1 indicates the pharmacokinetics are dose proportional. A slope greater than 1 indicates
the increase in PK is greater than proportional to dose.

Example   : PK_T2
Population : Pharmacokinetic

Table PK_T2

Statistical Analysis of log transformed plasma GSK3036656 Trough Concentration Assessing Steady
State

Parameter (Units)	Treatment	Day*	Back-Transformed Slope	90% Confidence Interval
Ctau (ng/mL)	<656 Dose 1>	12-14	x.xx	(x.xx, x.xx)
	<656 Dose 2>	12-14	x.xx	(x.xx, x.xx)
	<656 Dose 3>	12-14	x.xx	(x.xx, x.xx)
	<656 Dose 4>	12-14	x.xx	(x.xx, x.xx)
	<656 Dose 5>	12-14	x.xx	(x.xx, x.xx)

Mixed effect model including log(dose), day and log(dose)-by-day interaction as fixed effects and
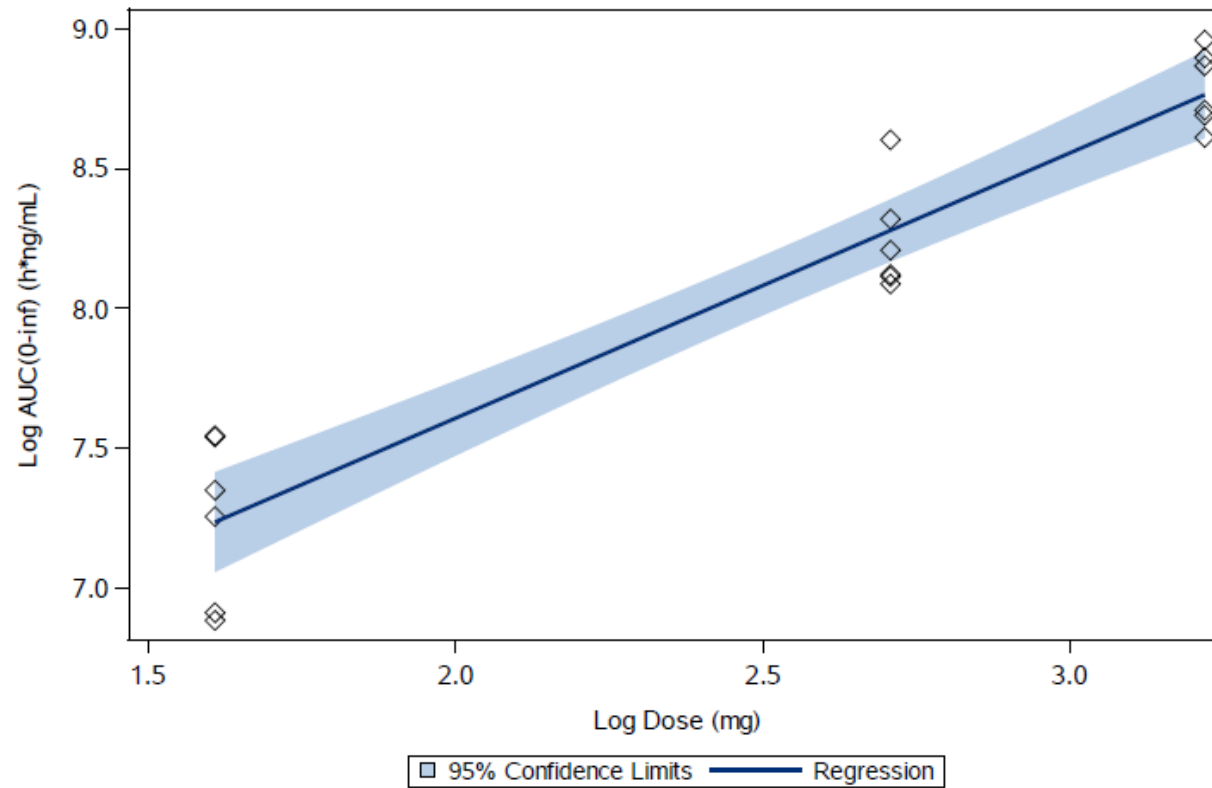subject as a random effect. An unstructured covariance structure was used.
A slope of 1 indicates steady state.
*Day 14 includes the Day 14 24 hour PK sample.

Example   : PK_F1
Population : Pharmacokinetic

Figure PK_F2

Scatterplot of Dose vs AUC(0-inf) including Regression Line - Part A

Example   : EFF_L1
Population : Efficacy

Table EFF_L1

Listing of Sputum Counts

Site ID: <11111>

Treatment / Unique subject Id. / Subject Id.	Age (Years)/ Sex/ Race Detail	DateTime / Study Day	CFU (CFU/mL)	Log10CFU (log10CFU/mL)	TTP (hours)
xxxxxx / xxxxxx / xxxxx	xx / <M/F> / xxxxx	YYYY-MM-DDTHH:MM / xx	x.xxx	x.xxx	x.xxx
		YYYY-MM-DDTHH:MM / xx	x.xxx	x.xxx	x.xxx

Note, mean values at each timepoint are displayed.

Example   : EFF_L2
Population : Safety

Table EFF_L2
Listing of Mycobacterial Data

Site Id.: <1111111>

Treatment / Unique subject Id. / Subject Id.	Age (Years)/ Sex/ Race Detail	Microscopy Collection Date / Time	Microscopy Result / Grading	GeneXpert Collection Date / Time	GeneXpert Result at baseline	GeneXpert Positive Rating at baseline
xxxxxx / xxxxxx / xxxxx	xx / <M/F> / xxxxx	XXXXX /HH:MM	< Positive / No AFB seen / No result / Not done> / < Scanty / 1+ / 2+ / 3+ / N/A>	XXXXX /HH:MM	<MTB NOT DETECTED / MTB DETECTED; Rif Resistance NOT DETECTED / MTB DETECTED; Rif Resistance DETECTED / MTB DETECTED; Rif Resistance INDETERMINATE / Invalid / Error / No result>	<High positive / Medium positive / Low positive / Very low positive / N/A>

…

Footnote: Note, Grading is presented as: 1=1+, 2=2+, 3=3+, 4=4+
Programmers note: For repeat results, display all available results, one row per repeat.

Example   : EFF_L3
Population : Safety

Table EFF_L3
Listing of Drug Susceptibility Data at Screening

Site Id.: <11111>

			RIF		INH		PZA		EMB	
Treatment / Unique subject Id. / Subject Id.	Age (Years)/ Sex/ Race Detail	Collection Date / Time	Result	Indeterminate Result Due To	Result	Indeterminate Result Due To	Result	Indeterminate Result Due To	Result	Indeterminate Result Due To
xxxxxx / xxxxxx / xxxxx	xx / <M/F> / xxxxx	XXXXX /HH:MM	<Susceptible / Resistant / Indeterminate / Not done / No result / N/A>	< Control tube failure / X200 error / X400 error / QC error / N/A >	<Susceptible / Resistant / Indeterminate / Not done / No result / N/A>	< Control tube failure / X200 error / X400 error / QC error / N/A >	<Susceptible / Resistant / Indeterminate / Not done / No result / N/A>	< Control tube failure / X200 error / X400 error / QC error / N/A >	<Susceptible / Resistant / Indeterminate / Not done / No result / N/A>	< Control tube failure / X200 error / X400 error / QC error / N/A >

…

RIF=Rifampicin, INH=Isoniazid, PZA=Pyrazinamide, EMB=Ethambutol
X200 error, X400 error and QC error are machine errors and have no clinical relevance.

Programmers note: For repeat results, display all available results, one row per repeat.

Example   : SAFE_L1
Population : Safety

Table SAFE_L1

Listing of Troponin Data

Site Id.: <11111>

Treatment / Unique subject Id. / Subject Id.	Age (Years)/ Sex/ Race Detail	Planned Time	Date / Study Day	Troponin Result (UG/L)	Normal Range (UG/L)
xxxxxx / xxxxxx / xxxxx	xx / <M/F> / xxxxx	Screening	xxxx / xx	x.xxx	<0-0.2 / 0-
		Day 3	xxxx / xx	x.xxx	0.7>
		Day 14	xxxx / xx	x.xxx	
xxxxxx / xxxxxx / xxxxx	xx / <M/F> / xxxxx	Screening	xxxx / xx	x.xxx	
		Day 3	xxxx / xx	x.xxx	
		Day 14	xxxx / xx	x.xxx	
…					

Note: Two Troponin assays were used during the study, the Stratus troponin I assay (normal range: 0-0.70 UG/L) and the Mini Vidas troponin I assay (normal range: 0-0.20 UG/L).