TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

MRC Clinical Trials Unit

Nix-TB
Efficacy Statistical Analysis Plan

Protocol Title: Protocol Title: A Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus pretomanid plus linezolid in Subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB).

Protocol Number: NiX-TB-(B-L-Pa).

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0.3 23 May2017	Incorporated comments from team after meeting on 22 May 2017
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1.0 11 July 2017	Final version approved

1. Introduction

This document outlines the efficacy statistical analysis plan (SAP) for the protocol Nix-TB, a phase 3 open-label clinical trial assessing the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus pretomanid plus linezolid in patients with pulmonary of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB).

Up to 200 patients will be enrolled and all patients will be treated with bedaquiline 400 mg once daily for 2 weeks then 200mg 3 times per week plus pretomanid 200mg once daily plus linezolid, initially at 600 mg bid, then amended on Jan 22, 2016, to 1200mg once daily.

Treatment duration will be 6 months, with the option to extend to 9 months if the patient remains culture positive at 4 months from start of treatment (and is not withdrawn from the study).

Patients who complete treatment will return for follow-up visits 1, 2 and 3 months after end of treatment then every 3 months up to 24 months after end of treatment. Patients who withdraw after ≤14 days of IMP administration will return for an Early Withdrawal visit only. Patients who withdraw after ≥15 days of IMP will return for the Early Withdrawal, and for the 3, 12 and 24 month follow up visits after their last dose of IMP.

The Data Safety Monitoring Committee (DSMC) will review the data at least every 6 months. In addition, interim analyses will be performed cumulatively on every 15 patients who complete treatment (or are withdrawn early). Consideration will be given to stopping the trial early for safety concerns or futility although there are no formal stopping rules. This document covers interim analyses after the first one done on the first 15 participants, and final analyses including the analyses for the New Drug Application (NDA). The NDA will be based on the first 45 patients reaching primary endpoint and additional data collected by that time point will also be summarised.

The primary efficacy analysis will be conducted using culture results from liquid culture (MGIT). This document covers

2. Primary Efficacy Endpoint

The primary efficacy endpoint will be the incidence of bacteriologic failure or relapse or clinical failure at 6 months after the end of therapy. See section 6 for the detailed definition of an "unfavourable response".

There will be three main analyses of the primary efficacy endpoint: An intent to treat (ITT) analysis; a modified intent to treat (MITT) analysis and a per protocol (PP) analysis.

The "unfavourable" rates in any defined 'ITT' population will likely be increased by factors other than bacteriologic or clinical treatment failure and relapse. The MITT analysis will therefore be considered primary for publication purposes. However, we recognize that FDA and other regulatory agencies will consider the ITT analysis primary for the purpose of the NDA filing.

NB: In the event that more than 10% of patients are culture positive at 4 months and have their treatment extended for further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients.

3. Definitions and data handling issues

3.1. Definitions

Positive culture refers to the culture being positive for M.tb. False positive or contaminated sputum cultures, without speciation data confirming presence of M.tb, will be treated as missing. Specimens classified as non-tuberculous mycobacteria (NTM) and negative for M.tb will be treated as contaminated. Full details of the bacteriology algorithm for reporting MGIT results can be found in Appendix 1. Two sputum samples per visit are collected at each visit throughout treatment and follow-up. The culture result for a given visit is established using all samples obtained for that visit. A positive culture takes precedence over a negative culture at the same visit.

Culture negative status is achieved when a patient produces at least 2 negative culture results at different visits (at least 7 days apart) without an intervening positive culture result for M.tb. The date of the first negative culture of these two is the date at which culture negative status was obtained. Once obtained, culture negative status continues until there are two positive cultures at different visits (at least 7 days apart), without an intervening negative culture, or until there is a single positive culture not followed by two negative cultures. Culture negative status can be achieved at any time during treatment or follow-up but before any re-treatment. Culture negative status can be re-established.

Patients with two contaminated or missing samples at a given visit will be asked to return to produce two more sputum samples.

Treatment failure is defined as being declared an unfavourable status (as defined in section 6) at or before the end of treatment or failing to attain culture negative status and being declared an unfavourable outcome or patient is withdrawn at or before the end of treatment for clinical (TB) reasons including being re-treated (or changing from protocol treatment) for TB.

Relapse is defined as failing to maintain culture negative status or being declared an unfavourable outcome after the end of treatment in those patients who attained culture negative status by the end of treatment, and had culture conversion to positive status with the **same** *Mycobacterium tuberculosis (M.tb)* strain or after the end of treatment in those patients who attained culture negative status by the end of treatment and were withdrawn for clinical (TB) reasons including being re-treated (or changing from protocol treatment) for TB. Details are given in Appendix 2.

Reinfection is defined as failing to maintain culture negative status or being declared an unfavourable outcome (including being withdrawn for clinical (TB) reasons including being re-treated or changing from protocol treatment for TB) after the end of treatment in those patients who attained culture negative status by the end of treatment and had culture conversion to positive status with a *Mycobacterium tuberculosis (M.tb)* strain that is **different** from the infecting strain at baseline. If reinfection cannot be distinguished from relapse, the patient will be assumed to have relapsed. A single positive sample will be sufficient for strain typing to compare to baseline. Full details are in Appendix 2.

The ***treatment period*** is defined as 6 months (total of 26 weeks) of the BPa therapy (linezolid may be stopped early) plus any days made up for interrupted doses of BPa therapy (or 9 months in those remaining culture positive at month 4 and who are not withdrawn).

The ***follow-up period*** is defined as the period after the last treatment dose to the end of follow-up.

3.2. Inability to produce sputum

In general, inability to produce sputum is treated as being equivalent to having a negative (favourable) culture result. This includes the rare situation where a patient who never achieves culture negative status due to inability to produce sputum, but completes follow-up without clinical or microbiological evidence of relapse. Such a patient will be considered to have a favourable outcome.

3.3. Isolated positive cultures

It is known that occasionally patients produce sputum samples that are "isolated positives", that is a positive culture preceded by a series of negative cultures and followed thereafter by at least 2 negative cultures without an intervening positive result. This phenomenon may be the result of a sealed cavity breaking down or laboratory contamination and does not in itself signify that the patient is relapsing. In the event of a single positive culture result occurring in a patient who has previously been classified as having culture negative status (in the absence of any retreatment), the patient will not be classified as a recurrence unless a second positive culture result is obtained at a separate visit (at least 7 days apart) without an intervening negative culture or unless the patient is lost to follow up or completes the study (and is unable to be brought back) before two negative cultures are obtained. As there is a higher incidence of positives with liquid culture and sometimes even serial "isolated positives" the clinical condition of the patient will also be considered in deciding whether the patient has an unfavourable outcome and re-treatment is indicated.

To expand a bit, most of the experience with isolated positives has been with solid culture. Because liquid culture is more sensitive, it is possible that more than one isolated positive may occasionally occur. Therefore, the clinical condition of the patient will also be considered when deciding whether re-treatment is indicated and in determining the outcome. For example, if a patient after being culture negative has two positive cultures in a row, but is deemed to be doing well clinically, the investigator may choose to leave the patient untreated on clinical grounds. In such a case, so long as two consecutive negative cultures are eventually obtained in the absence of treatment, the patient will not be classified as an unfavourable outcome.

3.4. Timing of events

In all analyses, visit date rather than day or week number will be used to define the timing of events. The 6-month regimen will be taken as a total of 26 weeks, i.e. 182 dosing days, from the start of therapy, after accounting for any treatment interruptions. For those who extend treatment to 9 months this will be 39 weeks (273 days) from start of therapy, again after accounting for any treatment interruptions.

For the end of treatment visit (months 6/9), a ±1-week window will be applied (as per the protocol). For the 3-monthly visits after the end of therapy, a window of ±2 weeks will be applied (as per the protocol). Additional programming will be required for cases where end of treatment date is not clearly recorded.

In the event that more than 10% of patients are culture positive at 4 months and have their treatment extended for a further 3 months, the primary endpoint analysis will be defined as 15 months from start of therapy for all patients. In this case the visit date for the endpoint analysis will be chosen as the one closest to 65 weeks (26+39) from start of therapy (unless patient is declared unfavourable before this date).

4. Analysis populations

Patients who are never culture positive during the baseline period, (screening through week 4) but are eligible based on documented M.tb by culture or molecular test within 3 months prior to screening will be included in all analysis populations.

The analysis populations for efficacy analyses are:

- The **Intent to treat (ITT)** population is defined as all patients excluding late screening failures (see 4.1)
- The **Modified intent to treat (MITT)** population is defined as the ITT population with extra exclusions (See 4.2)
- The **Per-protocol (PP)** population is defined as the MITT population with extra exclusions (see 4.3)

Exclusions from these populations will be reported as "unassessable" status and are described below.

4.1. Exclusions from ITT analysis (late screening failures)

1. Patients withdrawn from treatment because they were found to be ineligible (late exclusions from the study), based on data collected prior to enrollment, including patients who do not have documented evidence of M.tb within 3 months of screening. Note, reinfections will not be excluded from the ITT population.

4.2. Additional exclusions from MITT analysis

1. Patients who, having completed treatment, are lost to follow-up or withdrawn from the study, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart, without an intervening positive culture)

2. Women who become pregnant during treatment and stop their allocated treatment

3. Patients who died during treatment from violent or accidental cause (e.g. road traffic accident). N.B.: This does not include death from suicide, which will be considered an unfavourable outcome.

4. Patients who died during follow-up (after the end of treatment) with no evidence of failure or relapse of their TB, their last status being culture negative and their last positive culture result ("isolated positive culture") followed by at least two negative culture results at different visits (at least 7 days apart), and who have not already been classified as unfavourable.

5. Patients who, after being classified as having culture negative status, are re-infected with a new strain different from that with which they were originally infected. Reinfection will be defined specifically as a patient infected with a strain that is genetically different from the initial strain (see Appendix 2).

6. Patients who are able to produce sputum at their primary endpoint visit, whose sputum samples are all contaminated or missing, who cannot be brought back for repeat cultures, provided they have not already been classified as unfavourable and provided their last positive culture was followed by at least two negative cultures. N.B.: This does not apply to patients who are unable to produce sputum at 6 months after end of treatment, or to patients who are able to be brought back subsequently and produce negative cultures.

Patients in categories 1-6 above who had already been classified as having an unfavourable outcome will not be excluded.

4.3. Additional exclusions from PP analysis

1. Patients lost to follow-up or withdrawn before the end of treatment due to reasons other than treatment failure, unless they have already been classified as having an unfavourable outcome.

2. Patients whose treatment was modified or extended (beyond what is permitted in the protocol) for reasons (e.g. an adverse drug reaction) other than an unfavourable therapeutic response to treatment, unless they have already been classified as having an unfavourable outcome.

3. Patients not meeting the definition of having received an adequate amount of their allocated study regimen (see section 4.5 for definition), provided this is not due to unfavourable outcome.

4. Patients who are classified as "major protocol deviations for analysis" (see below), unless they have already been classified as having an unfavourable outcome on the basis of data obtained prior to the protocol deviation.

A list of all protocol deviations will be compiled throughout the course of the study.

A ***Major Protocol Deviation for Analysis*** is defined as a serious protocol deviation which is likely to affect to a significant degree the scientific value of the trial. These patients will be included in the ITT and MITT analyses, but not in the Per Protocol analysis. A list of all major protocol deviations for analysis will be approved by the study Coordinating Investigator before database lock.

A ***Minor Protocol Deviation*** is defined as a technical deviation which does not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial.

4.4. Lost to Follow-up or Early Withdrawal

Lost to Follow-up or Early Withdrawals *before* the end of the treatment (month 6 or 9) are considered as unfavourable outcomes for ITT and MITT. However, these patients will be excluded from the Per Protocol analysis. The MITT and Per Protocol analyses will consider Lost to Follow-up *after* end of treatment as unassessable unless at the time of default from follow-up the patient a) was already classified as having an unfavourable outcome, b) did not have culture negative status, or c) had a positive culture result ("isolated positive culture") not followed by at least two negative culture results at different visits (at least 7 days apart), in which cases the patient will be classified as having an unfavourable outcome. We believe this is the most appropriate approach for the primary analysis because together with the non-tuberculosis deaths, this group is likely to considerably out-number the bacteriological failures and relapses. These patients will be considered as having an unfavourable outcome in the ITT analysis.

There is a clear precedent for this analytic approach in other TB trials, and these trials also provide examples of why the inclusion of the losses to follow-up as unfavourable greatly affects the results.

Data from the Priftin trial which led to accelerated approval of rifapentine and a trial conducted by the International Union Against TB & Lung Disease (IUATLD) in African and Asian sites illustrate the problems associated with classifying all losses to follow-up and deaths as having an unfavourable outcome.

In the Priftin trial bacteriological relapses occurred in 5% of patients on the rifampicin based regimen compared to 11% on the rifapentine based regimen. Approximately one third of patients were lost to follow-up and when this group combined with patients unassessable for other reasons were added to the bacteriological failures, the rates increased to 53% and 57% respectively. The true bacteriological relapses were greatly outnumbered by these other groups. At the time of the licensing submission to the FDA it was recognised that because there were a substantial number of patients likely to be unassessable the main focus should be on the relapse rates. In the final statistical report the results were first reported excluding those unassessable and then assuming all losses had an unfavourable outcome and finally assuming all losses had a favourable outcome.

In the study conducted by the IUATLD the published failure/relapse rates 12 months after stopping treatment based on 1044 assessable patients were 4% for the control regimen and 10% and 14% in each of the experimental arms. If the 311 unassessable patients were considered to have an unfavourable outcome these rates would increase to 24%, 32% and 35% respectively. The 311 unassessable patients were not evenly distributed across the three trial arms. There were 42 deaths, of which 20 occurred in one of the experimental arms (the more efficacious of the two) and 11 in each of the other, a difference which was not considered to be due to the treatment, but due to chance. There were also imbalances among those without a bacteriological assessment (7 in one arm versus 19 and 22 in the other two arms) and in the distribution of losses to follow-up.

4.5. Definition of adequate treatment

The definition of adequate treatment sets a limit for the amount of treatment missed. Patients not taking the adequate amount of treatment by this definition will be excluded from the PP analysis.

Patients treated for 6 months with no treatment extension, to meet the definition of adequate treatment they must have taken at least 146 doses (80%) of their allocated 182 day (26 weeks) treatment regimen within 242 days of starting therapy (i.e. 26 weeks plus an allowable 60 day halt (including a maximum of 35 consecutive days) as per the protocol).

For patients who have their treatment extended to 9 months (39 weeks), to meet the definition of adequate treatment, they must have taken at least 219 doses (80%) within 333 days.

A dose is defined as taking the required daily dose of both pretomanid and bedaquiline.

4.6. Determining cause of death

A list of all ***TB-related*** and ***non-TB-related deaths*** will be generated and approved by a review committee of physicians not associated with the trial before database lock. Similarly, a list of violent or accidental deaths will be generated.

5. Baseline comparisons of key characteristics

The following baseline characteristics of patients will be summarised: age, gender, race, site, weight, height, BMI, smoking status, TB type (XDR /non-XDR), HIV status/CD4 count/on ARV, cavitation, initial bacterial load in sputum as indicated by baseline Time to Positivity (TTP) result from MGIT, drug resistance.

6. Classification of primary endpoint status

Patients will be classified as having a favourable, unfavourable or unassessable status at 6 months after the end of therapy.

6.1.1. Favourable status (all analyses)

Patients with a negative culture status at 6 months from end of therapy who had not already been classified as having an unfavourable outcome, and whose last positive culture result ("isolated positive culture") was followed by at least two negative culture results.

6.1.2. Unfavourable status in ITT population

Patients in the ITT analysis population who do not have a favourable outcome at 6 months from end of therapy will be considered to have an unfavourable response in the ITT analysis.

6.1.3. Unfavourable status in MITT population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during treatment, except from violent or accidental cause (e.g. road traffic accident), not including suicide (i.e., suicide will be considered an unfavourable outcome) or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase or
6. Patients requiring an extension of their treatment beyond that permitted by the protocol, a restart or a change of treatment for any reason except reinfection or pregnancy, or
7. Patients lost to follow up or withdrawn from the study before the end of treatment

6.1.4. Unfavourable status in PP population

1. Patients not classified as having achieved or maintained culture negative status when last seen, or
2. Patients previously classified as having culture negative status who, following the end of treatment, have two positive cultures without an intervening negative culture, (however, see Section 3.3 for an exception), or
3. Patients who had a positive culture not followed by at least two negative cultures when last seen, or
4. Patients dying from any cause during the treatment phase, except from violent or accidental cause (e.g. road traffic accident), not including suicide (i.e.., suicide will be considered an unfavourable outcome), or
5. Patients definitely or possibly dying from TB related cause during the follow-up phase, or
6. Patients requiring a restart or a change of treatment because of an unfavourable outcome with or without bacteriological confirmation, i.e. on bacteriological, radiographic or clinical grounds, unless due to reinfection with a new organism

7. Primary endpoint analysis

The MITT analyses will be considered primary. The proportion of assessable patients with a favourable and unfavourable outcome, with 95% confidence intervals, will be presented. For success, the lower bound of the 95% confidence interval for a favourable outcome should be above 50%. This MITT analysis is consistent with the TB literature over the past 50 years. **However, we recognize that for the purposes of the NDA, FDA and other regulatory agencies will consider the ITT analysis primary, where all patients who are not proven to have a favourable outcome will be classified as having an unfavourable outcome.**

8. Sensitivity analyses of primary endpoint analysis

In addition to analysing the primary endpoint data by ITT, MITT and PP, it is planned to conduct the following sensitivity analyses:

1. An analysis of the ITT, MITT and PP populations including only the XDR patients

2. An analysis of patients in the MITT and PP populations where reinfections are classified as unfavourable outcomes

3. An analysis of the MITT and PP populations treating all deaths as unfavourable

4. An analysis of the ITT, MITT and PP populations excluding patients who were never culture positive during the baseline period (screening through week 4), but were eligible based on documented M.tb by culture or molecular test within 3 months prior to screening.

9. Secondary efficacy analyses of primary endpoint

9.1. Time to event unfavorable outcome analysis

Time to an unfavourable outcome will be analysed with Kaplan Meier plots and Cox's proportional-hazards regressions analysis. These analyses will be performed according to ITT, MITT and PP endpoint classifications. Time to event will be calculated in days from the date of enrolment up to the first date associated with the reason for unfavourable status or (if favourable) the date of the 6 month after end of therapy visit.

10. Secondary efficacy endpoints

10.1. Incidence of bacteriologic failure or relapse at 24 months after the end of treatment

Efficacy analyses as described for the primary endpoint will be repeated for the 24 month after the end of treatment endpoint as a confirmatory analysis.

10.2 Time to sputum culture conversion to negative status

Time to culture negative status (first of two negative cultures without an intervening positive culture) will be analysed using survival analysis techniques, Kaplan Meier plots and Cox proportional hazard regression.

10.3 Culture conversion status at 4, 6, 8, 12 and 16 weeks

Patients will be classified as being culture positive, culture negative, dead or unassessable at 4, 6, 8, 12 and 16 weeks. Every effort will be made to obtain a sputum sample from all patients, but it is recognised that some patients may not have produced any sputum in the preceding week and may be unable to do so when requested. Patients who cannot produce sputum will be classified as being culture negative at that time point. The proportion culture negative will be those classified as being culture negative divided by the total considered culture negative, culture positive or have died. This proportion will be estimated from the Kaplan Meier estimates from the time to culture conversion to negative status analysis.

10.4 TB symptoms

Each TB symptom will be summarised by n (%): none (0), mild (1), moderate (2), severe (3) at each visit collected as per the protocol: baseline, week 8, end of treatment, 6 and 24 months from end of treatment.

In addition baseline and change from baseline score at each time point listed above for each symptom and for total symptom score will be summarised by mean, median, IQR and range.

10.5 Patient reported health status

Patient reported health status is measured by the 5 domains of EQ5D. These will be summarised at baseline, week 8, end of treatment, 6 and 24 months from end of treatment by randomised group and change from baseline at each follow-up assessment by mean, median, IQR and range by randomised group.

10.6 Weight

Baseline weight and change from baseline weight throughout treatment and at 6 and 24 months after the end of therapy will be summarised by mean, median, IQR and range.

11 Pharmacokinetics-Pharmacodynamics (PK-PD)analyses

Details of the PK parameter estimation and analysis are detailed in a separate PK SAP. PK-PD analyses will be described in a separate PK-PD SAP.

12 Sub-group analyses

To assess consistency of results, exploratory sub-group analyses of the primary endpoint on the MITT analysis population will be considered. For example, depending on numbers consideration will be given to subgroup analyses by: age; gender; race; smoking status; TB type (XDR vs not) HIV status/CD4 count; cavitation, initial bacterial load in sputum as indicated by baseline TTP result from MGIT; ARV taken or not during the treatment period.

13 Reasons for treatment failure as determined by the local PI

Reason(s) that led the site investigator to conclude that an individual patient failed treatment or relapsed will be classified as a) bacteriology alone, b) clinical deterioration alone, c) radiological deterioration alone, d) bacteriology plus clinical deterioration, e) bacteriology plus radiological deterioration, f) clinical deterioration plus radiological deterioration, or g) bacteriology plus clinical deterioration plus radiological deterioration. These classifications will be tabulated and compared to outcomes derived from the algorithm described in section 6.

14 Further exploratory analyses

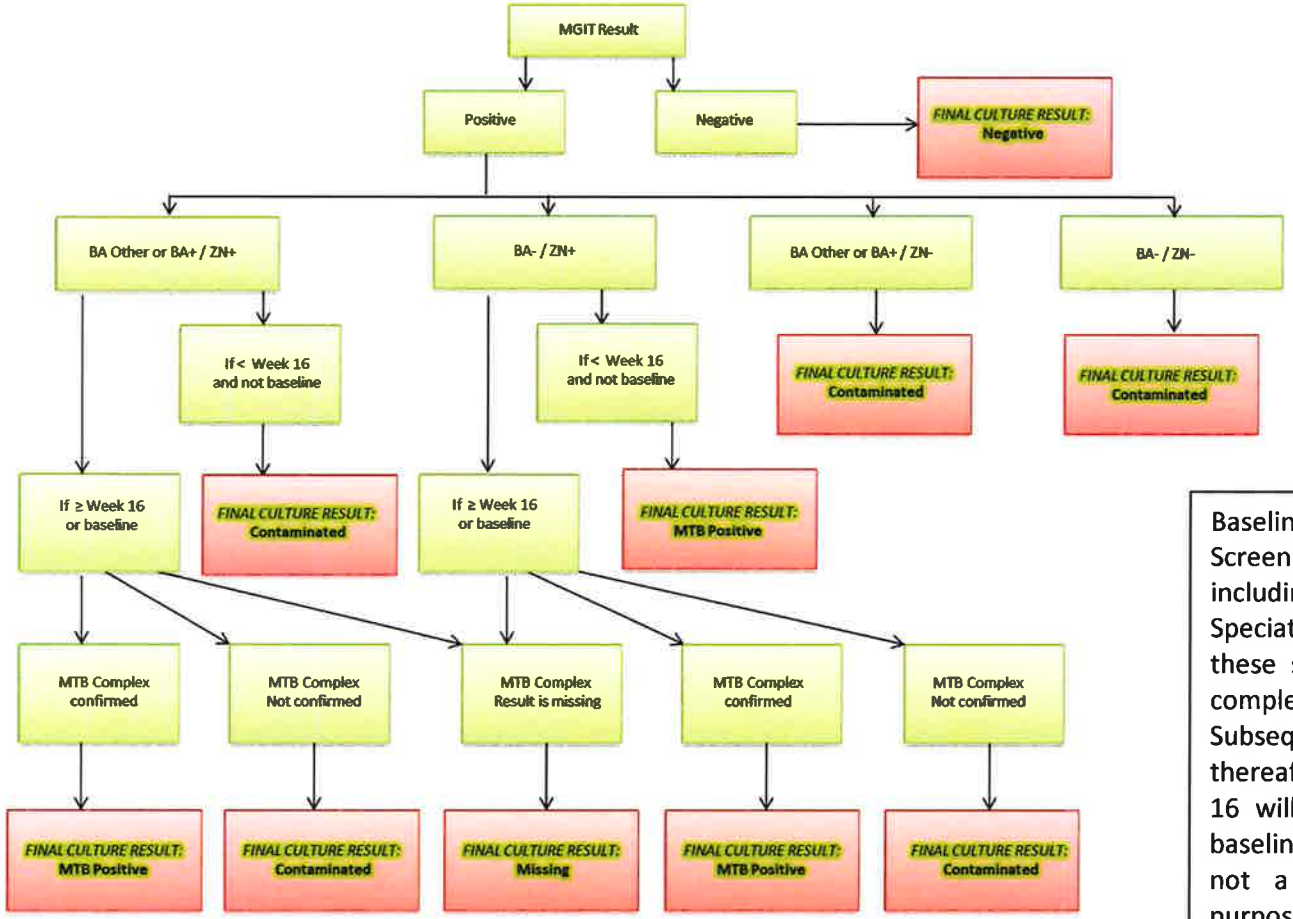
The exploratory efficacy endpoints and analyses are as follows:

- Evaluate whether any of the secondary endpoints predicts relapse-free cure.
- Correlation of time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity (the MPS50 value will be an assumed value from literature).

15 APPENDICES

15.1 Appendix 1 Algorithm for Interpretation of Positive MGIT Results

15.2 Figure A1. Algorithm for reporting MGIT final results



Baseline: Any visit from Screening up to (and including) week 4. Speciation will be done for these samples until a MTB complex is confirmed. Subsequent samples thereafter and before week 16 will be treated as post baseline (i.e. "<week 16 and not a baseline") for the purpose of this algorithm.

Table A2. Derived MGIT results per visit

Derived sample Culture Result (Visit X)	Derived Sample Culture Result (Visit X)	Final Derived Result for Visit X
Positive	Missing/Negative/Contaminated	Positive
Negative	Missing/Contaminated	Negative
Contaminated	Missing/Contaminated	Contaminated

15.2 Appendix 2 Interpretation of Relapse and Re-infection using Whole Genome Sequence (WGS) data

The purpose of the WGS analysis is to determine if the two M. tuberculosis strains from a given patient (positive culture at baseline and at or after the end of treatment) can be considered the **same** (treatment failure/bacteriologic failure or relapse/bacteriological relapse), or **different** (re-infection/bacteriological re-infection). To do this, WGS two M. tuberculosis strains are compared, the number of SNPs/variants determined, and the criteria outlined below followed. These cut offs have been determined from previously published reports (REMoxTB and RIFAQUIN trials) that show a clear genetic distinction between relapse and re-infection cases of M.tb infection.

- ≤12 SNPs different = Relapse
- ≥100 SNPs different = Reinfection
- >12 and <100 SNPs different = Indeterminate. These results will be reviewed on case by case basis and are likely to be rare. Additional sequence analysis may be performed and/or additional samples may need to be tested. Any additional investigations will be documented on the 'WGS Indeterminate Proforma' which also includes the final conclusion of 'relapse' or re-infection' based on this further review. A patient will be considered a relapse unless there is sufficient evidence to support a classification of re-infection.