CAPRISA 011

IMPROVING RETREATMENT SUCCESS (IMPRESS):
An open label randomized controlled clinical trial comparing a 24 week oral regimen containing Moxifloxacin with a 24 week standard tuberculosis (TB) drug regimen for the treatment of smear-positive pulmonary TB in patients previously treated for TB

STATISTICAL ANALYSIS PLAN

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Modifications to Statistical Analysis Plan after Trial Initiation

Version	Date	Changes from previous version
1	7 August 2017	
2	2 November 2018	- Addition of signature for statistician - Use of Fisher's exact test as an alternative to Chi-square test in section 6 - Move mention of log binomial/Poisson regression from 6.6 to 6.3 - Addition of use of the Gehan-Breslow-Wilcoxon test to 6.4

1. STUDY OBJECTIVES

1.1. Primary Objective

To determine if a Moxifloxacin-containing regimen, [Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Moxifloxacin (M)] of 24 weeks duration is superior to a control regimen [Isoniazid (H), Rifampicin(R), Pyrazinamide (Z), Ethambutol (E)] of 24 weeks duration in improving treatment outcomes in patients with recurrent TB.

1.2. Secondary Objectives

1. To determine the time to culture-conversion of the Moxifloxacin regimen and the Ethambutol regimen using data from 2-, 4-, 6-, and 8-week cultures
2. To compare the proportion of patients with any Grade 3 or 4 adverse reactions
3. To compare adverse events and 2-month culture conversion rates among HIV-infected patients vs. HIV-uninfected patients between the study arms
4. To compare the rates of treatment failure and recurrence of the intervention and control arm.
5. To compare TB cure rates at month 6 and at end of TB treatment between the intervention and control arm.

2. STUDY DESIGN

This is an open label randomized controlled clinical trial comparing two regimens for treatment of smear-positive pulmonary TB, among patients previously treated for TB. The primary objective is to determine if a Moxifloxacin-containing regimen, substituting Moxifloxacin for Ethambutol, of 24 weeks duration is superior to a control regimen of 24 weeks duration in improving treatment outcomes in patients with recurrent TB.

This study will include adults 18 years and over with a previous history of TB. HIV infected and uninfected patients will be included in the study as well as patients on ARVs provided that these are not contra-indicated with any of the study drugs. Patients with M tuberculosis

resistance to Rifampicin will be excluded at screening using Gene Xpert technology. A maximum of 330 participants will be included in the study.

Patients will be randomized in a 1:1 ratio to receive one of the two TB retreatment regimens, as outlined in the table below.

	Intensive Phase (2 months)	Continuation Phase
Intervention Arm	HRZM* daily (2 months)	HRM* daily (4 months)
Control Arm	HRZE* daily (2 months)	HR* daily (4 months)

* Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Moxifloxacin (M), Ethambutol (E)

The duration of TB treatment may increase due to a delay in the time to sputum conversion which will result in the extension of TB treatment beyond 6 months. Following treatment, participants will be followed up on a two-monthly basis for 12 months.

3. INTERIM DATA ANALYSIS AND DATA MONITORING

The CAPRISA SOP on DSMB preparations (SOP # CA STA 06) will be used to ensure that the quality of the data being used for this report is of high and reliable quality.

Interim results will include a summary of screening and enrolment, a summary of status for all enrolled participants (completed, discontinued early, possibly lost to follow-up, or continuing), retention rates, descriptive statistics of baseline variables (demographic, recent medical history), protocol violations (including both violations at enrollment/randomisation and violations after enrolment) and adverse events (including serious adverse events).

Data management quality indicators such as the total number of datafax CRF pages received, total number of QC notes placed on data received, QC rate per 100 pages, percent QC resolved, and number of days to QC resolution will be given.

For the safety data, adverse events occurring during the study will be summarised in frequency tables by study arm. Adverse events will be coded using the MedDRA system, version 15 or higher. Safety data will be summarised for all study participants who were consented, enrolled, and randomised to study arm, excluding those participants who never provided any safety data after enrollment.

No formal stopping rules are set. The Safety Monitoring Committee (SMC) should review all available safety data to determine whether there are any safety concerns and whether early termination of the study is warranted. There are circumstances in which some interpretation or flexibility may be required. If some indication of harm is found the DSMB should strongly consider taking action.

4. ANALYSIS POPULATION DEFINITIONS

All primary and most secondary analysis will be conducted based on the intention-to-treat (ITT) principle. However, for purposes of assessing the effectiveness of the implementation model, various analysis populations are defined as follows:

Intention-to-treat population

This population consists of all participants enrolled and randomised to the intervention and control arms. Individuals who will be identified as ineligible for enrolment based on criteria pre-randomisation criteria will be excluded. Moreover, individuals with no post-randomisation visit and no data collected will be excluded.

Per protocol Population

This is a subset of the ITT population, excluding all subsequent data collected from participants with a documented interruption of TB treatment for three or more consecutive months arising from:

- Missed visits,
- An adverse event

5. GENERAL STATISTICAL ISSUES

All tests will be two-sided, and the significance level will be 0.05.

Outliers will be identified by looking at summary statistics and scatter plots. All outliers detected will be verified from the source documentation. Outliers that have biologically impossible values will be excluded from all data summaries and analyses. If one (or several) outlier(s) change(s) the interpretation of the data substantially, two summaries and analyses will be done, one with and one without the outlier(s).

If a participant has missing data at a specific time point, data at all non-missing time points for the participant will be used and included in the summaries. Missing data will be ignored (i.e. treated as missing at random) unless patterns are identified which would potentially bias analysis results.

Where applicable, analyses will be stratified by HIV status.

All statistical analyses will be done using SAS (SAS Institute Inc., Cary) version 9.4 or higher.

6. STATISTICAL ANALYSIS

6.1. Participant disposition

The number and percentage of participants screened, reasons for not enrolling screened participants and enrolled in the study will be given. The reasons for termination will be given for all participants where available. A consolidated standard of reporting trials (CONSORT) diagram showing the flow of participants through the trial will be provided.

6.2. Analysis of baseline data

Baseline variables will be summarised for all participants in the ITT population. Age will be calculated as the difference between date of birth and the date of enrolment. If date of birth is not given, the age reported in years will be regarded as the age at enrolment. The following baseline measures will be summarised: Age, gender, BMI, HIV status, number of previous episodes of TB and other relevant medical and demographic characteristics collected at the screening and enrolment visits.

Measures of central tendency and dispersion for continuous variables will include means, medians, standard deviations, median and interquartile range. Categorical data will be summarised with frequencies and percentages. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. If any categorised continuous variables are to be included as covariates in statistical models, then a rationale for the choice of categorising cut points should be provided.

6.3. Primary objective

To determine if a Moxifloxacin-containing regimen, [Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Moxifloxacin (M)] of 24 weeks duration is superior to a control regimen [Isoniazid (H), Rifampicin(R), Pyrazinamide (Z), Ethambutol (E)] of 24 weeks duration in improving treatment outcomes in patients with recurrent TB.

To answer the primary objective of this study the culture conversion rates will be compared between the two treatment arms at the end of the intensive phase and at month 6, where culture conversion is defined as the first of two negative (or no growth) cultures at two different visits without an intervening positive culture. This will be done by calculating the proportion of culture conversions in each of the two arms and at each of the two time points and comparing these using the chi-square test or Fisher's exact test. Log binomial regression

or Poisson regression with robust variance will also be used to improve precision of the treatment effect estimates.

6.4. Secondary objective 1

To determine the time to culture-conversion of the Moxifloxacin regimen and the Ethambutol regimen using data from 2-, 4-, 6-, and 8-week cultures

Time to culture conversion is defined as the time from treatment initiation to the date of the first of two negative cultures at two different visits without an intervening positive culture. Kaplan–Meier curves and the Gehan-Breslow-Wilcoxon test will be used to compare time to culture conversion across the two arms. Proportional hazards regression will also be used to assess whether time to culture-conversion differs across the two arms.

6.5. Secondary objective 2

To compare the proportion of patients with any Grade 3 or 4 adverse reactions

Adverse events occurring during the study will be summarised in frequency tables by arm. The frequencies of Grade 3 and 4 adverse events will be compared between the two arms using the Fisher's exact test.

6.6. Secondary objective 3

To compare adverse events and 2-month culture conversion rates among HIV-infected patients vs. HIV-uninfected patients.

The culture conversion rates of HIV-negative patients at the end of the intensive phase will be compared to the rates of HIV-positive patients at the end of the intensive phase using the Cochran-Mantel-Haenszel test, stratifying by study arm.

Within each study arm, the number of adverse events from HIV-negative patients will be compared to the number from HIV-positive patients using the Fisher's exact test.

6.7. Secondary objective 4

To compare the rates of treatment failure and recurrence of the intervention and control arm.

This will be done by calculating the proportion of participants who do not have a negative culture result at end of treatment or who relapse post treatment in each of the two arms. The proportions will be compared these using the chi-square test or the Fisher's exact test.

6.8. Secondary objective 5

To compare TB cure rates at month 6 and at end of TB treatment between the Intervention and Control Arm

This will be achieved by calculating the proportion cured at month 6 and at the end of treatment in each of the two arms and comparing these proportions using the chi-square test or Fisher's exact test.

References

Collett, D. (1994). *Modelling Survival Data in Medical Research*. London: Chapman and Hall.

Rothman, K.J. and Greenland, S. (1998). *Modern Epidemiology*, 2nd Ed., Philadelphia: Lippincott - Raven.