

Mycotic Antimicrobial Localized Injection

Statistical Analysis Plan

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1. Background

Mycotic Antimicrobial Localized Injection (MALIN) is a randomized, double-masked, two-arm clinical trial. The purpose of this study is to determine if intrastromal injection with voriconazole in combination with topical natamycin is superior to topical natamycin alone. Study participant's eyes will be randomized to one of two treatment groups – 1.) Topical natamycin alone or 2.) Topical natamycin plus intrastromal voriconazole injections.

2. Sample Size and Randomization

If we enroll 70 study participants we estimate that we will have over 80% power to detect a 25% difference in repeat culture status (50% in the control group vs. 25% in the voriconazole group), assuming a two-tailed alpha 0.05% and no loss to follow up (since participants will be hospitalized after enrollment until the 3-day repeat cultures are taken). Participants will be randomized using random block sizes in Microsoft Excel (KJR).

3. Baseline Characteristics

Baseline characteristics between the 2 arms will be compared using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

4. Primary Analysis

The primary study analysis will be microbiological cure at 3 days. We will compare 3-day culture positivity between the two groups using a logistic regression model (dichotomous culture positive or culture negative outcome) controlling for baseline culture status. Protocol for obtaining cultures is outlined in the MOP.

5. Secondary Analyses

- We will compare BSCVA between the two groups, at the 3-month time period (between 2.5-3.5 months) using the Wilcoxon rank sum with a 2-sided alpha of 0.05. For study participants who experience perforation or undergo TPK this will be noted and a BSCVA will be performed prior to performing further surgery, this last observation will be carried forward (LOCF) as the 3-month BSCVA. An enhanced analysis using standard longitudinal modeling methods will be used to handle data from study participants who are lost to follow up.
- We will compare 7-day culture positivity between the two groups using a logistic regression model (dichotomous culture positive or culture negative outcome) controlling for baseline culture status
- Scar size as measured on clinical exam and photographs
- Corneal topography
- Corneal Thickness and scar size as measured by OCT
- IND-VFQ will be compared between the two groups controlling for baseline VFQ
- Analyses of perforations or other adverse events
- A cost effectiveness analysis will be performed

6. Interim Monitoring

A masked interim analysis will be conducted to re-evaluate sample size based on 3-day culture positivity when one-third of the data have been collected. A medical monitor will be appointed at UCSF to monitor any serious adverse events. A small DSMC at UCSF will be appointed to conduct an un-masked interim analysis to evaluate for futility or harm.