Statistical Analysis Plan

PROCLAIM – A Randomized, Double-Blind, Placebo-Controlled Trial to Assess the Efficacy and Safety of Misoprostol in the Prevention of Recurrence of Clostridium Difficile Infection in Adults

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Statistical Analysis Plan for PROCLaIM

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MISOPROSTOL IN THE PREVENTION OF RECURRENT CDI

A Randomized, Double-Blind, Placebo-Controlled Trial To Assess The Efficacy And Safety Of Misoprostol In The Prevention Of First Recurrence Of Clostridium Difficile Infection In Adults Aged 50 And Over

Statistical Analysis Plan

Version 1.1

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Introduction

This document describes the statistical design and analysis plan for a double-blinded, randomized 1:1 controlled trial to test the efficacy and safety of Misoprostol for the prevention of recurring clostridium difficile infection (rCDI). A total of 440 adults aged 18 years and older with a recent diagnosis of CDI will be recruited from 3 sites. Consenting patients will be randomized 1:1 to receive either misoprostol or matching placebo. For patients taking antibiotics, consenting patients will be contacted on the last regular business day before the seventh day of oral antibiotic treatment, to remind all patients to begin the treatment that they were randomized to on day 7 of their oral antibiotic treatment; patients not taking oral antibiotics will start taking misoprostol 7-10 days after a positive CDI lab test. All randomized patients who were taking antibiotics will continue to take oral antibiotics for an additional 4-7 days after starting misoprostol treatment (such that those participants have a 4-7 day overlap of antibiotic and misoprostol treatment), and begin taking an investigational 200 mcg oral misoprostol or placebo two times a day (200 mcg po BID) for 14 days. All randomized patients will be monitored for recurrence via phone call once per week for an additional 49 days (the total duration of study participation will be 62 days).

Treatment arms

Participants will be randomized to receive either:

a) Treatment: 200 µg oral misoprostol two times a day for 14 days
b) Control: Placebo two times a day for 14 days

Endpoints

Clinical recurrence of clostridium difficile infection (rCDI): the primary endpoint for this trial is recurrence of a clostridium difficile infection within 8 weeks after vancomycin is stopped (i.e. from four days after study treatment has begun to 60 days after study treatment has begun). Recurrence will be defined to have occurred when a participant concurrently meets all criteria for a clostridium difficile infection:

a) ≥3 unformed (loose or watery) stools within a 24-hour period;
b) A documented positive C. difficile toxin assay (enzyme immunoassay [EIA] or cellular cytotoxicity assay) or DNA PCR assay for toxigenic C. difficile from a stool sample collected while the subject was symptomatic; and
c) No other explanation for diarrhea (e.g. laxatives).

A patient will be considered to not have experienced rCDI if all of these criteria are not met within the 8 week follow up period.

Safety and tolerability: The two secondary endpoints for this trial are safety and tolerability. A participant will be defined to have experienced a safety outcome if there is a treatment-related adverse event, clinically relevant changes in physical examinations, or clinical safety laboratory testing. A participant will be defined as having experienced a tolerability outcome if the participant, the investigators, or a treating physician reduces the dosage or stops study treatment citing side effects or adverse events as the reason.

Exploratory endpoints: A number of exploratory endpoints are expected to be impacted by treatment and so are included in this study. These include:

- Serum biomarkers/toxin A and B antibodies from blood draws
- Recovery of bowel microbiota assessed from microbiome collection.
- For patients with recurrence, additional endpoints are:
    - Number of recurrences during the follow-up period.
    - Time to resolution of diarrhea.
    - Serum biomarkers/toxin A and B antibodies (from blood draws).
    - Severity of disease (for those with recurrence), determined using a combination of severity criteria used in Hospital specific guidelines, SHEA/IDSA guidelines, Zar criteria, or other sources:

        - WBC
        - Serum creatinine
        - Temperature
        - Albumin level
        - ICU or step down unit admission
        - Endoscopically or histologically confirmed pseudomembranous colitis
        - Toxic megacolon, perforation, colectomy, or septic shock requiring ICU admission and pressors
        - Hospital readmission
        - Validated quality of life instrument

Final analysis

The final analysis for this trial will occur after all enrolled subjects have been followed for 8 weeks all queries have been resolved, and the database has been locked.

Descriptive analysis

Initially, the study sample will be described by demographics, clinical characteristics and primary, secondary and exploratory endpoints. The study sample will be described both overall and stratified by treatment arm. Categorical variables will be described using frequencies and percentages. Continuous variables will be described using means and standard deviations and/or medians and interquartile ranges. Data visualization and summary statistics will be used to evaluate distributional assumptions and to guide selection of data transformations or use of non-parametric alternatives where appropriate.

Analysis of primary endpoints

The main analysis will be a Fisher's Exact test to compare the proportion (rate) of recurrence between treatment arms. The null hypothesis to be tested is that the proportions do not differ between treatment arms.

A difference in the primary endpoint between treatment groups will be declared if the two-tailed p-value is less than 0.048. Because any efficacy claim will be based on a single comparison of the primary endpoint between treatment arms, no adjustment for multiple testing will be made for this analysis.

Analysis of secondary endpoints

The safety and tolerability endpoints will be compared between study arms using a Fisher's Exact test with a significance level of 0.025 (i.e. 0.05/2). This controls the overall type 1 error rate for a claim on safety and tolerability at 5%.

Intent-to-treat analysis

The final analysis for this trial will use the intent-to-treat principle with no modifications. With this approach, participants will be grouped according to the arm to which they were assigned regardless of whether they received the control or the treatment.

Adjusted analysis

There are a number of key factors that might affect endpoints independently of any treatment effect. We will use logistic regression to separately model the odds of rCDI, safety and tolerability as a function of treatment arm adjusted for demographics, baseline disease severity, comorbidities, and site (as a random variable). Statistical models will be constructed following best practices. Briefly, the primary endpoint is rCDI is a dichotomous outcome of yes/no. This will be modeled as logistic regression controlling for treatment, baseline severity, age, sex, pertinent labs. One of the secondary endpoints is time to resolution of diarrhea which will be modeled using time-to-event analysis controlling for baseline severity, age, sex, labs.

Subgroup analysis

There are no expected subgroups based on mechanism of action. Subgroup analyses will be pursued if there is an interaction between the subgrouping variable and the treatment variable. For example, we will test the interaction between sex and treatment. If the interaction is significant, we will separately estimate the treatment effect for males and females. Recognizing that the power for finding interactions is low and the importance of understanding heterogeneity of treatment effects is high, we will use a significance level of 10%. The following subgrouping variables will be considered:

- Age (<65 v ≥65 yrs)
- Race (Black, white, other)
- Ethnicity (Hispanic or latino v not Hispanic or latino)
- Sex (male v female)

Subgroup analyses will follow the same approach as the primary analyses whereby an unadjusted analysis will be used to test the primary and key secondary endpoints followed by generation of a statistical model. We will not make any adjustments for multiplicity in these analyses.

Exploratory analyses

Exploratory endpoints will be compared between treatment arms. Continuous variables will be compared using student's t-test or the non-parametric equivalent (Mann-Whitney U test) if distributional assumptions are not met. Ordinal variables will be compared using the Mann-Whitney U-test. Categorical variables will be compared using Fisher's Exact test. Adjusted analyses may be utilized.

Randomization

Participants will be randomized to receive either treatment or control upon confirmation that the patient has responded to oral vancomycin treatment (day 7 of vancomycin treatment). Randomization will use a randomly permuted small blocks approach with stratification by site, sex and severity of illness, as defined by IDSA criteria for severity (if bloodwork is not available, the patient will be assumed to be "non-severe"):

- Non-severe: Leukocytosis with a WBC count of ≤15,000 cells/mL and serum creatinine <1.5 mg/dL
- Severe: Leukocytosis with a WBS count >15,000 cells/mL or serum creatinine >1.5 mg/dL
- Fulminant: Hypotension or shock, ileus, megacolon

Interim analysis

We will perform an interim safety analysis after 44 patients (10% of accrual) have completed study treatment (14 days after randomization). It is expected that of the first 44 patients, although there might be dose adjustments, there will be no greater than 5 withdrawals due to diarrhea events during the period of co-administration with vancomycin. If more than 5 diarrheal events occur among the first 44 patients which require study withdrawal during the co-administration period, enrollment will be interrupted for safety concerns. All currently enrolled participants will be followed to completion and the data will be analyzed to estimate conditional power; no statistical testing will be performed. The data will be presented to the DSMB to determine whether the study should proceed or not. If no more than 5 diarrhea events occur among the first 44 patients which require study withdrawal, the study will continue without interruption of enrollment.

A planned interim analysis will be conducted after the 176th participant has completed the 63 days of follow up, with accrual continuing during this time. This will allow the study to be terminated early in the event there is a less than acceptable chance of detecting the desired effect, therefore not wasting funds or exposing patients to unnecessary risk with no commensurate benefit. We propose the interim analysis for efficacy will be completed using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary to account for the 2 interim analyses and the final analysis. The significance boundary for final analysis will be $P \leq .048$. The interim analysis for futility will be based on the stochastic curtailment method. The interim analyses for futility will be performed by calculation of conditional power, an estimate of the probability that the study shows a statistically significant effect on the primary endpoint, i.e. a reduction in the rate of recurrence, given the results to date and assumptions regarding outcome through the end of the study. A recommendation to stop the trial for futility will require a conditional power below 30%, under the observed efficacy trend at the time of interim analysis, with two-sided type I error less than 5%. The proposed sample size of 196 per arm is adjusted for the interim analyses, i.e., types I and II errors.

Power and sample size calculations

Participants will be considered enrolled at the time of randomization. With 196 participants in each group (392 total participants), there will be 80% power to detect a relative reduction in rCDI of 40% when the control rCDI rate is 30%. We expect a drop-out rate of 10%, therefore, we will randomize 440 participants to account for attrition and sill achieve the expected power.

The participants who drop-out will be described and balance checked between the two groups of participants.

Missing data

Participants are not evaluable on their primary outcome will be excluded from the primary analysis. Similarly, participants not evaluable on the key secondary outcomes will be excluded. For statistical modeling, multiple imputation will be used to resolve missing data on predictor variables.

Sensitivity analyses will be conducted including these participants under various assumptions of treatment effect (e.g. treatment resulting in the worst outcome and placebo the best; treatment resulting in the best outcomes and placebo the worst.)