Statistical Analysis Plan (SAP): (Protocol NA-2024-01)

Official Title: Double-Blind, Placebo-Controlled, Parallel-Group Randomized Controlled Trial to Evaluate the Efficacy and Safety of Nimsai Herbal in Patients with Grade 2-3 Hemorrhoids

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1. Introduction

This Statistical Analysis Plan (SAP) outlines the detailed methodology for the statistical analysis of data collected during Protocol NA-2024-01, double-blind, placebo-controlled, parallel-group Randomized Controlled Trial evaluating the efficacy and safety of Nimsai Herbal in patients with Grade 2-3 hemorrhoids. This SAP is developed in conjunction with the study protocol (Protocol ID: NA-2024-01) and adheres to the principles of ICH Good Clinical Practice (GCP).

2. General Statistical Approach

- Analysis Populations: Analyses will be conducted on an intention-to-treat (ITT) basis, including all randomized participants regardless of treatment adherence or protocol deviations. A per-protocol (PP) sensitivity analysis will also be performed to assess the robustness of the primary findings, including only participants who completed the study as per protocol and had no major deviations.
- Missing Data Handling: Missing data for primary and secondary outcomes will be handled using appropriate methods, primarily multiple imputation if data are considered missing at random (MAR). Sensitivity analyses using Last Observation Carried Forward (LOCF) or complete case analysis will also be performed where appropriate.
- Software: Statistical analyses will be performed using validated statistical software, specifically SAS (Statistical Analysis System) or R.
- Significance Level: All statistical tests will be two-tailed, and a significance level of $\alpha=0.05$ will be used to determine statistical significance.
- Interim Analysis: No interim analyses are planned for this study, given its short duration (10 days) and the low expected risk of serious adverse events (SAEs).

3. Outcome Measures and Statistical Analysis

This section details the statistical methods for each predefined outcome measure.

3.1. Primary Outcome: Hemorrhoid Regression Rate

- Name: Hemorrhoid Regression Rate
- Definition: Percentage of participants achieving a clinical response, defined as a ≥75% reduction in composite hemorrhoid severity score from baseline.
- Time Frame: Day 10 (end of treatment and follow-up period)
- Statistical Test: Chi-square test
- Method: Comparison of categorical data (proportion of participants achieving ≥75% reduction) between the Nimsai Herbal group and the placebo group.
- Effect Size: Risk Difference with a 95% Confidence Interval (CI).
- Power Calculation: Based on an assumed 50% regression rate in the Nimsai Herbal group and 20% in the placebo group, a sample size of 150 participants per arm (total 300) provides >90% power to detect a statistically significant difference at an $\alpha=0.05$ (two-tailed) significance level.

3.2. Secondary Outcomes

3.2.1. Visual Analog Scale (VAS) Symptom Score Change

- Name: Visual Analog Scale (VAS) Symptom Score Change
- Definition: Mean change in self-reported hemorrhoid symptom severity from baseline to Day 10, measured on a 0–10 Visual Analog Scale.
- Time Frame: Baseline to Day 10
- Statistical Test: Mann-Whitney U test
- Method: Non-parametric comparison of continuous data (change in VAS scores) between the Nimsai Herbal and placebo groups. This test is chosen due to the expected non-normal distribution of patient-reported symptom scores.
- Effect Size: Mean Difference with a 95% CI.
- Adjustment: Baseline VAS scores may be included as a covariate in sensitivity analyses to account for any residual imbalance or improve precision.

3.2.2. Symptom Resolution Rate

- Name: Symptom Resolution Rate
- Definition: Percentage of participants reporting complete resolution of baseline hemorrhoid symptoms (pain, bleeding, itching, swelling), defined as a composite severity score of 0.
- Time Frame: Day 10
- Statistical Test: Chi-square test
- Method: Comparison of categorical data (proportion of participants with complete symptom resolution) between the Nimsai Herbal and placebo groups.
- Effect Size: Risk Ratio with a 95% CI.
- Adjustment: Logistic regression may be used to adjust for baseline hemorrhoid severity or other relevant covariates in supplementary analyses.

3.3. Safety Outcomes

3.3.1. Incidence of Mild Gastrointestinal Discomfort

- Name: Incidence of Mild Gastrointestinal Discomfort
- Definition: Percentage of participants reporting mild gastrointestinal adverse events (e.g., nausea, bloating, dyspepsia) during the study period.
- Time Frame: Baseline to Day 10
- Statistical Test: Fisher’s Exact test
- Method: Comparison of categorical incidence data between the Nimsai Herbal and placebo groups. Fisher's Exact test is chosen due to the expected low event frequencies.
- Effect Size: Risk Difference with a 95% CI.

3.3.2. Incidence of Serious Adverse Events (SAEs) and Withdrawals Due to Adverse Events

- Name: Incidence of Serious Adverse Events (SAEs) / Incidence of Withdrawals Due to Adverse Events
- Definition: Percentage of participants experiencing SAEs or discontinuing treatment/withdrawing due to AEs.
- Time Frame: Baseline to Day 10
- Statistical Test: Fisher’s Exact test (if events occur)
- Method: Comparison of incidence data between groups. If no events are observed in either group, descriptive reporting will be provided (0% incidence).
- Effect Size: Risk Difference with a 95% CI.

3.3.3. Incidence of Transient Diarrhea in Diabetic Participants

- Name: Incidence of Transient Diarrhea in Diabetic Participants
- Definition: Number of diabetic participants experiencing transient diarrhea (resolving spontaneously without intervention or withdrawal) during the early treatment period (Days 1–3).
- Time Frame: Days 1–3
- Statistical Test: Not applicable for a single event or very rare events.
- Method: Descriptive reporting with qualitative context ("rare, <1% incidence"), as formal statistical analysis is not feasible or appropriate for isolated events.
- Effect Size: Not calculated.

4. Baseline Characteristics Analysis

- Descriptive statistics (mean ± SD for continuous variables, n/% for categorical variables) will be used to summarize baseline characteristics for each treatment arm.
- Statistical tests (t-tests for continuous variables, chi-square tests for categorical variables) will be performed to confirm the balance of baseline characteristics between the Nimsai Herbal and placebo groups, ensuring randomization effectively distributed participant characteristics.