Full Clinical Study Protocol: (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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Abbreviations

- AE: Adverse Event
- CRF: Case Report Form
- DSMB: Data Safety Monitoring Board
- GCP: Good Clinical Practice
- ICH: International Conference on Harmonisation
- ICF: Informed Consent Form
- IPD: Individual Participant Data
- IRB: Institutional Review Board
- ITT: Intention-to-Treat
- LOCF: Last Observation Carried Forward
- NCT: National Clinical Trial (ID)
- PP: Per-Protocol
- RCT: Randomized Controlled Trial
- SAE: Serious Adverse Event
- SAP: Statistical Analysis Plan
- SD: Standard Deviation
- VAS: Visual Analog Scale

1. Introduction

1.1. Background on Hemorrhoidal Disease Hemorrhoidal disease (HD) is a highly prevalent anorectal condition affecting millions globally, characterized by symptoms such as bleeding, pain, itching, swelling, and prolapse. Despite its widespread occurrence, the traditional understanding of hemorrhoids as mere varicosities or venous dilatations has proven insufficient in explaining their complex pathogenesis, high recurrence rates, and the limited efficacy of many conventional treatments. Current therapeutic approaches predominantly focus on symptomatic relief or surgical removal, often overlooking the underlying mechanisms.

1.2. The War-Drill Model and Sine Qua Non Hypothesis Nimsai Academia proposes a paradigm shift in understanding HD through the "War-Drill Model." This model posits that venous congestion, rather than primary venous dilatation, is the fundamental and indispensable prerequisite (Sine Qua Non Hypothesis) for the development and progression of hemorrhoidal disease. This congestion leads to secondary vascular deformation and the manifest symptoms. The model categorizes HD into two distinct modes:

- War Mode Hemorrhoids: Characterized by chronic venous congestion often driven by systemic or local inflammatory conditions (inflammatory bowel disease, anal fissures, liver cirrhosis, chronic constipation). These hemorrhoids may serve as an early biological warning system for up to 20 potential underlying pathologies, necessitating a comprehensive diagnostic workup and systemic therapeutic intervention.
- Drill Mode Hemorrhoids: Characterized by transient vascular engorgement primarily due to hormonal fluctuations (pregnancy, menopause). These are typically self-limiting and may resolve spontaneously once the hormonal influence subsides. The "Parola Phenomenon," a clinical maneuver developed by Nimsai Academia, is hypothesized to differentiate between War Mode and Drill Mode hemorrhoids with high sensitivity and specificity (reported 94% sensitivity and 91% specificity), thereby guiding appropriate diagnostic and therapeutic strategies.

1.3. Rationale for Nimsai Herbal Intervention Nimsai Herbal is a proprietary botanical formulation specifically designed to target the underlying venous congestion proposed by the War-Drill Model. Its active components – *Centella asiatica* extract, *Curcuma longa* extract, and *Piper nigrum* extract – are selected for their venotonic, anti-inflammatory, antioxidant, and

bioavailability-enhancing properties. By addressing the root cause of venous congestion, Nimsai Herbal is hypothesized to offer a more effective and sustainable treatment approach compared to symptomatic or localized therapies. The systemic nature of Nimsai Herbal aligns with the War-Drill Model's emphasis on underlying systemic or local inflammatory conditions contributing to hemorrhoidal pathogenesis.

1.4. Study Rationale and Justification This randomized controlled trial (RCT) is designed to rigorously evaluate the efficacy and safety of Nimsai Herbal in patients with Grade 2-3 hemorrhoids. The study will not only assess the clinical benefits of Nimsai Herbal but also provide further clinical validation for the War-Drill Model and its implications for diagnosis and treatment. Establishing the efficacy and safety of Nimsai Herbal could lead to a significant improvement in patient care, reduce recurrence rates, and potentially yield substantial global healthcare savings by facilitating early diagnosis of underlying conditions and reducing the need for invasive procedures.

2. Study Objectives

2.1. Primary Objective To evaluate the efficacy of Nimsai Herbal capsules in achieving hemorrhoid regression, defined as a ≥75% reduction in composite hemorrhoid severity score from baseline to Day 10, compared to placebo in patients aged 18-70 years with symptomatic Grade 2-3 internal hemorrhoids.

2.2. Secondary Objectives

- To assess the mean change in self-reported hemorrhoid symptom severity using a Visual Analog Scale (VAS) from baseline to Day 10.
- To determine the percentage of participants achieving complete resolution of baseline hemorrhoid symptoms (composite severity score = 0) by Day 10.
- To explore the clinical utility of the War-Drill Model in guiding treatment response and diagnostic pathways.
- To evaluate the proportion of participants experiencing a significant reduction in individual symptoms (bleeding, pain, itching, swelling) by Day 10.

2.3. Safety Objectives

- To determine the incidence of mild gastrointestinal discomfort (nausea, bloating, dyspepsia) in both treatment groups during the 10-day intervention.
- To assess the incidence of Serious Adverse Events (SAEs) in both treatment groups during the 10-day intervention.
- To determine the incidence of participant withdrawals due to adverse events in both treatment groups during the 10-day intervention.
- To specifically monitor and report the incidence of transient diarrhea in diabetic participants during the first three days of the intervention.

3. Study Design

3.1. Overall Design This is a prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial. Participants aged 18-70 years with symptomatic Grade 2-3 internal hemorrhoids will be randomized in a 1:1 ratio to either the Nimsai Herbal group or the placebo group. The intervention period will be 10 consecutive days.

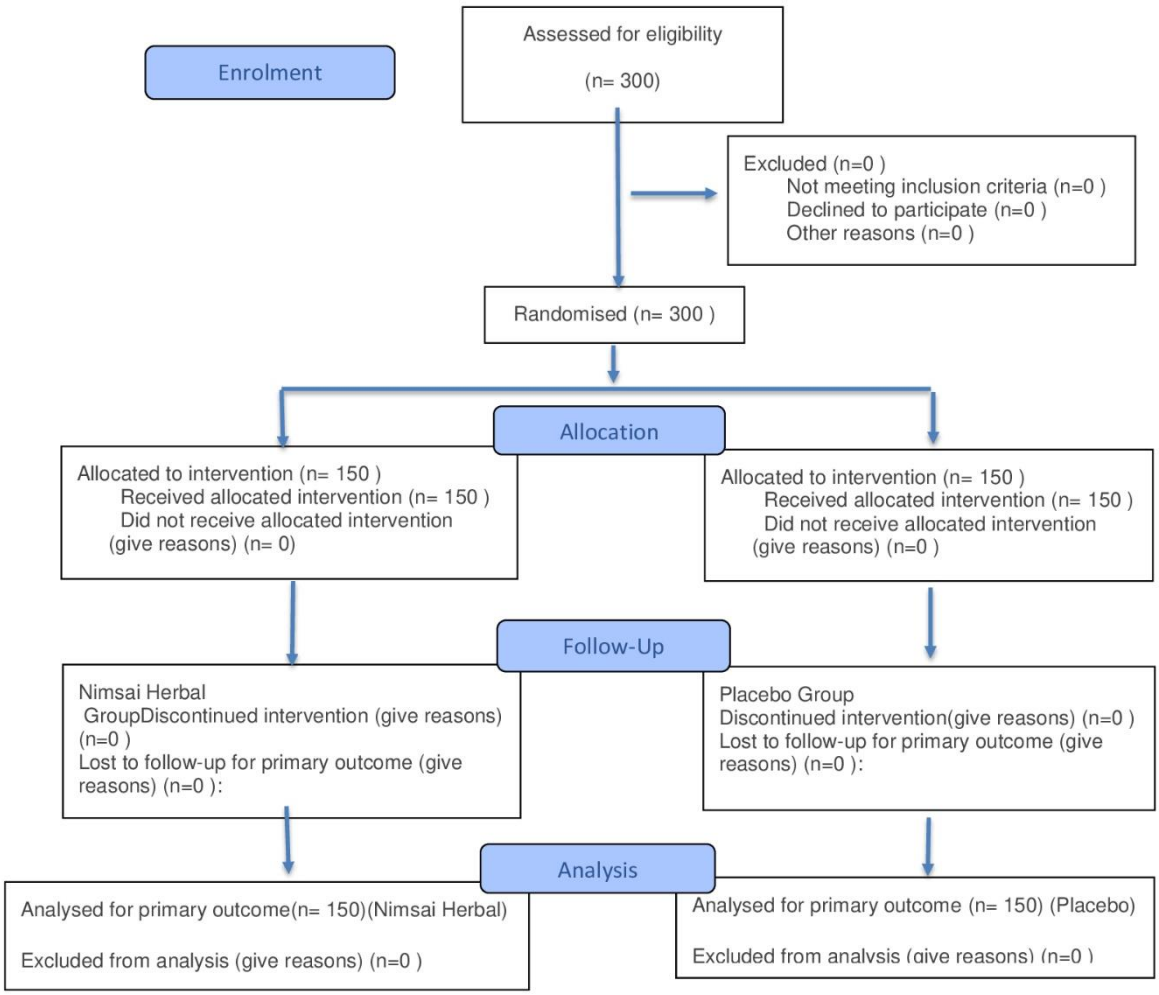
3.2. Study Period and Duration

- Overall Study Period: October 10, 2021, to November 14, 2021. This period includes participant screening, enrollment, 10-day intervention, and final data collection.
- Intervention Duration: 10 days for each participant.
- Total Study Duration per Participant: Approximately 10-14 days (including screening and final assessment).

3.3. Enrollment and Sample Size

- Planned Enrollment: A total of 300 participants will be enrolled (150 in the Nimsai Herbal group and 150 in the placebo group).
- Sample Size Justification: A sample size of 150 participants per arm (total 300) provides >90% power to detect a 30% difference in hemorrhoid regression rate (assuming 50% regression in the Nimsai Herbal group vs. 20% in the placebo group) with a two-sided alpha level of 0.05. This calculation accounts for potential minor dropouts.

3.4. Study Flow Diagram



4. Study Population

4.1. Inclusion Criteria Participants must meet all of the following criteria to be eligible for enrollment:

- Males and females aged 18 to 70 years, inclusive, at the time of signing the Informed Consent Form (ICF).
- Diagnosis of symptomatic internal hemorrhoids, clinically and endoscopically confirmed as Grade 2 or 3 according to the Goligher classification system.
- History of hemorrhoidal symptoms (e.g., bleeding, pain, itching, swelling, discomfort) persisting for more than 6 weeks prior to screening.
- Willingness and ability to provide written informed consent.
- Willingness and ability to comply with all study procedures, schedules, and follow-up requirements.
- Able to understand and communicate effectively in the local language of the study site.

4.2. Exclusion Criteria Participants will be excluded if they meet any of the following criteria:

- Diagnosis of Grade 1 or Grade 4 hemorrhoids.
- Any known anorectal malignancy or suspicion of malignancy (colorectal cancer, anal canal carcinoma, inflammatory bowel disease affecting the anorectum, severe anal fissures or fistulas requiring immediate surgical intervention).
- Active bleeding from sources other than hemorrhoids (diverticulitis, inflammatory bowel disease).
- Currently pregnant or lactating women, or women of childbearing potential not using an effective method of contraception.
- Known hypersensitivity or allergy to any component of Nimsai Herbal capsules or placebo ingredients.
- Significant systemic diseases including, but not limited to, severe cardiovascular disease (unstable angina, recent myocardial infarction), severe renal impairment (end-stage renal disease), severe hepatic dysfunction (decompensated cirrhosis), or uncontrolled diabetes mellitus (HbA1c > 9%).
- Any medical or psychiatric condition that, in the opinion of the investigator, might compromise the participant's safety, ability to complete the study, or the integrity of the study data.
- Participation in another interventional clinical trial within 30 days prior to screening or during the current study.
- Use of concurrent treatments for hemorrhoids (other oral supplements, topical creams, suppositories) within 7 days prior to screening or during the study period.
- History of hemorrhoidectomy or other invasive hemorrhoid procedures (banding, sclerotherapy) within the last 6 months.

4.3. Participant Recruitment Participants will be recruited through local advertising (posters in clinics, online advertisements, local media) at Nimsai Academia, Türkiye. All recruitment materials will be reviewed and approved by the Nimsai Academia Ethics Committee. Potential participants will undergo a preliminary phone screening to assess initial eligibility before scheduling an in-person screening visit.

4.4. Screening and Enrollment Procedures

- Screening Visit (Day -2 to Day 0):
    - Review of inclusion/exclusion criteria.
    - Detailed medical history including current and past medications.
    - Physical examination including digital rectal examination and anoscopy/endoscopy to confirm hemorrhoid grade.
    - Baseline assessment of hemorrhoid symptoms using a composite severity score (0-40) and VAS (0-10).
    - Collection of demographic data (age, sex).
    - Laboratory tests (complete blood count, liver and kidney function tests, fasting glucose/HbA1c for diabetic participants) to rule out underlying conditions as per exclusion criteria.
    - Informed consent process (detailed in Section 12.2).
- Enrollment (Day 0):
    - Participants meeting all inclusion and no exclusion criteria and who have provided informed consent will be officially enrolled.
    - Baseline data captured in CRFs and participant diary initiated.
    - Randomization will occur on Day 0.

5. Study Intervention

5.1. Nimsai Herbal Capsules (Active Arm)

- Formulation: Each Nimsai Herbal capsule contains 600 mg of a proprietary blend of standardized extracts: *Centella asiatica*, *Curcuma longa*, and *Piper nigrum*. The capsules are formulated for consistent potency, purity, and bioavailability, and manufactured under strict Good Manufacturing Practice (GMP) conditions.
- Dosage and Administration: One (1) Nimsai Herbal capsule (600 mg) will be administered orally, once daily, with water, preferably at a consistent time each day (morning).
- Packaging: Identical in appearance, size, color, and packaging to the placebo capsules to maintain blinding.

5.2. Placebo Capsules (Control Arm)

- Formulation: Each placebo capsule contains inert ingredients (microcrystalline cellulose, starch, coloring agents) and is devoid of any active pharmacological properties.
- Dosage and Administration: One (1) placebo capsule will be administered orally, once daily, with water, preferably at a consistent time each day.
- Packaging: Identical to the Nimsai Herbal capsules in appearance, size, color, and packaging to ensure effective blinding.

5.3. Administration Schedule and Adherence Monitoring

- Participants in both arms will receive their assigned study capsules sufficient for 10 days of treatment.
- Adherence Monitoring:
    - Daily Participant Diaries: Participants will record daily administration of the study capsule in their provided diary.
    - Pill Counts: At the end of the 10-day intervention (Day 10), remaining capsules will be counted to objectively assess adherence.
    - Investigator Inquiry: Investigators will periodically inquire about adherence during scheduled follow-up visits.
- Non-adherence (missing more than 2 doses) will be documented as a protocol deviation, but participants will remain in the Intention-to-Treat (ITT) analysis.

5.4. Concomitant Medications and Prohibited Therapies

- Participants will be instructed to avoid any other medications or therapies for hemorrhoids (oral, topical, or invasive procedures) during the study period.
- A list of all concomitant medications (prescription, over-the-counter, herbal supplements) will be recorded at screening and monitored throughout the study. Use of medications deemed essential for pre-existing conditions (antihypertensives, antidiabetics) will be permitted and documented.
- Prohibited therapies will include other venotonics, systemic anti-inflammatory drugs specifically for hemorrhoids, and any new laxatives or stool softeners unless medically necessary and documented.

6. Randomization and Blinding

6.1. Randomization Procedure

- Eligible participants will be randomized in a 1:1 ratio to either the Nimsai Herbal group or the placebo group.
- A computer-generated randomization sequence will be prepared by an independent third party (a contract research organization or a statistician not involved in study conduct) prior to the start of the study.
- The randomization sequence will be stratified by hemorrhoid severity (Grade 2 vs. Grade 3) to ensure an even distribution of severity across treatment arms.
- Study medication kits will be pre-packaged and labeled with unique randomization numbers. Once a participant is enrolled, the next sequential randomization number will be assigned.

6.2. Blinding Method This study will employ a quadruple-blind design, meaning the participant, the care provider, the investigator, and the outcomes assessor will all be blinded to the treatment assignment.

- Product Appearance: Nimsai Herbal and placebo capsules are identical in appearance, color, taste, and packaging.
- Packaging and Labeling: Study medication will be packaged in identical, opaque containers with only the randomization number and essential safety information displayed.
- Allocation Concealment: The randomization list will be securely maintained by the independent third party and will not be accessible to study personnel or participants.

6.3. Unblinding Procedures

- Emergency Unblinding: In the event of a medical emergency where knowledge of the assigned treatment is absolutely necessary for the participant's care (severe adverse reaction suspected to be related to the study product), emergency unblinding may occur. This will be performed by authorized personnel (unblinded pharmacist or designated study staff) following a pre-defined procedure. The reason for unblinding and the time/date will be thoroughly documented.
- Planned Unblinding: The full unblinding of the study results will only occur after the completion of all data collection, database lock, and final statistical analyses have been performed. An unblinded statistician, not involved in interim analyses or study conduct, will have access to the unblinded data for final analysis.

7. Outcome Measures

7.1. Primary Outcome Measure

- Name: Hemorrhoid Regression Rate
- Definition: The percentage of participants achieving a clinical response, defined as a ≥75% reduction in their composite hemorrhoid severity score from baseline to Day 10. The composite score is derived from the sum of clinician-assessed scores for four key symptoms: bleeding, pain, itching, and swelling. Each symptom is rated on a 0-10 scale (0 = no symptom, 10 = most severe symptom), resulting in a total possible score range of 0-40.
- Time Frame: Measured at Day 10, representing the end of the intervention period.
- Unit of Measure: Percentage of Participants.

Assessment Method: Clinician assessment by blinded investigators using standardized Case Report Forms (CRFs). Investigator training will include calibration exercises to ensure consistent scoring at Nimsai Academia.

7.2. Secondary Outcome Measures

7.2.1. Visual Analog Scale (VAS) Symptom Score Change

- Name: Visual Analog Scale (VAS) Symptom Score Change
- Definition: The mean change from baseline in self-reported overall hemorrhoid symptom severity, as recorded by participants on a 0-10 Visual Analog Scale (0: no symptoms, 10: most severe symptoms).
- Time Frame: Baseline to Day 10.
- Unit of Measure: Score (0-10 scale).
- Assessment Method: Daily participant-reported diaries.

7.2.2. Symptom Resolution Rate

- Name: Symptom Resolution Rate
- Definition: The percentage of participants achieving complete resolution of all baseline hemorrhoid symptoms (i.e., composite severity score = 0) by Day 10.
- Time Frame: Measured at Day 10.
- Unit of Measure: Percentage of Participants.
- Assessment Method: Based on participant daily diaries and confirmed by clinician assessment at Day 10.

7.2.3. Reduction in Individual Symptom Scores

- Name: Mean Reduction in Individual Symptom Scores (Bleeding, Pain, Itching, Swelling)
- Definition: Mean change from baseline to Day 10 for each individual symptom (bleeding, pain, itching, swelling) as assessed by the investigator using the 0-10 scale.
- Time Frame: Baseline to Day 10.
- Unit of Measure: Score (0-10 scale).
- Assessment Method: Clinician assessment via CRFs.

7.2.4. Clinical Utility of the War-Drill Model

- Name: Association of War-Drill Model Classification with Treatment Response
- Definition: Evaluation of the association between initial classification (War Mode vs. Drill Mode) using the Parola Phenomenon and treatment response (hemorrhoid regression, symptom resolution) in both active and placebo arms.
- Time Frame: Classification at Baseline, outcomes at Day 10.
- Unit of Measure: Statistical association (Odds Ratio).
- Assessment Method: Clinical assessment for Parola Phenomenon at screening, correlated with primary and secondary outcomes.

7.3. Safety Outcome Measures

7.3.1. 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, mild abdominal discomfort).

- Time Frame: Baseline to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Daily participant diaries and direct inquiry by investigators at each visit, documented on CRFs.

7.3.2. Incidence of Serious Adverse Events (SAEs)

- Name: Incidence of Serious Adverse Events (SAEs)
- Definition: Percentage of participants experiencing SAEs as defined by ICH GCP guidelines (death, life-threatening event, inpatient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or any other important medical event).
- Time Frame: Baseline to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Continuous monitoring, immediate reporting to IRB/DSMB, and documentation on CRFs.

7.3.3. Incidence of Withdrawals Due to Adverse Events

- Name: Incidence of Withdrawals Due to Adverse Events
- Definition: Percentage of participants discontinuing the study intervention or withdrawing from the study entirely due to an adverse event.
- Time Frame: Baseline to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Documented on CRFs, with reasons for withdrawal clearly recorded.

7.3.4. Incidence of Transient Diarrhea in Diabetic Participants

- Name: Incidence of Transient Diarrhea in Diabetic Participants
- Definition: The number of diabetic participants who experience transient diarrhea (defined as a temporary increase in stool frequency/looseness resolving spontaneously within 24-48 hours without requiring specific intervention or study withdrawal) during the first three days of the intervention.
- Time Frame: Days 1-3.
- Unit of Measure: Number of Participants.
- Assessment Method: Specific daily inquiry by investigators and recording in participant diaries and CRFs for diabetic participants.

8. Study Procedures and Schedule of Events

The study duration for each participant is 10 days of intervention, preceded by a screening period. All procedures will be meticulously documented.

8.1. Overview of Visits and Assessments

Activity/Visit	Screening (Day -2 to Day 0)	Day 0 (Baseline/Randomization)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10 (Final Assessment)
Informed Consent	X											
Eligibility Assessment	X											
Demographics	X											
Medical History	X											
Physical Exam (incl. DRE/Anoscopy)	X (Baseline)											X (Final)
Parola Phenomenon	X											
Baseline Labs	X											
Randomization		X										
Study Product Dispensing		X										
Study Product Administration		X	X	X	X	X	X	X	X	X	X	X
Daily Participant Diary (Symptoms, AEs, Adherence)		X	X	X	X	X	X	X	X	X	X	X
Investigator Assessment (Symptoms, AEs)		X			X				X			X
Pill Count												X
Concomitant Medications	X											X
SAE Reporting	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary	As necessary

8.2. Detailed Daily Documentation and Procedures (Day 1 to Day 10)

This section outlines the precise documentation required on a daily basis for each participant throughout the 10-day intervention period, ensuring meticulous capture of all relevant data points. Each entry corresponds to specific sections within the Case Report Forms (CRFs) and Participant Daily Diary (refer to Appendix A and B).

- Day 0: Baseline & Randomization
  - Participant Arrival: Confirmation of eligibility, review of exclusion criteria.
  - Informed Consent: Signed and dated ICF obtained by qualified staff.
  - Demographics: Age, sex, and other relevant demographic data recorded.
  - Medical History: Detailed medical history, including relevant comorbidities and prior hemorrhoid treatments, documented.
  - Physical Examination: Comprehensive physical exam, including Digital Rectal Examination (DRE) and anoscopy/endoscopy to confirm Grade 2-3 hemorrhoids and rule out other anorectal pathologies. Baseline hemorrhoid imagescaptured.
  - Parola Phenomenon Assessment: Performed and results documented to classify War vs. Drill Mode.
  - Baseline Assessments:
    - Investigator-assessed composite hemorrhoid severity score (Bleeding, Pain, Itching, Swelling: 0-10 each).
    - Participant-reported overall symptom severity via VAS (0-10).
  - Concomitant Medications: List of all current medications reviewed and documented.
  - Study Product Dispensing: Randomized study product (Nimsai Herbal or Placebo) dispensed with clear instructions for daily 600 mg (one capsule) oral administration.
  - Participant Diary Training: Participants thoroughly instructed on how to complete the daily diary, including symptom scoring, AE recording, and adherence tracking.
  - Documentation: All collected data rigorously recorded in Day 0 CRFs. Participant begins daily diary entry for Day 0 (first dose taken).
- Day 1: First Intervention Day
  - Participant Diary: Entry for Day 1.
    - Confirmation of study product administration (daily dose taken: Yes/No).
    - Self-reported overall symptom severity (VAS 0-10).
    - Presence/absence and description of any new or worsening adverse events (AEs). Specific inquiry for any gastrointestinal discomfort.
  - Investigator Review: Optional brief check-in to confirm initial dosing and address any immediate concerns. Documentation of any AEs reported.
  - Documentation: Daily diary entry collected/reviewed (or prepared for review at Day 3).
- Day 2: Second Intervention Day
  - Participant Diary: Entry for Day 2.
    - Confirmation of study product administration.
    - Self-reported overall symptom severity (VAS 0-10).
    - Presence/absence and description of any AEs. Specific inquiry for transient diarrhea in diabetic participants.
  - Documentation: Daily diary entry collected/reviewed (or prepared for review at Day 3).
- Day 3: Mid-Intervention Assessment
  - Participant Visit: Brief in-person or remote contact.
  - Participant Diary Review: Investigator reviews Day 0-3 diary entries for completeness, symptom trends, and AE reporting. Queries participant regarding any unclear entries.

- Investigator Assessment: Clinician-assessed composite hemorrhoid severity score recorded. Specific inquiry about any gastrointestinal discomfort (nausea, bloating, etc.) and particularly for diabetic participants, the occurrence of transient diarrhea (Days 1-3) and its resolution.
- Concomitant Medications: Review of any new medications initiated since Day 0.
- Documentation: Day 3 CRFs completed, documenting investigator assessments and AE review. Diary entries for Day 0-3 collected.

- Day 4, Day 5, Day 6, Day 7, Day 8, Day 9: Ongoing Daily Intervention
  - Participant Diary: Daily entries for each respective day.
    - Confirmation of study product administration.
    - Self-reported overall symptom severity (VAS 0-10).
    - Presence/absence and description of any new or ongoing AEs.
  - Investigator Review: Optional periodic remote check-ins to monitor participant well-being and adherence. Document any AEs reported.
  - Documentation: Daily diary entries maintained by the participant for later collection/review at Day 10. For Day 7, if a remote check-in occurs, relevant CRFs are updated.
- Day 10: Final Assessment & Study Completion
  - Participant Visit: In-person final assessment.
  - Study Product Return & Pill Count: All remaining study capsules (both dispensed and unused) are collected and counted to calculate adherence.
  - Participant Diary Collection & Review: The complete participant diary (Day 0-10) is collected. Investigator performs a thorough review for completeness, consistency, symptom trends, and detailed AE reporting across the entire 10-day period. Any discrepancies or unclear entries are resolved with the participant.
  - Investigator Assessment:
    - Final clinician-assessed composite hemorrhoid severity score recorded.
    - Assessment of overall clinical improvement.
    - Physical examination (DRE/Anoscopy) repeated to evaluate physical signs of hemorrhoid regression. Post-treatment hemorrhoid images captured.
  - Adverse Event Review: Comprehensive review of all AEs experienced throughout the study, assessing severity, causality, and outcome. All AEs are documented on CRFs. Particular attention is given to SAEs.
  - Concomitant Medications: Final review and documentation of any changes in concomitant medications.
  - Study Completion: Participants completing all study procedures are considered study completers. Reasons for early withdrawal (if any) are documented.
  - Documentation: All collected data rigorously recorded in Day 10 CRFs.

8.3. Post-Treatment Follow-up While the primary intervention and assessment period concludes on Day 10, participants will be informed about the optional 6-month long-term follow-up study (Protocol NA-2024-02), which will assess recurrence rates, long-term safety, and quality of life. This is for future study planning and not part of the current protocol's scope, beyond informing participants.

9. Data Management and Quality Control

9.1. Data Collection Instruments (CRFs, Diaries)

- Case Report Forms (CRFs): Standardized, pre-printed CRFs will be used for all investigator-collected data, including eligibility, demographics, medical history, physical examinations, symptom assessments, adverse events, concomitant medications, and study product accountability. CRFs will be designed for clarity and ease of data entry. (Refer to Appendix A for CRFs).
- Participant Daily Diaries: Designed for self-reporting of daily symptom severity (VAS), adherence, and occurrence of AEs. Diaries will be simple, clear, and include instructions in the local language. (Refer to Appendix B for Participant Daily Diary).

9.2. Data Entry and Validation

- Data from CRFs and participant diaries will be entered into a secure, validated electronic data capture (EDC) system.
- Double Data Entry: A subset of CRFs (10%) may undergo double data entry by independent personnel to ensure accuracy.
- Data Validation Checks: The EDC system will incorporate automated validation checks for data range, consistency, and completeness (mandatory fields, logical checks between related variables).
- Query Management: Discrepancies identified during data entry or validation will generate queries that are sent back to the study sites for resolution by the investigator. All queries and their resolutions will be documented.

9.3. Data Quality Assurance

- Training: All study personnel involved in data collection and management will receive comprehensive training on the protocol, CRFs, EDC system, and GCP principles.
- Monitoring Visits: Study monitors will conduct regular on-site or remote monitoring visits to ensure adherence to the protocol, data accuracy, and regulatory compliance.
- Audits: Independent audits may be conducted by the sponsor or regulatory authorities to assess overall study conduct and data integrity.

9.4. Source Data Verification

- A percentage of data points (100% of primary and safety outcomes, 20% of secondary outcomes) will be verified against original source documents (hospital records, clinic notes, laboratory reports) to confirm accuracy and completeness.

9.5. Data Security and Confidentiality

- All participant data will be handled with strict confidentiality in accordance with applicable data protection regulations (GDPR equivalents, local privacy laws).
- Participants will be assigned a unique study identification number, and all study-related documents will be de-identified where possible.
- The EDC system will have robust security measures, including password protection, access control, audit trails, and data encryption.
- Only authorized personnel will have access to study data. Physical documents will be stored in locked cabinets in secure locations.

10. Statistical Analysis Plan

10.1. Analysis Populations

- Intention-to-Treat (ITT) Population: All randomized participants will be included in the primary efficacy analysis, analyzed according to their assigned treatment group, regardless of actual treatment received or protocol deviations. This reflects a real-world scenario.
- Per-Protocol (PP) Population: A subset of the ITT population, including only participants who complete the study without major protocol deviations, who demonstrate acceptable adherence (≥80% of doses taken), and who have evaluable primary outcome data. This population will be used for sensitivity analyses to assess the robustness of the ITT findings.

10.2. Missing Data Handling

- Primary Method: Multiple imputation will be used for missing outcome data, assuming data are Missing At Random (MAR).
- Sensitivity Analyses: Last Observation Carried Forward (LOCF) or complete case analysis will be conducted as sensitivity analyses to assess the impact of different missing data assumptions.

10.3. Statistical Software and Significance Level

- Statistical analyses will be performed using validated statistical software packages (SAS, R).
- All statistical tests will be two-sided, with a significance level (α) set at 0.05.

10.4. Primary Outcome Analysis

- Hemorrhoid Regression Rate: Compared between the Nimsai Herbal and placebo groups using a Chi-square test. The effect size will be reported as a Risk Difference with its 95% Confidence Interval (CI).

10.5. Secondary Outcome Analysis

- VAS Symptom Score Change: The mean change from baseline will be compared between groups using a Mann-Whitney U test due to potential non-normal distribution of symptom scores. The effect size will be reported as a Mean Difference with 95% CI. Baseline VAS scores may be included as a covariate in sensitivity analyses (ANCOVA).
- Symptom Resolution Rate: Compared between groups using a Chi-square test. The effect size will be reported as a Risk Ratio with 95% CI. Logistic regression may be used to adjust for baseline severity.
- Individual Symptom Scores: Mean changes will be compared using appropriate parametric (t-test) or non-parametric (Mann-Whitney U) tests based on data distribution.

10.6. Safety Outcome Analysis

- Incidence of Mild Gastrointestinal Discomfort, SAEs, Withdrawals: Frequencies and percentages will be presented for both groups. Comparisons will be made using Fisher's Exact test for categorical data, particularly where low event counts are expected. Risk Differences with 95% CI will be reported.
- Transient Diarrhea in Diabetic Participants: This will be reported descriptively as the number and percentage of affected participants. No formal statistical test will be applied due to expected rarity.

10.7. Baseline Characteristics Analysis

- Descriptive statistics (mean ± SD for continuous variables; frequencies and percentages for categorical variables) will summarize baseline characteristics for both treatment groups.
- T-tests (for continuous variables) and Chi-square tests (for categorical variables) will be used to confirm that the randomization process resulted in balanced groups.

10.8. Subgroup Analyses

- Exploratory subgroup analyses may be conducted to investigate potential differential treatment effects based on baseline characteristics such as hemorrhoid grade (Grade 2 vs. Grade 3), age categories (18-40 years vs. 41-70 years), or initial War vs. Drill Mode classification. These analyses will be considered hypothesis-generating and interpreted cautiously.

11. Safety Reporting

11.1. Definition of Adverse Events (AEs) and Serious Adverse Events (SAEs)

- Adverse Event (AE): Any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.
- Serious Adverse Event (SAE): Any AE occurring at any dose that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is otherwise considered by the investigator to be an important medical event.

11.2. Reporting Procedures for AEs and SAEs

- AEs: All AEs will be recorded in the participant's daily diary and subsequently transferred to the CRF by the investigator. Information collected will include onset date, resolution date, severity (mild, moderate, severe), relationship to study product (not related, unlikely related, possibly related, probably related, related), and outcome.
- SAEs: All SAEs must be reported immediately (within 24 hours of investigator awareness) to the Sponsor and the central IRB. Detailed SAE reports will include all relevant clinical information, causality assessment, and outcome. Follow-up reports will be submitted as new information becomes available.

11.3. Data Safety Monitoring Board (DSMB)

- An independent Data Safety Monitoring Board (DSMB) will be established to provide ongoing safety oversight. The DSMB will comprise independent experts in gastroenterology, clinical pharmacology, and biostatistics, who are not involved in the conduct of this study.
- The DSMB will receive blinded aggregated safety data on a weekly basis during the intervention phase.
- The DSMB will have the authority to recommend modifications to the protocol, temporary suspension, or termination of the study if significant safety concerns arise.

12. Ethical Considerations

12.1. Institutional Review Board (IRB) Approval This protocol, the Informed Consent Form (ICF), participant recruitment materials, and any subsequent amendments will be reviewed and approved by the Nimsai Academia Ethics Committee prior to study initiation at Nimsai Academia. The study will not commence until full Ethics Committee approval has been obtained.

12.2. Informed Consent Process

- Written informed consent will be obtained from every participant prior to the performance of any study-specific procedures.
- The investigator or a designated qualified member of the study team will thoroughly explain the study objectives, procedures, potential risks and benefits, alternatives, and the participant's right to withdraw at any time without penalty.
- Participants will be given sufficient time to read the ICF, ask questions, and consider their participation before signing. A copy of the signed ICF will be provided to the participant.

12.3. Participant Rights and Confidentiality

- The rights and well-being of all participants will be protected throughout the study in accordance with the Declaration of Helsinki and ICH GCP guidelines.
- Participant confidentiality will be maintained at all times. All data collected will be de-identified through the use of unique participant identification numbers. No individual participant's name or other direct identifiers will be used in any reports or publications. Access to confidential records (medical history, consent forms) will be restricted to authorized personnel only.

12.4. Data Protection Regulations All data collection, processing, and storage will comply with applicable local and international data protection regulations (GDPR equivalents, HIPAA, local privacy laws) to ensure the privacy and security of participant information.

13. Investigator Responsibilities

13.1. General Responsibilities The Principal Investigator at Nimsai Academia is responsible for the overall conduct of the study in accordance with this protocol, ICH GCP, and all applicable regulatory requirements.

13.2. Training and Qualification All investigators and study staff will be qualified by education, training, and experience to perform their assigned tasks. They will receive specific training on this protocol, study procedures, and data collection tools.

13.3. Protocol Adherence Investigators are responsible for ensuring strict adherence to the approved protocol. Any deviations from the protocol must be documented, justified, and reported to the Sponsor and IRB/EC as required.

14. Data Handling and Record Retention

14.1. Documentation Standards All study data will be recorded accurately, completely, and legibly on CRFs, participant diaries, and source documents. Any corrections will be made according to GCP guidelines, ensuring the original entry remains legible and the correction is dated and initialed.

14.2. Retention Period All study-related documents, including CRFs, ICFs, source documents, and regulatory approvals, will be retained for a minimum of 15 years after the completion of the study or as required by local regulations, whichever is longer. Documents will be stored in a secure, accessible location.

15. Publication Policy

The results of this study, whether positive, negative, or inconclusive, will be submitted for publication in peer-reviewed scientific journals within 12 months of database lock and primary analysis completion. All authors will adhere to established authorship guidelines. Individual participant data (IPD) sharing will be facilitated in accordance with relevant data sharing policies.

16. References

1. Atabiner C. The War-Drill Model of Hemorrhoid Pathogenesis. Research Square. 2025. https://doi.org/10.21203/rs.3.rs-6607959/v1
2. Sun Z, Migaly J. Review of hemorrhoid disease. Clin Colon Rectal Surg. 2016;29(1):22-9.
3. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline for Good Clinical Practice E6(R2). 1996; R2: 2016.
4. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. JAMA. 2013;310(20):2191-4.

17. Appendices

17.1. Appendix A: Case Report Forms (CRFs)

17.2. Appendix B: Participant Daily Diary

17.3. Appendix C: Informed Consent Form (ICF)