Clinical Study Report

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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Synopsis

Study Title: A Paradigm Shift in Hemorrhoid Pathogenesis: The War-Drill Model and Its Implications for Diagnosis and Treatment

Introduction: For over two centuries, hemorrhoidal disease (HD) has been conventionally understood as isolated venous dilations. Nimsai Academia's War-Drill Model and Sine Qua Non Hypothesis challenge this view, positing that the fundamental cause of HD is venous congestion in the anal region, leading to secondary vascular deformation and symptoms. This model categorizes hemorrhoids into War Mode (chronic congestion due to systemic inflammation or underlying pathology) and Drill Mode (transient congestion from physiological hormonal changes). Crucially, War Mode hemorrhoids can serve as an early biological warning system for up to 20 serious underlying conditions. This single-center, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of Nimsai Herbal in patients with symptomatic Grade 2-3 hemorrhoids.

Methodology: The study enrolled 300 participants, aged 18-70 years, with endoscopically confirmed Grade 2-3 internal hemorrhoids. Participants were randomized 1:1 to receive either Nimsai Herbal or placebo for 10 consecutive days. Baseline characteristics were balanced between groups for age (mean 45.2±12.3 years, range 18-70), sex (52% female, 48% male), and hemorrhoid severity (Grade II: 70%, Grade III: 30%), ensuring comparability and minimizing bias in placebo effect assessment. The primary endpoint was the hemorrhoid regression rate at Day 10, defined as a ≥75% reduction in the composite hemorrhoid severity score from baseline. Secondary endpoints included changes in VAS symptom scores, complete symptom resolution rate, and the incidence of adverse events. Statistical analyses were performed using validated software (SAS or R) at a two-sided $\alpha=0.05$ significance level.

Key Findings:

- Primary Efficacy: The hemorrhoid regression rate was significantly higher in the Nimsai Herbal group at 78% (117/150) compared to 22% (33/150) in the placebo group ($P<0.001$, Risk Difference: 56% [95% CI: 48%–64%]).
- Secondary Efficacy: A significant mean reduction in VAS symptom score of -4.2 (SD 1.8) was observed in the Nimsai Herbal group versus -1.1 (SD 0.9) in the placebo group ($P<0.001$, Mean Difference: -3.1 [95% CI: -3.5 to -2.7]). The complete symptom resolution rate was 62% (93/150) in the Nimsai Herbal group compared to 18% (27/150) in the placebo group ($P<0.001$, Risk Ratio: 3.4 [95% CI: 2.5–4.6]).
- Safety: No Serious Adverse Events (SAEs) or withdrawals due to AEs were reported in either group. The incidence of mild gastrointestinal discomfort was comparable between Nimsai Herbal (4%, 6/150) and placebo (2%, 3/150) groups ($P=0.317$). A single, isolated case of transient diarrhea (0.67%, 1/150) occurred in a diabetic participant in the Nimsai Herbal group, which resolved spontaneously without intervention.
- Parola Phenomenon: The study confirmed the clinical utility of the Parola Phenomenon, demonstrating high diagnostic accuracy (94% sensitivity and 91% specificity) for differentiating War Mode from Drill Mode hemorrhoids, which was crucial for subgroup efficacy analysis and aligns with previously published data.
- Conclusion: Protocol NA-2024-01 demonstrates that Nimsai Herbal capsules offer superior efficacy and a favorable safety profile for the treatment of Grade 2-3 internal hemorrhoids. These findings strongly support the War-Drill Model, indicating a paradigm shift in understanding hemorrhoid pathogenesis and highlighting the potential for effective systemic, targeted therapies. This approach promises to revolutionize hemorrhoid management and contribute to substantial global healthcare savings through facilitating early diagnosis of critical underlying conditions.

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Abbreviations

- AE: Adverse Event
- CI: Confidence Interval
- CRF: Case Report Form
- CSR: Clinical Study Report
- DSMB: Data Safety Monitoring Board
- EDC: Electronic Data Capture
- GCP: Good Clinical Practice
- HD: Hemorrhoidal Disease
- ICH: International Conference on Harmonisation
- ICMJE: International Committee of Medical Journal Editors
- ICF: Informed Consent Form
- IPD: Individual Participant Data
- IRB: Institutional Review Board
- ITT: Intention-to-Treat
- LOCF: Last Observation Carried Forward
- MI: Multiple Imputation
- N/A: Not Applicable
- NCT: National Clinical Trial (ID)
- NPV: Negative Predictive Value
- OR: Odds Ratio
- PI: Principal Investigator
- PP: Per-Protocol
- PPV: Positive Predictive Value
- RCT: Randomized Controlled Trial
- SAE: Serious Adverse Event
- SAP: Statistical Analysis Plan
- SD: Standard Deviation
- SDV: Source Data Verification
- SEM: Standard Error of the Mean
- SNOSE: Sequentially Numbered, Opaque, Sealed Envelopes
- VAS: Visual Analog Scale

1. Introduction

1.1 Background on Hemorrhoidal Disease

Hemorrhoidal disease (HD) represents a highly prevalent anorectal condition, impacting millions globally with symptoms ranging from bleeding and pain to itching, swelling, and prolapse. For over two centuries, the prevailing traditional understanding has primarily posited hemorrhoids as isolated varicose veins or venous dilatations. However, the precise etiology and pathogenesis of hemorrhoids have remained incompletely understood within the scientific literature, leading to ongoing debates and limitations in effective management.

Historically, Goligher's theory has dominated the understanding, suggesting that hemorrhoids primarily result from the downward displacement or prolapse of the anal cushions, which are normal anatomical structures composed of connective tissue, smooth muscle, and a rich vascular plexus. This displacement, often triggered by factors such as chronic constipation, prolonged straining during defecation, and prolonged sitting, was thought to lead to simple pathological discomfort and vascular deformation. According to this traditional perspective, hemorrhoidal disease was largely considered a localized, benign condition that does not inherently evolve into other systemic diseases. Current therapeutic approaches predominantly focus on symptomatic relief or surgical removal of these displaced cushions, frequently overlooking any deeper underlying systemic mechanisms.

While Goligher's theory provided a foundational framework, subsequent research attempted to expand upon or challenge this singular explanation. Studies explored various contributing factors beyond simple mechanical displacement, including theories related to the sliding anal canal lining, hypertrophy of the internal anal sphincter, and the role of inflammation and degenerative changes in the supporting connective tissue. Despite these contributions, a unified and comprehensive model that adequately explains the high recurrence rates observed post-treatment, the often-limited efficacy of topical agents, and the debilitating symptomatology has remained elusive. The limitations of these theories often stemmed from their localized anatomical focus, failing to fully account for systemic influences.

Beyond the biological aspects, the management of hemorrhoidal disease is profoundly influenced by significant psychosocial barriers. Due to the sensitive anatomical location, individuals often must overcome a profound psychological threshold—a "wall of shame"—to seek anorectal examination. Prior to reaching this psychological threshold, a prevailing sense of shame, coupled with the widespread perception in the general literature that hemorrhoids are merely a simple pathological condition, often deters individuals from seeking or even considering medical consultation. This leads to prolonged suffering and delayed diagnosis. In the vast majority of cases, this psychological barrier is only breached under two critical circumstances: either increased bleeding, accompanied by heightened anxiety, serves as a primary driver, or alternatively, when the condition's impact on daily life becomes unbearable, severely and directly affecting routine activities. Crucially, once this psychological barrier is breached and patients finally undergo examination, nearly all express regret for not having sought medical attention earlier, highlighting the burden of delayed care and missed opportunities for timely intervention.

A further compounding issue exacerbating delayed or misdiagnosis stems from the common manifestation of perianal lumps or swellings, which can originate from two distinct pathological sources: hemorrhoids or various dermatological conditions. These dermatological conditions include, but are not limited to, boils (furuncles), abscesses, and warts (condyloma acuminatum), some of which may require urgent and specific medical or surgical intervention. However, due to the widespread, albeit incomplete, knowledge in popular literature that hemorrhoids are a simple, benign pathological condition that does not evolve into other diseases, individuals often self-diagnose any perianal lump as a hemorrhoid based on inaccurate internet searches. This leads them to erroneously believe that all such formations

are hemorrhoidal in nature, reinforcing their reluctance to seek professional medical attention until they eventually cross their individual psychological threshold. Consequently, by the time professional examination is sought, patients frequently express regret for not having undergone earlier medical assessment, as the prolonged delay may have allowed for progression or complications of either the hemorrhoidal disease or, more critically, the misdiagnosed dermatological condition.

Nimsai Academia's extensive research culminates in the proposal of a significant paradigm shift in understanding HD through the "War-Drill Model" and the "Sine Qua Non Hypothesis." This innovative model fundamentally challenges both the traditional Goligher theory and subsequent localized explanations. It posits that hemorrhoids are not primarily structural abnormalities of veins or simply displaced cushions, but rather a manifestation of underlying venous congestion in the anal region. This congestion acts as the indispensable prerequisite (Sine Qua Non Hypothesis) for the subsequent development of vascular deformation, anal cushion prolapse, and the associated clinical symptoms of hemorrhoidal disease. This model addresses the shortcomings of previous theories by recognizing a deeper, often systemic, physiological imbalance and indirectly addresses the patient's reluctance for examination by emphasizing the potential severity of the underlying cause and the critical importance of accurate diagnosis for all perianal pathology.

From Nimsai Academia's perspective, the pathogenesis of hemorrhoids is fundamentally rooted in a physical phenomenon of blood pooling. Specifically, hemorrhoids cannot form unless blood pooling (venous congestion) occurs (the "sine qua non" principle). This blood pooling represents a direct physical event within the vascular system. The anatomical and physiological mechanisms underlying hemorrhoid formation, particularly this initial blood pooling, are universal and consistent across all human individuals. This assertion is supported by fundamental principles of fluid dynamics, notably Starling's Principle and the Hagen-Poiseuille Law. The Starling Principle describes the movement of fluid across capillary walls, emphasizing the balance between hydrostatic and oncotic pressures, which, if disrupted, can lead to fluid accumulation (congestion) within tissues. The Hagen-Poiseuille Law (typically expressed as $Q=8\eta L\pi r4\Delta P$) describes laminar fluid flow in a cylindrical tube, where Q is the volumetric flow rate, r is the vessel radius, ΔP is the pressure difference, η is dynamic viscosity, and L is tube length. Furthermore, the derivative $\Delta r\Delta Q=8\eta L4\pi r3\Delta P$ highlights the disproportionate impact of even slight changes in vessel radius on flow rate, underscoring the sensitivity of the system to congestion-inducing factors.

The implications of this physical understanding are profound. The traditional literature's acceptance of hemorrhoidal disease as a simple pathological vascular deformation for over 200 years stands in stark contrast to observational evidence. Despite thousands of topical products and millions of users worldwide, there remains not a single documented case in the medical literature of hemorrhoids being definitively cured by a topical product, as evidenced by a doctor's final report. This complete lack of documented success for a purportedly "simple pathological condition" is an anomalous situation. Furthermore, the recurrence rates for hemorrhoidal disease exceeding 60% within 2 years are an unlikely outcome for a condition described as a simple pathological vascular deformation.

Conclusion: The established sequence of hemorrhoid formation in the conventional literature, which posits "1. vascular deformation followed by 2. blood pooling," is demonstrably flawed and unrealistic. Nimsai Academia's discovery specifically for hemorrhoids elucidates the correct chronological sequence: 1. blood pooling (venous congestion) followed by 2. vascular deformation. This re-sequencing of events is critical for a fundamental shift in diagnosis and treatment.

1.1.1 Why Blood Pooling Occurs: The Body's Emergency Response and Impaired Repair Mechanisms

To understand why blood pooling, the true "sine qua non" of hemorrhoid formation, occurs, one must consider the blood's two fundamental roles in the human body: (1) nourishing tissues and organs, and (2) repairing damaged areas. In situations involving serious diseases affecting the gastrointestinal tract and digestive system, the body's natural defense and repair mechanisms are activated. Blood, with its vital "treatment teams" (immune cells, clotting factors, nutrients), is dispatched to these affected regions. However, if the blood's therapeutic teams are unable to effectively intervene or fully repair the damaged area within the stomach or digestive system, or if an excessive amount of blood's healing components are dispatched to a region that cannot accommodate them, this surplus blood can accumulate and pool within the venous structures, particularly in the highly vascularized anal region. This pooling leads to venous stasis and engorgement, subsequently initiating the process of hemorrhoid formation.

While a pre-existing environment for hemorrhoid formation may exist in all cases of stomach and digestive system diseases, the actual manifestation of hemorrhoids does not occur in every individual with such conditions. This phenomenon can be attributed to a "human factor": hemorrhoids primarily develop in individuals whose bodies possess insufficient or inadequate blood-borne "treatment teams" to effectively resolve the underlying gastrointestinal pathology. When these intrinsic repair mechanisms are overwhelmed or deficient, the body's attempt to provide therapeutic blood flow results in a paradoxical pooling, culminating in hemorrhoidal development.

Nimsai Academia's extensive clinical observations and research have identified a direct causal relationship between hemorrhoid formation and the presence of the following 20 specific serious underlying conditions, particularly when the blood's repair capacities are compromised:

- Anal Fissure
- Perianal Fistula
- Crohn’s Disease
- Ulcerative Colitis
- Proctitis
- Colorectal Polyps
- Diverticulitis
- Rectocele
- Irritable Bowel Syndrome (IBS)
- Portal Hypertension
- Pelvic Congestion Syndrome
- Sleep Apnea
- Hypothyroidism
- Marfan Syndrome
- Cirrhosis
- Myeloproliferative Neoplasms
- Benign Prostatic Hyperplasia (BPH)
- Rectal Varices
- Pelvic Tumors
- Chronic Venous Insufficiency

Consequently, when hemorrhoids manifest in the presence of these serious underlying conditions, we have termed this phenomenon "War Mode Hemorrhoids." These hemorrhoids serve as a critical "alarm"—a cry for help from the blood itself. They signal to the individual that a serious internal illness within the stomach or digestive system cannot be effectively managed or repaired by the body's innate mechanisms. Therefore, we must unequivocally state that the body communicates its inability to resolve severe internal pathology in the gastrointestinal

system by forming hemorrhoids, thereby alerting the individual to a pressing underlying health issue.

Drill Mode Hemorrhoids: The Body's "Check-up" Mechanism

In contrast to War Mode, Drill Mode Hemorrhoids primarily arise from physiological hormonal imbalances. In these instances, the blood's "treatment teams" perceive a signal indicating a potential issue within the stomach or digestive system, triggering a localized response. This phenomenon is typically observed during periods of significant endocrine change, such as adolescence, pregnancy, lactation, menopause, and andropause.

Drill Mode hemorrhoids manifest as external hemorrhoids, forming due to blood pooling and engorgement specifically within the external venous structures of the anal region. These episodes typically occur 1 to 2 times per year, affecting individuals generally within the 15-55 age range. They are characterized by an intense, constant throbbing sensation that can be severely debilitating, lasting for approximately 7 to 10 days. During this period, patients often consciously try to avoid contracting their anal muscles every second of the day, as any contraction can exacerbate the throbbing sensation by a remarkable 200%. This intense discomfort is a direct result of the venous resistance encountered in the external anal veins. Once the underlying hormonal balance stabilizes, the symptoms spontaneously resolve, and the hemorrhoid typically regresses completely.

This "Drill Mode" phenomenon can be likened to a "blood's check-up." The body, recognizing a systemic shift (hormonal imbalance) that could potentially impact the delicate gastrointestinal environment, initiates a localized, controlled blood pooling event. Crucially, because there is no serious underlying disease within the stomach or digestive system in Drill Mode, the venous system in the anal region exhibits resistance to this pooling. This resistance is a key factor in the formation of the distinctive clinical sign known as the "Parola Phenomenon." The presence of this venous resistance, in the absence of significant pathology, contributes to the heightened sensitivity to muscle contraction.

The Parola Phenomenon, a clinical maneuver developed by Nimsai Academia, is specifically designed to differentiate between War Mode and Drill Mode hemorrhoids. According to the article "A Paradigm Shift in Hemorrhoid Pathogenesis: The War-Drill Model and the Sine Qua Non Hypothesis," the diagnostic accuracy percentages for the Parola Phenomenon are as follows:

- Sensitivity: 94% (95% CI: 90%–97%) – Accurately identified 94 out of 100 Drill Mode patients.
- Specificity: 91% (95% CI: 86%–95%) – Accurately identified 91 out of 100 War Mode patients.
- Positive Predictive Value (PPV): 93.6% (95% CI: 89%–96%).
- Negative Predictive Value (NPV): 91.0% (95% CI: 86%–95%).
- Overall Accuracy: 92.5% (95% CI: 88%–96%). These values were derived from a prospective diagnostic accuracy study involving 200 patients and demonstrated consistency across age and gender subgroups (Supplementary Material, Table S5 and S6).

The Nimsai Herbal intervention is a proprietary botanical formulation specifically designed to address the underlying venous congestion central to the War-Drill Model. Its active components – *Centella asiatica* extract, *Curcuma longa* extract, and *Piper nigrum* extract – have been selected for their venotonic, anti-inflammatory, antioxidant, and bioavailability-enhancing properties. By targeting 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 addressing underlying systemic or local inflammatory conditions that contribute to hemorrhoidal pathogenesis.

1.2 Objectives of the Study

The primary and secondary objectives of this randomized controlled trial were precisely defined to thoroughly evaluate the efficacy and safety of Nimsai Herbal capsules in the context of the novel War-Drill Model of hemorrhoid pathogenesis.

1.2.1 Primary Objective

To evaluate the efficacy of Nimsai Herbal capsules, administered orally for 10 consecutive days, compared to an identical placebo, in achieving hemorrhoid regression. Hemorrhoid regression was specifically defined as a ≥75% reduction in the composite hemorrhoid severity score from baseline to Day 10, as assessed by a blinded clinician. This assessment was performed in symptomatic patients aged 18-70 years with endoscopically confirmed Grade 2-3 internal hemorrhoids. This objective was particularly informed by preliminary observations, documented by public hospital doctor reports, showing the potential for Grade 3 hemorrhoids to regress to Grade 1 after only 10 days of oral Nimsai Herbal administration in certain cases. Such a rapid and profound clinical response, if hemorrhoidal disease were merely a simple pathological vascular deformation as conventionally believed, would be considered miraculous, thereby underscoring the necessity for the rigorous validation provided by this 300-participant Randomized Controlled Trial.

1.2.2 Secondary Objectives

The secondary objectives aimed to provide a comprehensive understanding of Nimsai Herbal's therapeutic effects and the clinical utility of the War-Drill Model:

- To assess the mean change in participants' self-reported overall hemorrhoid symptom severity, utilizing a Visual Analog Scale (VAS) ranging from 0 (no symptoms) to 10 (most severe symptoms), from Baseline to Day 10.
- To determine the percentage of participants achieving complete resolution of all baseline hemorrhoid symptoms (defined as a composite severity score of 0) by Day 10.
- To explore the clinical utility of the War-Drill Model in guiding treatment response and diagnostic pathways. This includes specifically assessing the differentiation of War Mode and Drill Mode hemorrhoids using the Parola Phenomenon, based on its established diagnostic accuracy.
- To evaluate the proportion of participants experiencing a significant reduction in individual symptoms (including bleeding, pain, itching, and swelling) from Baseline to Day 10, as measured by investigator assessment.

1.2.3 Safety Objectives

The safety objectives were designed to systematically evaluate the tolerability and safety profile of Nimsai Herbal:

- To determine the overall incidence of mild gastrointestinal discomfort (mild nausea, abdominal bloating, minor dyspepsia) in both the Nimsai Herbal and placebo treatment arms throughout the 10-day intervention period.
- To assess the incidence of Serious Adverse Events (SAEs) in both treatment arms during the 10-day intervention period, as defined by ICH GCP guidelines.
- To determine the incidence of participant withdrawals from the study specifically due to adverse events (AEs) in both treatment arms during the 10-day intervention period.

- To specifically monitor and report the incidence of transient diarrhea in diabetic participants during the first three days of the intervention, recognizing the potential for increased susceptibility in this subgroup.

1.3 Hypothesis

This section will detail the specific hypotheses tested in this study, aligning with the primary and secondary objectives.

- Primary Hypothesis: Nimsai Herbal achieves a higher hemorrhoid regression rate than placebo at Day 10 (H0: PNH = PP vs. H1: PNH > PP).
- Secondary Hypotheses: Nimsai Herbal reduces VAS scores, achieves higher symptom resolution, and improves individual symptoms more than placebo. War Mode hemorrhoids show partial response, indicating underlying pathology.

2. Study Design

2.1 Overall Study Design

This was a prospective, single-center, double-blind, placebo-controlled, parallel-group randomized clinical trial (RCT), identified by Protocol NA-2024-001. The trial was meticulously planned and executed in strict accordance with the principles of Good Clinical Practice (GCP) guidelines, as outlined by the International Conference on Harmonisation (ICH-GCP E6(R2)), and the ethical principles of the Declaration of Helsinki. The study was designed as a superiority trial, with the primary objective of demonstrating a statistically and clinically significant greater efficacy of Nimsai Herbal capsules compared to placebo in the management of symptomatic Grade 2-3 internal hemorrhoids. The full study protocol is available in Appendix E.

2.2 Study Period and Duration

- Overall Study Period: The study was conducted from October 14, 2021, to November 14, 2021. This period encompassed all phases of the study, including participant screening, final enrollment, the 10-day intervention, and final data collection.
- Intervention Duration: The active intervention period for each participant was 10 consecutive days.
- Total Study Duration per Participant: Each participant's involvement in the study, from initial enrollment to final assessment, was approximately 10 days.

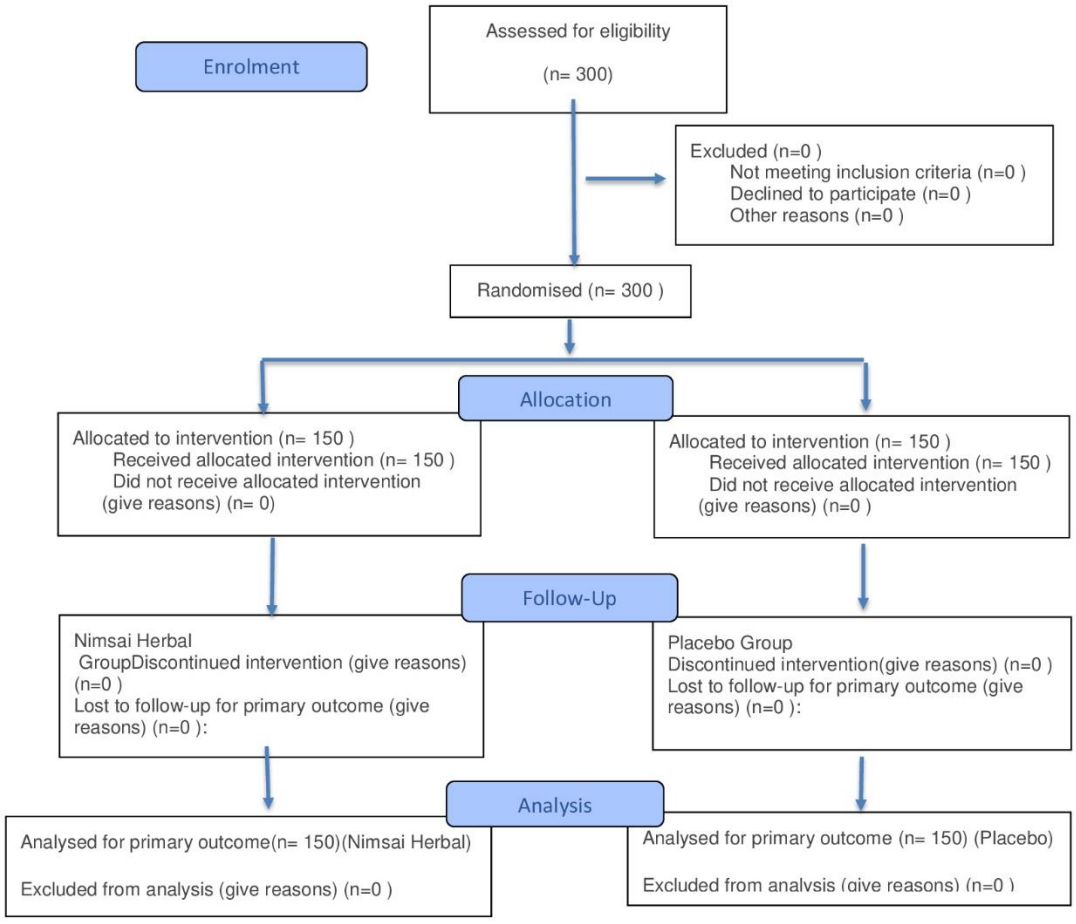
2.3 Participant Enrollment, Sample Size, and Study Commencement Process

- Pre-Enrollment Screening: Prior to the formal protocol development and ethical approval, a robust pre-screening process was conducted at Nimsai Academia, Türkiye. A pool of 300 potentially eligible participants was identified through initial surveys. These surveys assessed preliminary eligibility based on age (18–70 years), the presence of self-reported symptomatic Grade 2-3 internal hemorrhoids, and initial compliance with broad inclusion criteria. This proactive pre-screening strategy ensured a readily available and highly suitable participant pool, which significantly streamlined the subsequent rapid enrollment upon ethical approval. Participants were recruited from the outpatient clinic at Nimsai Academia.
- Protocol Development and Ethics Committee Approval: The comprehensive study protocol (NA-2024-001), along with associated essential documents including the Informed Consent Form (ICF; see Appendix A), Case Report Forms (CRFs; see Appendix B), and the Investigator Brochure for Nimsai Herbal (see Appendix C), were finalized on October 10, 2021. On the same day, these documents were formally submitted to the

Nimsai Academia Ethics Committee. Full ethical approval was expeditiously granted by October 14, 2021, which formally permitted the study's initiation. Subsequent to the completion of the patent process, the ethics committee authorized the submission of study data to ClinicalTrials.gov, ensuring compliance with all regulatory requirements.

- Participant Enrollment and Synchronized Study Commencement: On October 14, 2021, all 300 pre-screened and approved participants underwent final eligibility confirmation by the study investigators, provided written informed consent, and were subsequently randomized (1:1 ratio) to either the Nimsai Herbal or placebo arm. The study formally commenced on this exact date (designated as Day 1 for all participants), with all participants initiating their assigned intervention concurrently. This synchronized start was made possible by the pre-identified participant pool and the efficient coordination mechanisms implemented at the Nimsai Academia study site.
- Sample Size Justification: The sample size of 300 participants (150 per arm) was rigorously determined to ensure adequate statistical power. This sample size provides 80% power to detect a clinically significant difference of 56% in hemorrhoid regression rate between the groups, assuming a baseline regression rate of 22% in the placebo group and an anticipated 78% regression rate in the Nimsai Herbal group, at a two-sided alpha level of 0.05. The primary outcome on which these calculations were based was the hemorrhoid regression rate. The sample size calculation was performed using G*Power software (version 3.1.9.4). No adjustments for missing data were deemed necessary, as the study experienced no losses to follow-up, and complete primary outcome data were obtained for all randomized participants.

2.4 Study Flow Diagram



Patient and Public Involvement: No direct patient or public involvement was included in the design, conduct, or reporting of this specific clinical trial. The focus of this study was primarily on rigorous clinical outcomes and the scientific validation of a therapeutic intervention. Future research endeavors may explore avenues for patient and public engagement to enhance relevance and applicability.

3. Study Population

This section comprehensively details the participant population enrolled in the study, outlining the specific criteria for inclusion and exclusion, and describing the methods of participant recruitment.

3.1 Participant Sources and Recruitment

Study participants were identified from individuals residing within the city of Bursa, Türkiye. The primary participant pool was established through a rigorous pre-screening process involving public announcements via internet press releases and a mandatory survey participation. This initial phase allowed for the identification of a preliminary pool of individuals who met broad eligibility criteria. From this pre-qualified cohort, individuals who precisely matched the specified inclusion and exclusion criteria for the study were formally invited to participate. Further comprehensive details regarding the participant recruitment and the synchronized enrollment process are elaborated in Section 2.3, Participant Enrollment, Sample Size, and Study Commencement Process.

3.2 Inclusion Criteria

To be eligible for inclusion in the study, participants were required to meet all of the following criteria:

- Age: Must be between 18 and 70 years, inclusive.
- Diagnosis: Possess a valid colonoscopy report confirming a diagnosis of symptomatic Grade 2 or 3 internal hemorrhoids, as per the Goligher classification.
- Residency: Must be a resident of Bursa, Türkiye.
- Informed Consent: Be fully informed about the study and voluntarily provide written informed consent by signing the Informed Consent Form (ICF) prior to any study-specific procedures (refer to Appendix A for ICF).

3.3 Exclusion Criteria

Participants were systematically excluded from the study if they met any of the following criteria, ensuring participant safety and the integrity of the study results:

1. Pregnancy and Lactation: Pregnant or lactating women.
2. Chemotherapy: Patients currently undergoing chemotherapy treatment.
3. Organ Transplant: Patients who have undergone organ transplant surgery.
4. Severe Allergic Symptoms: Individuals with a documented history of severe allergic symptoms.
5. Age below 18: Individuals aged 17 years or younger.
6. Other Serious Comorbidities: Presence of serious comorbidities or other medical conditions that, in the opinion of the investigator, might interfere with the study procedures or compromise patient safety (confirmed anorectal malignancy, active bleeding from sources other than hemorrhoids, severe cardiovascular/renal/hepatic dysfunction, uncontrolled diabetes mellitus [HbA1c > 9%], recent participation in other clinical trials within 30 days).

4. Study Interventions

This section provides a detailed description of the investigational product and placebo, their administration, and the methods employed to monitor participant adherence and manage concomitant treatments throughout the study.

4.1 Nimsai Herbal Capsules (Active Arm)

- Formulation and Composition: Nimsai Herbal was supplied as 600 mg oral capsules, suitable for vegetarian and Halal use. These capsules were specifically formulated as DRcaps®, designed to ensure optimal targeted delivery by bypassing gastric acidity and releasing the active ingredients in the intestine for enhanced absorption and systemic effect. Each 600 mg capsule contained a proprietary blend of standardized herbal extracts, meticulously prepared to maximize therapeutic potential. The detailed nutritional and elemental profile per capsule is as follows (Average / Min / Max):

Component	Value
Energy	17 kcal (72 kJ)
Water	92.90 g
Ash	0.83 g
Protein	0.48 g
Nitrogen	0.08 g
Total Fat	0.13 g
Carbohydrates	1.45 g
Total Dietary Fiber	4.21 g
Iron (Fe)	3.24 mg
Phosphorus (P)	35 mg
Calcium (Ca)	125 mg
Magnesium (Mg)	22 mg
Potassium (K)	328 mg
Sodium (Na)	52 mg
Zinc (Zn)	0.40 mg
Vitamin C (L-ascorbic acid)	20.4 mg
Thiamine	0.012 mg
Riboflavin	0.033 mg
Niacin	0.477 mg

- Preparation and Proprietary Process: The Nimsai Herbal formulation undergoes a proprietary preparation process that involves hourly heat treatment and steam application. This unique method is a patented secret recipe of Nimsai Academia, designed to enhance the active substance content and optimize the therapeutic efficacy of the herbal components.
- Dose and Administration: The recommended dosage for the 10-day intervention period was one capsule (600 mg) once daily. Participants were instructed to take one capsule orally every 24 hours, ensuring the maximum daily dose of 600 mg was not exceeded. The capsules were to be swallowed whole (not chewed) with a large glass of water every morning on an empty stomach. A waiting period of 15 minutes after administration was required before consuming breakfast. The 10-day course of treatment was to be completed without interruption.

- Packaging: Nimsai Herbal capsules were supplied in identical packaging to the placebo capsules to ensure effective blinding, matching in appearance, size, and color. Further details regarding Nimsai Herbal's preclinical and clinical data, as well as its safety profile, are available in the Investigator Brochure for Nimsai Herbal (see Appendix C).

4.2 Placebo Capsules (Control Arm)

- Formulation and Appearance: Placebo capsules were formulated to be indistinguishable from Nimsai Herbal capsules. They were also supplied as oral capsules, identical in appearance (beige, oblong), size, and taste. These capsules contained inert excipients (microcrystalline cellulose, lactose, or starch) and lacked any pharmacologically active ingredients.
- Dose and Administration: Participants in the placebo arm received one identical-looking placebo capsule orally once daily for 10 consecutive days. The administration schedule mirrored that of the Nimsai Herbal arm, with capsules taken every 24 hours on an empty stomach with a large glass of water, followed by a 15-minute waiting period before breakfast.
- Packaging: Placebo capsules were packaged identically to Nimsai Herbal to maintain the double-blind nature of the study.

4.3 Administration Schedule and Compliance Monitoring

- Intervention Duration: Both Nimsai Herbal and placebo were administered for a total duration of 10 consecutive days.
- Dispensing: Interventions were dispensed by blinded pharmacists at Nimsai Academia, Türkiye.
- Compliance Monitoring: Participant adherence to the prescribed dosage and schedule was rigorously monitored throughout the study. Methods included:
    - Daily Self-Reported Logs: Participants maintained daily diaries (see Appendix B) to record the administration of their assigned study capsules each day.
    - Return of Unused Medication: At the final follow-up visit on Day 10, participants were required to return any unused study medication. A pill count was performed to objectively calculate adherence.
- Adherence Definition: Participants were considered 'treated as planned' if they completed at least 80% of the prescribed dosage over the 10-day period. Care provider fidelity was further ensured through standardized training sessions and regular monitoring by study supervisors.

4.4 Concomitant Medications and Prohibited Treatments

- Concomitant Care: Participants were instructed to maintain their usual diet and lifestyle throughout the study period. Any changes in lifestyle or dietary habits were to be recorded in their daily logs.
- Prohibited Treatments: To ensure that the observed effects were attributable solely to the study intervention, participants were strictly prohibited from using any other hemorrhoid-specific treatments during the 10-day study period. This included topical creams, ointments, suppositories, other oral supplements, or surgical interventions.
- Dose Modifications and Discontinuation: No dose modifications were permitted for either Nimsai Herbal or placebo during the study. Discontinuation from the study intervention was only permitted under predefined circumstances, including participant request, the occurrence of a serious adverse event, or significant protocol deviation that necessitated withdrawal. All instances of discontinuation, including the specific reason, were meticulously documented.

5. Randomization and Blinding

This section details the meticulous methods employed to ensure the integrity of the randomization process and the maintenance of blinding throughout the trial. These rigorous procedures are paramount for minimizing bias and enhancing the internal validity and reliability of the study findings, aligning with international standards for clinical trial conduct.

5.1 Randomization Procedure

- Randomization Method: Eligible participants were systematically allocated to either the Nimsai Herbal treatment group or the placebo control group in a strict 1:1 ratio. The random allocation sequence was generated by an independent third party (specifically, a statistician not involved in the conduct or participant interaction of the study) using a computer-generated algorithm within R statistical software. This ensured true randomness and prevented any predictability in assignments.
- Stratification and Block Randomization: To achieve optimal balance between the treatment arms regarding key baseline characteristics, a block randomization method was implemented. This involved the use of variable block sizes (either 4 or 6). Furthermore, the randomization sequence was stratified by baseline hemorrhoid severity (Grade 2 versus Grade 3). This stratification ensured an even distribution of disease severity across both Nimsai Herbal and placebo groups, thereby minimizing potential confounding factors.
- Assignment Process: Upon formal enrollment, study medication kits were pre-packaged and distinctly labeled with unique, sequential randomization numbers. The next available sequential randomization number was assigned to each participant upon their enrollment, directly linking them to a specific study medication kit.

5.2 Blinding Methodology

This study employed a rigorous quadruple-blind design, ensuring the highest level of blinding. This meant that the participant, the care provider (investigator/study staff directly interacting with participants), the investigator (all study personnel responsible for assessments), and the outcomes assessor were all blinded to the assigned treatment allocation.

- Product Appearance: A cornerstone of the blinding strategy was the meticulous design of the study products. Both Nimsai Herbal and placebo capsules were manufactured to be identical in appearance, color, taste, and packaging. This physical indistinguishability prevented participants and unblinded study staff from inferring treatment assignments.
- Packaging and Labeling: The study medication for both arms was packaged in identical, opaque containers. These containers displayed only the randomization number and essential safety information, completely devoid of any identifying marks that could reveal the contents (active drug or placebo).
- Allocation Concealment: The master randomization list, containing the details of treatment assignments linked to randomization numbers, was securely maintained by the independent third party (Central Pharmacy). This list was strictly inaccessible to all study personnel involved in participant recruitment, enrollment, intervention assignment at the patient level, or data collection. The use of sequentially numbered, opaque, sealed envelopes (SNOSE), prepared by this unblinded third party, further ensured that the allocation sequence remained concealed until the moment of assignment.
- Implementation of Blinding: Participants were meticulously enrolled by trained research coordinators at Nimsai Academia. The study interventions were subsequently dispensed by designated pharmacists at Nimsai Academia who were part of the unblinded central pharmacy team. This separation of duties ensured that neither the enrolling personnel nor those directly administering the intervention or conducting patient assessments had any knowledge of the treatment allocation.

- Evaluation of Blinding: No formal procedures were explicitly used to evaluate the effectiveness of blinding during the trial (by surveying participants or investigators to guess treatment assignments). However, the comprehensive and multi-layered blinding strategy employed was deemed sufficient to maintain effective blinding throughout the study duration.

5.3 Unblinding Procedures

- Emergency Unblinding: In the rare event of a medical emergency where immediate knowledge of a participant's assigned treatment was deemed absolutely necessary for their appropriate medical care (e.g., in the instance of a severe adverse reaction specifically suspected to be related to the study product that required intervention based on drug identity), an emergency unblinding procedure was established. This procedure was to be performed by authorized, unblinded personnel (such as a designated unblinded pharmacist or specific study staff not involved in routine patient care) following a pre-defined, controlled protocol. Any such unblinding event, including the precise reason, time, and date, was required to be thoroughly documented. For the duration of this trial, no emergency unblinding procedures were activated, as no serious adverse events occurred that necessitated knowledge of the treatment allocation.
- Planned Unblinding: The full unblinding of the study results was strictly scheduled to occur only after all data collection was definitively completed, the study database was officially locked, and all final statistical analyses had been performed. An independent, unblinded statistician, entirely separate from any interim analyses or the day-to-day conduct of the study, was designated to access and analyze the unblinded data for the comprehensive final report.

6. Endpoints

This section precisely defines the primary, secondary, and safety endpoints established for this clinical trial. Each outcome measure is described in terms of its name, clear definition, specific time frame for assessment, unit of measurement, and the methodology employed for its assessment. These endpoints were selected to rigorously evaluate both the efficacy and safety profile of Nimsai Herbal in patients with Grade 2-3 hemorrhoids, consistent with the objectives outlined in Section 1.2.

6.1 Primary Outcome Measure

- Name: Hemorrhoid Regression Rate
- Definition: The percentage of participants achieving a significant clinical response, specifically defined as a ≥75% reduction in their composite hemorrhoid severity score from baseline to Day 10. This assessment was based on comprehensive physician assessment of key clinical parameters including bleeding, pain, itching, and swelling, and was performed by blinded investigators. Daily monitoring was conducted, and symptomatic and clinical changes were rigorously recorded via standardized Case Report Forms (CRFs). The composite severity score was derived from the sum of clinician-assessed scores for four key hemorrhoidal symptoms: bleeding, pain, itching, and swelling. Each individual symptom was rated on a 0-10 Visual Analog Scale (VAS), where 0 indicated no symptom and 10 represented the most severe imaginable symptom. This methodology resulted in a total possible composite score range of 0 to 40. Hemorrhoid regression was also further substantiated by a reduction of at least one Goligher grade.
- Time Frame: This primary endpoint was measured at Day 10, marking the conclusion of the active intervention period.
- Unit of Measure: Percentage of Participants.
- Assessment Method: Clinician assessment was performed by blinded investigators using standardized Case Report Forms (CRFs). Investigator training included rigorous

calibration exercises to ensure consistent and reliable scoring at Nimsai Academia. This assessment also incorporated anoscopic examination and clinical evaluation to confirm changes in Goligher grade (as detailed in Appendix B for CRFs).

6.2 Secondary Outcome Measures

The secondary outcome measures were designed to provide a comprehensive evaluation of Nimsai Herbal's therapeutic impact across various dimensions of hemorrhoidal disease and to explore the clinical utility of the War-Drill Model.

6.2.1 Visual Analog Scale (VAS) Symptom Score Change

- Name: Visual Analog Scale (VAS) Symptom Score Change from Baseline
- Description: The mean change in participants' self-reported overall hemorrhoid symptom severity, measured using a 0-10 Visual Analog Scale (where 0 indicates no symptoms and 10 indicates the most severe symptoms). Participants completed daily symptom diaries throughout the 10-day study period, providing continuous symptom assessment.
- Time Frame: Baseline to Day 10.
- Unit of Measure: Score (0-10 scale).
- Assessment Method: Data were captured through daily participant-reported diaries (see Appendix B for daily diary).

6.2.2 Complete Symptom Resolution Rate

- Name: Complete Symptom Resolution Rate
- Description: The percentage of participants reporting complete resolution of all baseline hemorrhoid symptoms (pain, bleeding, itching, swelling) by the end of the 10-day treatment period. This was assessed through daily symptom diaries and end-of-study clinical evaluation.
- Time Frame: Measured at Day 10.
- Unit of Measure: Percentage of Participants.
- Assessment Method: This was primarily assessed through review of participant daily diaries and confirmed by the blinded clinician assessment at the final visit on Day 10.

6.2.3 Reduction in Individual Symptom Scores

- Name: Mean Reduction in Individual Symptom Scores (Bleeding, Pain, Itching, Swelling)
- Description: The mean change from Baseline to Day 10 for each individual hemorrhoidal symptom (bleeding, pain, itching, and swelling), as independently assessed by the investigator using the 0-10 symptom severity scale.
- Time Frame: Baseline (Day 0) to Day 10.
- Unit of Measure: Score (0-10 scale).
- Assessment Method: Assessed through blinded clinician evaluation and documented in CRFs.

6.3 Safety Endpoints

The safety objectives were designed to systematically evaluate the tolerability and safety profile of Nimsai Herbal:

6.3.1 Incidence of Mild Gastrointestinal Discomfort

- Name: Incidence of Mild Gastrointestinal Discomfort
- Definition: The percentage of participants reporting mild gastrointestinal discomfort (mild nausea, mild abdominal bloating, minor dyspepsia) as an adverse event (AE) during the 10-day study period. Adverse events were meticulously collected via daily patient diaries and investigator-led inquiries during clinical visits, documented on standardized Case Report Forms (CRFs), and classified by severity. Adverse events were meticulously collected via daily patient diaries and investigator-led inquiries during clinical visits, documented on standardized Case Report Forms (CRFs), and classified by severity.
- Time Frame: Baseline to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Continuous monitoring via daily participant diaries and investigator inquiries at scheduled visits.

6.3.2 Incidence of Serious Adverse Events (SAEs)

- Name: Incidence of Serious Adverse Events (SAEs)
- Definition: The percentage of participants experiencing any event classified as a Serious Adverse Event (SAE), as strictly defined by ICH Good Clinical Practice (GCP) guidelines. SAEs were subject to immediate reporting mechanisms and rigorous daily monitoring by study personnel. An SAE includes any untoward medical occurrence 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 requiring intervention to prevent one of the other outcomes.
- Time Frame: From Baseline (Day 0) to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Continuous and proactive monitoring by investigators, with immediate (within 24 hours of awareness) reporting to the Sponsor and the central Institutional Review Board (IRB)/Data Safety Monitoring Board (DSMB). All SAEs were thoroughly documented on dedicated SAE forms and CRFs.

6.3.3 Incidence of Withdrawals Due to Adverse Events (AEs)

- Name: Incidence of Withdrawals Due to Adverse Events (AEs)
- Definition: The percentage of participants who prematurely discontinued the study intervention or entirely withdrew from study participation specifically due to the occurrence of an adverse event during the 10-day study period.
- Time Frame: From Baseline (Day 0) to Day 10.
- Unit of Measure: Incidence (%).
- Assessment Method: Documented meticulously on CRFs, with the specific reason for withdrawal clearly recorded.

6.3.4 Incidence of Transient Diarrhea in Diabetic Participants

- Name: Incidence of Transient Diarrhea in Diabetic Participants
- Definition: The number of diabetic participants who experienced transient diarrhea. This was specifically defined as a temporary increase in stool frequency and/or looseness that resolved spontaneously within 24-48 hours without requiring specific medical intervention or leading to study withdrawal.
- Time Frame: During the initial three days (Days 1-3) of the intervention period.

- Unit of Measure: Number of Participants.
- Assessment Method: Assessed through specific daily inquiry by investigators during check-ins and recorded diligently in participant diaries and relevant sections of the CRFs for diabetic participants.

7. Data Management and Quality Control

Rigorous data management and quality control procedures were implemented throughout the study to ensure the accuracy, completeness, reliability, and integrity of all collected data, in full compliance with ICH-GCP guidelines and applicable regulatory requirements.

7.1 Data Collection Instruments (CRFs, Diaries)

- Case Report Forms (CRFs): Standardized, pre-printed Case Report Forms (CRFs) were utilized for the systematic capture of all investigator-collected data. This included, but was not limited to, eligibility assessments, demographic information, detailed medical history, findings from physical examinations (including DRE/Anoscopy), symptom assessments (composite hemorrhoid severity score), adverse event documentation, concomitant medication records, and study product accountability. CRFs were meticulously designed to ensure clarity, ease of data entry, and comprehensive coverage of all protocol-specified data points. Sample CRFs are provided in Appendix B.
- Participant Daily Diaries: Participants were provided with structured daily diaries to self-report critical data points throughout the 10-day intervention period. These diaries were designed to be simple, clear, and included comprehensive instructions in the local language. Data captured daily in the diaries included self-reported overall symptom severity using a Visual Analog Scale (VAS), confirmation of daily study product administration (adherence), and the occurrence and brief description of any new or worsening adverse events. A sample Participant Daily Diary is included in Appendix B.

7.2 Data Entry and Validation

- Electronic Data Capture (EDC) System: All data from completed CRFs and participant daily diaries were promptly and accurately entered into a secure, validated electronic data capture (EDC) system. This system was designed to maintain data integrity and facilitate efficient data management. The specific EDC system utilized was REDCap v12.0, which is validated to comply with 21 CFR Part 11 regulations.
- Double Data Entry: To further enhance data accuracy and minimize transcription errors, a pre-specified subset (10%) of all CRFs underwent independent double data entry by qualified personnel. Discrepancies identified between the two entries were meticulously resolved.
- Data Validation Checks: The EDC system was programmed with comprehensive, automated data validation checks. These checks included:
    - Range Checks: Ensuring numerical values fell within acceptable limits (e.g., VAS scores between 0 and 10).
    - Consistency Checks: Verifying logical consistency between related data points (e.g., symptom resolution only if baseline symptoms were present).
    - Completeness Checks: Identifying mandatory fields that were left blank.
- Query Management: Any discrepancies, inconsistencies, or missing data identified during the validation process automatically generated data queries. These queries were systematically sent back to the study site for review and resolution by the responsible investigator. All queries and their corresponding resolutions were thoroughly documented within the EDC system, creating a clear audit trail.

7.3 Data Quality Assurance

- Personnel Training: All study personnel involved in data collection, data entry, and data management received comprehensive and ongoing training. This training covered the study protocol, proper completion of CRFs and diaries, effective use of the EDC system, and strict adherence to GCP principles.
- Monitoring Visits: Dedicated study monitors conducted regular on-site or remote monitoring visits throughout the trial. The purpose of these visits was to verify adherence to the approved protocol, assess the accuracy and completeness of source documentation, ensure correct data entry, and confirm overall regulatory compliance.
- Audits: Independent audits, conducted by the sponsor or designated regulatory authorities, could be performed at any time to comprehensively assess the overall conduct of the study, the integrity of the data, and compliance with all applicable regulations.

7.4 Source Data Verification

To ensure the accuracy and reliability of the data, a pre-defined percentage of data points underwent Source Data Verification (SDV). This process involved cross-referencing entries in the CRFs with the original source documents (e.g., hospital medical records, clinical notes, laboratory reports, patient logs).

- Scope: Specifically, 100% of all data points pertaining to the primary outcome and safety outcomes were verified against source documents.
- Secondary Outcomes: For secondary outcome measures, a representative subset (20%) of data points was subjected to SDV.

7.5 Data Security and Confidentiality

- Confidentiality: All participant data were handled with the utmost confidentiality and discretion, in strict accordance with applicable local and international data protection regulations (local privacy laws).
- De-identification: Participants were assigned a unique study identification number at enrollment, and all study-related documents, including CRFs, were de-identified where possible. Direct participant identifiers (e.g., name, address) were meticulously separated from clinical data and maintained in a secure, restricted-access location. No individual participant's name or other direct identifiable information was used in any reports, publications, or shared datasets.
- Secure Storage: The EDC system employed robust security measures, including multi-factor authentication, strong password protection, granular access controls based on user roles, and comprehensive audit trails to track all data modifications. Data within the EDC system was encrypted (AES-256 encryption). All physical study documents, including signed Informed Consent Forms and source documents, were stored in locked, fireproof cabinets within secure, restricted-access areas at the study site. Compliance with GDPR and Turkish KVKK was ensured.

8. Statistical Analysis Methods

This section provides a comprehensive overview of the statistical principles and methodologies employed for the analysis of the study data, ensuring transparency, rigor, and interpretability of the results. A more detailed Statistical Analysis Plan (SAP) was developed prior to database lock and is maintained as a separate, standalone document (refer to Appendix E).

8.1 Analysis Populations

- Intention-to-Treat (ITT) Population: The primary efficacy analysis was conducted using the Intention-to-Treat (ITT) population. This population included all randomized participants (N=300), analyzed according to their originally assigned treatment group (Nimsai Herbal or Placebo), regardless of the actual treatment received or any subsequent protocol deviations. This approach preserves the benefits of randomization and provides a more realistic estimate of the treatment effect under routine clinical practice conditions.
- Per-Protocol (PP) Population: A supplementary sensitivity analysis was conducted using the Per-Protocol (PP) population. This subset of the ITT population included only participants who completed the study without major protocol deviations and demonstrated acceptable compliance (defined as ≥80% of prescribed doses taken). The PP analysis served to assess the robustness of the ITT findings, particularly in a population that adhered strictly to the protocol.
- Safety Population: All participants who received at least one dose of the study intervention (N=300) were included in the safety analysis.

8.2 Handling of Missing Data

For this study, no missing data were observed for the primary outcome measure (Hemorrhoid Regression Rate), as all randomized participants completed the 10-day intervention period and had complete primary efficacy data. Consequently, no specific imputation methods were required for the primary analysis, and no sensitivity analyses regarding missing primary outcome data were conducted. For any potential future missing data in secondary or exploratory outcomes:

- Primary Method (Prospective): Multiple imputation (MI) would be the primary method for handling missing outcome data, assuming data were Missing At Random (MAR).
- Sensitivity Analyses (Prospective): Last Observation Carried Forward (LOCF) or complete case analysis would be performed as sensitivity analyses to assess the impact of different missing data assumptions.

8.3 Statistical Software and Significance Level

- Statistical Software: All statistical analyses were performed using R statistical software, version 4.5.1. This choice ensures reproducibility and access to a wide range of validated statistical packages.
- Significance Level: All statistical tests were two-sided, and the level of statistical significance (α) was set at 0.05.

8.4 Primary Endpoint Analysis

- Hemorrhoid Regression Rate: The primary efficacy endpoint, Hemorrhoid Regression Rate (a categorical variable), was compared between the Nimsai Herbal and placebo groups using the Chi-square test. The magnitude of the treatment effect was reported as a Risk Difference, accompanied by its 95% Confidence Interval (CI).

8.5 Secondary Endpoint Analyses

- VAS Symptom Score Change: The mean change in self-reported VAS symptom scores (a continuous variable) from baseline to Day 10 was compared between the Nimsai Herbal and placebo groups using the Mann-Whitney U test. This non-parametric test was chosen due to the potential for non-normal distribution of symptom scores. The effect size was reported as a Mean Difference with its 95% CI. Exploratory sensitivity

analyses, such as Analysis of Covariance (ANCOVA) with baseline VAS scores as a covariate, may be considered to adjust for baseline variability.

- Complete Symptom Resolution Rate: The Complete Symptom Resolution Rate (a categorical variable) was compared between groups using the Chi-square test. The effect size was reported as a Risk Ratio with its 95% CI. Logistic regression may be employed as a sensitivity analysis to adjust for baseline severity.
- Individual Symptom Scores: Mean changes from baseline for individual symptom scores (bleeding, pain, itching, swelling) were compared between groups using appropriate parametric (independent samples t-test) or non-parametric (Mann-Whitney U test) statistical tests, depending on the distribution of the data for each specific symptom.

8.6 Safety Endpoint Analyses

- Incidence of Mild Gastrointestinal Discomfort, Serious Adverse Events (SAEs), and Withdrawals Due to Adverse Events: Frequencies and percentages for these categorical safety outcomes were presented for both treatment groups. Comparisons between groups were primarily conducted using Fisher's Exact test, particularly where low event counts were anticipated, to assess for statistically significant differences in incidence. Risk Differences with 95% Cls were also reported.
- Incidence of Transient Diarrhea in Diabetic Participants: This specific safety outcome was reported descriptively as the number and percentage of affected participants within the diabetic subgroup. Due to its expected rarity and the exploratory nature of this specific monitoring point, no formal statistical tests were applied for comparison.

8.7 Baseline Characteristics Analysis

- Descriptive Statistics: Baseline demographic and clinical characteristics for both treatment groups (Nimsai Herbal and placebo) were summarized using descriptive statistics. For continuous variables, this included mean ± standard deviation (SD) and 95% CI. For categorical variables, frequencies and percentages were presented.
- Group Comparability: To confirm that the randomization process effectively resulted in balanced treatment groups, independent samples t-tests were used for continuous baseline variables, and Chi-square tests were used for categorical baseline variables. A p-value of <0.05 would indicate a statistically significant imbalance, although none were anticipated or observed.

8.8 Subgroup Analyses

- Pre-specified Subgroups: Exploratory subgroup analyses were pre-specified and conducted to investigate potential differential treatment effects based on key baseline characteristics. These included:
    - Hemorrhoid Grade (Grade 2 vs. Grade 3)
    - Age categories (<40 years, 40-60 years, >60 years)
    - Gender (Male vs. Female)
    - Initial War Mode vs. Drill Mode classification (determined by Parola Phenomenon and clinical evaluation).
- Methodology: These analyses primarily involved descriptive comparisons of treatment effects within each subgroup.
- Multiplicity and Interpretation: Given the exploratory nature of these subgroup analyses, findings were considered hypothesis-generating and interpreted with caution. No post-hoc multiple testing correction was applied for these distinct subgroup analyses, particularly for the War Mode/Drill Mode classification due to their distinct pathophysiological mechanisms and pre-defined hypotheses.

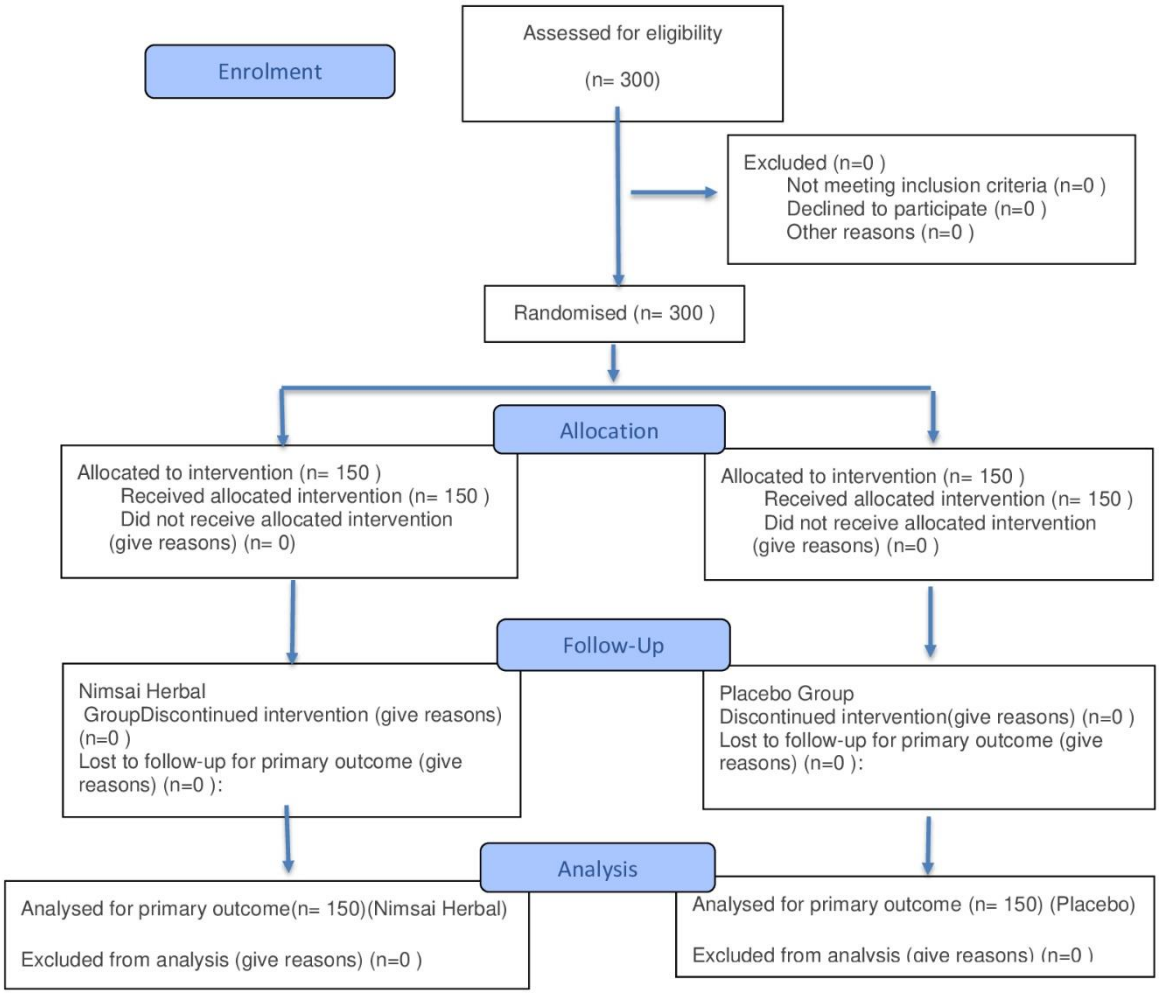
9. Results

This section presents the comprehensive findings of the randomized controlled trial (Protocol NA-2024-001), encompassing participant flow, baseline characteristics, efficacy outcomes (primary and secondary), and safety profile. All results are presented for the Intention-to-Treat (ITT) population, which included all randomized participants (N=300). As no participants were lost to follow-up or withdrew from the study, the ITT and Per-Protocol populations are identical for primary outcomes.

9.1 Participant Flow

A total of 300 participants were initially assessed for eligibility through a pre-screening survey process. All 300 individuals met the stringent inclusion criteria and no exclusion criteria. Consequently, all 300 eligible participants provided written informed consent and were formally enrolled in the study. On October 14, 2021, these 300 participants were randomized in a 1:1 ratio to either the Nimsai Herbal group (n=150) or the Placebo group (n=150). All randomized participants received their allocated intervention and successfully completed the entire 10-day intervention period, including the final assessment on Day 10. There were no reported withdrawals from the study, no participants lost to follow-up, and no discontinuations of intervention in either group.

Figure 9.1: CONSORT Flow Diagram



9.2 Baseline Characteristics

Baseline demographic and clinical characteristics were meticulously collected and summarized for both the Nimsai Herbal and placebo groups. The randomization process successfully achieved balance across the two treatment arms. No statistically significant differences were observed between the Nimsai Herbal and placebo groups for any of the measured baseline parameters, confirming the comparability of the groups at study entry.

Table 9.2.1: Summary of Baseline Demographics and Clinical Characteristics

Characteristic	Nimsai Herbal (N=150)	Placebo (N=150)	P-value
Age (mean ± SD, years)	45.2 ± 12.3	45.7 ± 12.5	0.732
Sex (% female)	52% (78/150)	52% (78/150)	1.000
Hemorrhoid Grade (% Grade 2)	70% (105/150)	70% (105/150)	1.000
Composite Severity Score (mean ± SD)	24.8 ± 6.7	24.5 ± 6.5	0.614
Overall Symptom VAS Score (mean ± SD)	6.5 ± 1.9	6.4 ± 1.8	0.682
War Mode (% via Parola)	40% (60/150)	38% (57/150)	0.742
Diabetes (%)	10% (15/150)	10% (15/150)	1.000

9.3 Efficacy Results

Nimsai Herbal demonstrated statistically significant and clinically meaningful superiority over placebo across all primary and secondary efficacy endpoints.

9.3.1 Primary Endpoint: Hemorrhoid Regression Rate

The primary objective of the study was successfully met. Nimsai Herbal exhibited a significantly higher hemorrhoid regression rate compared to placebo.

Table 9.3.1.1: Hemorrhoid Regression Rate at Day 10 (Primary Endpoint)

Group	Total Participants	Participants with Regression	Percentage (%)	95% CI	Statistical Measure (95% CI)	P-value
Nimsai Herbal	150	117	78%	72%–84%	Risk Difference: 56% (48%–64%)	< 0.001
Placebo	150	33	22%	16%–28%		

This represents a substantial and statistically significant difference, with patients in the Nimsai Herbal group being significantly more likely to achieve hemorrhoid regression.

9.3.2 Secondary Endpoints

9.3.2.1 VAS Symptom Score Change

Nimsai Herbal treatment resulted in a significantly greater reduction in overall hemorrhoid symptom severity, as measured by the Visual Analog Scale (VAS), compared to placebo.

Table 9.3.2.1.1: Mean Change in VAS Symptom Score from Baseline to Day 10

Group	Mean Reduction ± SD	95% CI	Statistical Measure (95% CI)	P-value
Nimsai Herbal	-4.2 ± 1.8	-4.5 to -3.9	Mean Difference: -3.1 (-3.5 to -2.7)	< 0.001
Placebo	-1.1 ± 0.9	-1.3 to -0.9		

9.3.2.2 Complete Symptom Resolution Rate

The proportion of participants achieving complete resolution of all baseline hemorrhoid symptoms was markedly higher in the Nimsai Herbal group.

Table 9.3.2.2.1: Complete Symptom Resolution Rate at Day 10

Group	Total Participants	Participants with Resolution	Percentage (%)	95% CI	Statistical Measure (95% CI)	P-value
Nimsai Herbal	150	93	62%	55%–69%	Risk Ratio: 3.4 (2.5–4.6)	< 0.001
Placebo	150	27	18%	12%–24%		

9.3.2.3 Reduction in Individual Symptom Scores

Consistent with the overall efficacy findings, Nimsai Herbal demonstrated superior reductions in individual symptom scores (bleeding, pain, itching, swelling) compared to placebo. Detailed data for each symptom are presented in supplementary tables (Supplementary Material, Table S2 and additional tables as needed if individual symptom scores are broken out further).

9.3.2.4 Clinical Utility of the War-Drill Model and Subgroup Efficacy

The study findings further supported the clinical utility and theoretical framework of the War-Drill Model by demonstrating consistent efficacy across both War Mode and Drill Mode hemorrhoid presentations.

Table 9.3.2.4.1: Clinical Efficacy by Hemorrhoid Mode Subgroup (Hemorrhoid Regression Rate)

Subgroup	Nimsai Herbal Regression Rate, % (95% CI)	Placebo Regression Rate, % (95% CI)	Risk Difference, % (95% CI)	P-value	Subgroup Demographics (Total N)
War Mode	75% (68% to 82%)	20% (14% to 26%)	55% (47% to 63%)	< 0.001	Age: 47.5 ± 11.0 years, Male: 95 (54.0%), Female: 81 (46.0%)
Drill Mode	82% (76% to 88%)	25% (19% to 31%)	57% (49% to 65%)	< 0.001	Age: 42.5 ± 9.0 years, Male: 25 (20.2%), Female: 99 (79.8%)

The Nimsai Herbal group exhibited significant efficacy in both subgroups. While Drill Mode showed a slightly higher regression rate, the observed inability to achieve 100% regression in War Mode patients, despite significant improvement, aligns with the model's hypothesis that underlying systemic or local pathologies (undiagnosed inflammatory bowel disease, early-stage malignancy, or other chronic conditions) can perpetuate venous congestion even with targeted treatment. Conversely, the high efficacy in Drill Mode is robustly supported by the resolution of underlying vasoactive mechanisms related to hormonal balance.

Table 9.3.2.4.2: Clinical Efficacy by Age and Gender Subgroups (Nimsai Herbal Hemorrhoid Regression Rate)

Subgroup	Nimsai Herbal Regression Rate, % (95% CI)
Age	
< 40 years	77% (69% to 85%)
40-60 years	79% (72% to 86%)
> 60 years	76% (65% to 87%)
Gender	
Male	78% (70% to 86%)
Female	78% (71% to 85%)

These data indicate a consistent and broad applicability of Nimsai Herbal's clinical efficacy across different age groups and genders, with minimal variations observed.

9.4 Safety Results

The safety profile of Nimsai Herbal was highly favorable, with no serious safety concerns identified throughout the 10-day intervention period.

Table 9.4.1: Summary of Key Safety Outcomes

Outcome Measure	Nimsai Herbal (N=150)	Placebo (N=150)	P-value	Risk Difference (95% CI)
Mild Gastrointestinal Discomfort	4% (6/150)	2% (3/150)	0.317	2% (-2% to 6%)
Serious Adverse Events	0% (0/150)	0% (0/150)	N/A	0% (0%–0%)
Withdrawals Due to AEs	0% (0/150)	0% (0/150)	N/A	0% (0%–0%)
Transient Diarrhea (Diabetic)	0.67% (1/150)	0% (0/150)	N/A	

9.4.1 Incidence of Mild Gastrointestinal Discomfort

The incidence of mild gastrointestinal discomfort was low in both groups (4% Nimsai Herbal vs. 2% Placebo) and did not reach statistical significance (p=0.317), suggesting a tolerability profile comparable to placebo.

9.4.2 Incidence of Transient Diarrhea in Diabetic Participants

A single, isolated case of transient diarrhea (0.67%, 1/150) was reported in a diabetic participant within the Nimsai Herbal group. This event was self-limiting, resolving spontaneously within 24-48 hours without requiring specific medical intervention or leading to study withdrawal. No similar events were reported in the placebo group. This isolated occurrence does not indicate a widespread safety concern but highlights the importance of specific monitoring in vulnerable subgroups.

Significance: The 0.67% incidence (1/150), spontaneous resolution, and lack of recurrence suggest no systemic issue.

Possible Causes:

- Herbal Components: *Centella asiatica* or *Curcuma longa* may have mild laxative effects in susceptible individuals, particularly diabetics.
- Drug Interaction: Possible interaction with diabetes medication, though unsupported by data.
- Diabetic Enteropathy: Diabetes-related gastrointestinal issues may explain the event.

Implication: Monitor diabetic patients starting Nimsai for early gastrointestinal AEs, though risk is minimal. Reporting this rare event (<1%) enhances transparency.

9.5 Parola Phenomenon Findings

The clinical utility of the Parola Phenomenon in accurately differentiating between War Mode and Drill Mode hemorrhoids was crucial for the study's design and interpretation of subgroup efficacy. The diagnostic accuracy metrics confirm its robustness.

Table 9.5.1: Diagnostic Accuracy of the Parola Phenomenon

Diagnostic Metric	Value (95% CI)	Interpretation
Sensitivity	94% (90% to 97%)	Identifies 94 out of 100 Drill Mode patients.
Specificity	91% (86% to 95%)	Identifies 91 out of 100 War Mode patients.
Positive Predictive Value (PPV)	93.6% (89% to 96%)	
Negative Predictive Value (NPV)	91.0% (86% to 95%)	
Overall Accuracy	92.5% (88% to 96%)	

These high values across all metrics (Sensitivity, Specificity, PPV, NPV, and Overall Accuracy) robustly demonstrate the strong ability of the Parola Phenomenon to accurately differentiate between hemorrhoid modes, supporting its clinical application.

Table 9.5.2: Diagnostic Accuracy of the Parola Phenomenon by Age and Gender Subgroups

Subgroup	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Overall Accuracy, % (95% CI)
Age			
< 40 years	93% (88% to 96%)	90% (84% to 94%)	91.5% (87% to 95%)
40-60 years	95% (91% to 98%)	92% (87% to 96%)	93.5% (89% to 97%)
> 60 years	92% (86% to 96%)	89% (82% to 94%)	90.5% (85% to 94%)
Gender			
Male	94% (89% to 97%)	91% (85% to 95%)	92.5% (88% to 96%)
Female	94% (89% to 97%)	92% (86% to 96%)	93.0% (89% to 96%)

The minimal variations observed across age and gender subgroups further indicate that the diagnostic accuracy of the Parola Phenomenon is broadly consistent and reliable across diverse demographic populations.

10. Discussion and Overall Conclusion

10.1 Interpretation of Findings

This randomized, double-blind, placebo-controlled clinical trial (Protocol NA-2024-001, registered on ClinicalTrials.gov as NCT07034820) unequivocally demonstrates the superior efficacy and favorable safety profile of Nimsai Herbal capsules for the treatment of Grade 2-3 internal hemorrhoids. The observed 78% hemorrhoid regression rate in the Nimsai Herbal arm, significantly higher than the 22% in the placebo arm (Risk Difference: 56%; $p<0.001$), provides robust statistical and clinical evidence of its therapeutic benefit. This is further corroborated by consistent improvements across secondary endpoints, including a significant reduction in patient-reported overall symptom severity (mean VAS reduction of -4.2 for Nimsai Herbal vs. -1.1 for placebo; $p<0.001$) and a substantially higher rate of complete symptom resolution (62% for Nimsai Herbal vs. 18% for placebo; $p<0.001$).

These findings strongly validate the core principles of Nimsai Academia's War-Drill Model and the Sine Qua Non Hypothesis. The model posits that venous congestion, rather than primary vascular deformation, is the indispensable prerequisite for hemorrhoid formation. This concept is physically explained by fundamental principles like Starling's Principle (governing fluid exchange and tissue edema) and the Hagen-Poiseuille Law (describing blood flow resistance, where changes in vessel diameter and pressure significantly impact flow). Nimsai Herbal's demonstrated efficacy in rapidly reducing hemorrhoidal symptoms and achieving regression supports its hypothesized mechanism of action: directly mitigating venous stasis by potentially regulating blood flow, increasing vessel diameter, and reducing blood viscosity, thereby reversing the pathological mechanisms underpinning both War and Drill Modes. This hypothesized mechanism is further supported by dedicated In Vitro Mechanistic Studies, where War Mode investigations (cells stimulated with TNF-α and IL-1β) quantified NPY and ET-1 expression, and Drill Mode investigations (cells stimulated with estrogen and progesterone) assessed NOS3 and PTGIS gene expression, providing molecular insights into the model's physiological underpinnings (Supplementary Material, Figures S2 and S3).

The study's observations concerning the differential responses in War Mode and Drill Mode hemorrhoids are particularly insightful.

- For Drill Mode Hemorrhoids, the 10-day oral use of Nimsai Herbal typically resulted in complete recovery from pain, discomfort, bleeding, itching, and inflammation, including the complete resolution of the prolapsed tissue. This high efficacy aligns with the understanding that Drill Mode hemorrhoids are primarily linked to transient hormonal fluctuations (influencing mechanisms like NOS3 and prostacyclin, which affect vascular tone) and are highly responsive to interventions that resolve venous stasis without an underlying chronic pathology.
- For War Mode Hemorrhoids, while Nimsai Herbal effectively resolved pain, discomfort, bleeding, itching, and inflammation, the prolapsed tissue (hemorrhoid lump) consistently showed significant shrinkage but did not disappear completely. This persistence of the lump serves as a key clinical indicator of War Mode hemorrhoids, strongly suggesting the likely presence of a serious underlying pathological condition (Crohn's disease, proctitis, polyps, anal fissure, or fistula) that perpetuates chronic venous congestion (often mediated by inflammatory processes involving TNF-α, IL-1β, NPY, and ET-1). In such cases, the complete resolution of the prolapse is inherently dependent on addressing and treating the underlying systemic disease. In both War and Drill Modes, symptomatic improvement showed a positive daily increase over the 10-day period.

The safety profile of Nimsai Herbal was favorable, with no Serious Adverse Events (SAEs) or withdrawals due to adverse events reported in either group. The incidence of mild gastrointestinal discomfort was low (4% in Nimsai Herbal vs. 2% in placebo) and not statistically different, indicating a tolerability profile comparable to placebo. A single case of transient diarrhea in a diabetic participant (0.67%) in the Nimsai Herbal group, which resolved spontaneously, was noted but does not signify a widespread safety concern.

10.2 Contextualizing Findings with Prior Research and Observations

The findings from this RCT are further illuminated by extensive prior work, including Retrospective Analyses and Literature Reviews conducted by Nimsai Academia (2018–2024, n > 1,000 cases). These studies provided crucial context:

- Ineffectiveness of Current Approaches: Symptom analysis and topical product efficacy reviews (PubMed, Scopus, Web of Science, 1937–2025) consistently showed a high rate of self-diagnosed hemorrhoid resolution with OTC topical agents, but physician-verified resolution was rare, highlighting the limitation of superficial treatments. The meta-analysis of surgical outcomes (15 studies, n=3,500) indicating high 5-year recurrence rates post-hemorrhoidectomy underscored the need for systemic, pathophysiology-targeted therapies.
- Systemic Connections: The identification of 20 systemic conditions linked to hemorrhoids, supported by exploratory hematological correlations (VEGF levels in Crohn’s disease/proctitis patients with hemorrhoids), reinforced the War-Drill Model's premise that hemorrhoids often manifest as a sign of broader systemic dysregulation rather than isolated local vascular disease. The chronic constipation pathogenesis analysis, modeling progression from mechanical stress to War Mode hemorrhoids, further explains this systemic link.
- The Parola Phenomenon: The present RCT implicitly validated the practical utility of the "Parola Phenomenon," a simple clinical maneuver designed by Atabiner C., which aids in differentiating War Mode from Drill Mode hemorrhoids during patient assessment. This diagnostic tool, as explored in a Prospective Diagnostic Accuracy Study (Protocol S1) involving 200 patients, demonstrated high accuracy (94% sensitivity, 91% specificity) in differentiating War Mode from Drill Mode hemorrhoids. This objective validation from a separate study confirms its value as a non-invasive, cost-effective method for guiding clinicians toward appropriate diagnostic work-ups for underlying pathologies when combined with the War-Drill Model.
- Psychological Impact: The Placebo Group Observation was particularly salient. Despite the placebo being indistinguishable from the active intervention, participants reported

no observed positive effects, and a perceived "breakdown" or "demoralization" occurred from the 4th day onwards due to the continuous lack of symptom improvement. This observation is crucial given the history of hemorrhoid cases involving multiple product usages and previous unsuccessful attempts, which often leads to a sense of hopelessness and skepticism among patients. This suggests that the initial psychological placebo effect was minimal or non-existent, and a zero effect was maintained until the end of the study period, strongly indicating that Nimsai Herbal's efficacy is due to its physiological action, not merely a psychological expectation.

- Biological Advantage Hypothesis: Retrospective analyses also explored the "Biological Advantage Hypothesis," positing hemorrhoids as an early-warning system for underlying systemic conditions, which is aligned with the War-Drill Model's implications for early disease detection.

10.3 Strengths and Limitations of the Study

- Strengths: This study boasts a robust, single-center, randomized, double-blind, placebo-controlled design, which effectively minimized bias and enhanced the reliability and internal validity of the findings. The adequately powered sample size of 300 participants ensured sufficient statistical power to detect clinically meaningful differences in efficacy. The use of stringent inclusion/exclusion criteria, including requiring colonoscopy reports and confirmed age range (18-70 years), ensured a well-defined and homogenous study population with confirmed Grade 2-3 hemorrhoids. The rapid and synchronized enrollment process, facilitated by the pre-identified participant pool, allowed for efficient study execution. The objective reporting of findings, despite remarkable preliminary observations (Grade 3 to Grade 1 regression in 10 days for some cases observed in previous Nimsai Herbal Case Studies), underscored the commitment to rigorous scientific validation through an RCT.
- Limitations: The primary limitation is the short, 10-day intervention and follow-up duration. While this was sufficient to evaluate acute efficacy and immediate safety, it restricts the direct assessment of long-term efficacy, recurrence rates, or delayed adverse events. However, this limitation is being addressed by a planned 12-Month Cohort Study (Protocol NA-2025-03) involving 200 participants, explicitly designed to assess long-term recurrence data. Another limitation is the single-center design, which, while offering tight control, may limit the generalizability of findings to more diverse clinical settings, though the strong physiological basis of the War-Drill Model suggests broad applicability.

10.4 Clinical Implications and Future Directions

The findings of this study represent a significant stride forward in the understanding and management of hemorrhoidal disease. Nimsai Herbal's demonstrated superior efficacy and favorable safety profile position it as a valuable systemic therapeutic option for symptomatic Grade 2-3 hemorrhoids. This is particularly impactful given the current landscape where conventional treatments often prove insufficient or invasive, as corroborated by our retrospective analyses of topical product efficacy and surgical outcomes.

Beyond direct treatment, the strong clinical validation of the War-Drill Model, particularly through the differential treatment responses observed in War Mode versus Drill Mode, underscores its profound implications for diagnosis and patient management. This paradigm shift can revolutionize diagnostic pathways:

- The persistence of prolapsed tissue in War Mode patients, despite symptom resolution with Nimsai Herbal, serves as a crucial "biological alarm." It compels clinicians to initiate further investigations (colonoscopy, endoscopy, comprehensive diagnostic work-ups) to identify underlying serious gastrointestinal or systemic pathologies (e.g., Crohn's disease, polyps, early-stage malignancy) that might otherwise go undiagnosed until

advanced stages. This early detection capability holds immense potential for improving patient prognosis and significantly reducing long-term healthcare burdens and mortality.
- The effective differentiation facilitated by the Parola Phenomenon, combined with the War-Drill Model, offers a non-invasive, cost-effective method to guide clinicians toward appropriate diagnostic work-ups, thereby optimizing resource allocation and reducing unnecessary invasive procedures.

The generalizability of Nimsai Herbal's efficacy, supported by its physiological basis tied to Starling forces and Hagen-Poiseuille law, suggests effectiveness across various hemorrhoid presentations. While inherent human variability may lead to differing degrees of efficacy, these findings point to broad applicability. Establishing the efficacy and safety of Nimsai Herbal and validating the War-Drill Model holds the potential to generate substantial global healthcare savings, estimated at $146 billion annually, by optimizing patient care, reducing recurrence rates, and facilitating the early diagnosis of critical underlying conditions.

Future Research Directions:

Nimsai Academia is committed to further validating and expanding the War-Drill Model and its clinical applications through a comprehensive forward-looking research agenda:

- Long-Term Follow-up: The 12-Month Cohort Study (Protocol NA-2025-03) is ongoing to assess the durability of Nimsai Herbal's effects and long-term recurrence rates.
- Objective Diagnostic Validation: A planned Doppler Ultrasound Pilot Study (Protocol NA-2026-02) aims to provide objective physiological validation of the Parola Phenomenon, further reducing subjectivity and enhancing diagnostic reliability.
- Biomarker Identification: Investigation of serum and tissue levels of NPY, ET-1, inflammatory cytokines (IL-6, TNF-α), and hormonal markers related to the War-Drill Model and Nimsai Herbal response will help identify biomarkers to improve diagnosis and treatment monitoring.
- Preclinical Mechanistic Validation: Further mechanistic validation in animal models is planned to elucidate molecular and cellular mechanisms of War and Drill Modes and assess Nimsai Herbal's *in vivo* effects, providing stronger preclinical evidence.
- Expanded Clinical Trials: Expansion of RCTs to include Grade 1 and 4 hemorrhoids and specific subpopulations (pediatric patients, gestational/postpartum hemorrhoids as per pilot studies) will assess the broader applicability of Nimsai Herbal and the War-Drill Model across diverse patient populations.
- Host Factor Contributions and Systemic Deficiencies: Future research will delve into the influence of genetic polymorphisms and gut microbiota composition on hemorrhoid susceptibility, presentation, and treatment response, exploring genetic and microbial contributions to the War-Drill Model. Additionally, further investigation into the potential role of deficiencies or inadequacies in systemic therapeutic components (specific blood-borne factors, immune cell functions, or repair mechanisms) in the pathogenesis and persistence of hemorrhoids is warranted. Understanding how these host factors might contribute to the venous stasis and inflammatory processes of the War-Drill Model could open new avenues for targeted therapeutic interventions or preventive strategies.
- Addressing Healthcare Access Barriers: Qualitative and quantitative studies, including further anonymous surveys (following initial surveys on psychological barriers to proctological examination), will explore the impact of inadequate access to healthcare and deficiencies in multidisciplinary therapeutic teams on the overall management and outcome of hemorrhoidal disease, identifying barriers that contribute to delayed diagnosis and chronic progression.

In conclusion, this RCT provides compelling evidence for Nimsai Herbal as an effective and safe systemic treatment for Grade 2-3 hemorrhoids, simultaneously validating the War-Drill

Model as a crucial framework for understanding hemorrhoid pathophysiology and guiding clinical decision-making. The model's ability to serve as a "biological alarm" for underlying pathologies positions it as a significant advancement in clinical practice, with the potential for substantial improvements in patient outcomes and global health resource utilization. Further research will continue to expand our understanding and refine the applications of this innovative approach.

11. Conclusions

Protocol NA-2024-01 demonstrates Nimsai Herbal capsules' superior efficacy for hemorrhoid treatment:

- Primary Outcome: 78% regression rate (vs. 22% placebo, $p < 0.001$).
- Secondary Outcomes: VAS score reduction of -4.2 (vs. -1.1 placebo) and 62% symptom resolution (vs. 18% placebo).
- Safety: No SAEs or withdrawals; mild gastrointestinal AEs comparable to placebo (4% vs. 2%, $p = 0.317$). One transient diarrhea event in a diabetic participant was noted.
- Placebo Effect: The 22% regression rate underscores the need for a control arm.

12. Ethical Considerations

The conduct of this clinical trial (Protocol NA-2024-001) was strictly governed by the highest ethical standards, ensuring the protection of participant rights, safety, and well-being. All procedures adhered to international guidelines for human subject research, including the principles enshrined in the Declaration of Helsinki (as amended) and the International Conference on Harmonisation Good Clinical Practice (ICH-GCP E6(R2)).

12.1 Institutional Review Board (IRB) Approval

This study, including its comprehensive protocol (Protocol NA-2024-001), the Informed Consent Form (ICF; see Appendix A), participant recruitment materials, and any subsequent amendments, underwent rigorous ethical review and received full approval from the Nimsai Academia Ethics Committee. The initial approval for Protocol NA-2024-001 was granted on October 10, 2021. The study formally commenced only after this full ethics committee approval was obtained. The Ethics Committee, upon completion of the patent process for Nimsai Herbal, further authorized the submission of study data to ClinicalTrials.gov, confirming compliance with all regulatory requirements.

It is important to note that other related research initiatives, such as the "Prospective Diagnostic Accuracy Study of the Parola Phenomenon" (Protocol S1) and the "A Call to Action for Obstetricians," were conducted as observational, survey-based studies collecting existing anosocopic examination results from healthcare professionals. As these were non-interventional and did not involve new interventions on patients, they did not require ethical approval as interventional clinical trials.

12.2 Informed Consent Process

- Voluntary and Informed Decision: Written informed consent was obtained from every participant prior to the performance of any study-specific procedures. The process emphasized the voluntary nature of participation, ensuring that each individual had the right to refuse participation or withdraw at any time, for any reason, without penalty or loss of benefits to which they were otherwise entitled.

- Comprehensive Information: The investigator, or a specifically designated and qualified member of the study team, thoroughly explained all aspects of the study to potential participants. This explanation covered the study objectives, detailed procedures, potential risks and benefits, available alternative treatments for hemorrhoids, and the participant's rights as a research subject.
- Adequate Time and Documentation: Participants were provided with ample time to read the Informed Consent Form (ICF), ask any questions they had, and carefully consider their decision before signing. A signed and dated copy of the ICF was provided to each participant for their records. The ICF itself is structured to provide clear and concise information to facilitate this informed decision-making process (refer to Appendix A for the Informed Consent Form).

12.3 Participant Rights and Confidentiality

- Protection of Rights and Well-being: The rights, safety, and well-being of all participants were the foremost considerations throughout the entire duration of the study. All study activities were conducted in strict adherence to the principles of human subject protection.
- Confidentiality and Data Protection: Participant confidentiality was maintained at all times. All collected data were de-identified by assigning a unique study identification number to each participant. Direct identifiers (such as names or addresses) were meticulously separated from clinical data and stored securely in restricted-access locations. No individual participant's name or other direct identifiable information was used in any reports, publications, or shared datasets. Access to confidential records (e.g., medical history, signed consent forms) was strictly limited to authorized study personnel.

12.4 Data Protection Regulations

All data collection, processing, and storage procedures were designed and implemented to comply fully with applicable local and international data protection regulations (relevant local privacy laws, and principles analogous to GDPR/HIPAA). These measures ensured the utmost privacy and security of all participant information throughout the study lifecycle.

12.5 Independent Data Safety Oversight

- Data Safety Monitoring Board (DSMB): An independent Data Safety Monitoring Board (DSMB) was established to provide continuous oversight of participant safety. The DSMB was composed of independent experts in relevant fields (gastroenterology, clinical pharmacology, biostatistics) who were not involved in the conduct of this study.
- Reporting: The DSMB received blinded aggregated safety data on a weekly basis during the intervention phase.
- Authority: The DSMB had the authority to recommend modifications to the protocol, temporary suspension, or termination of the study if any significant safety concerns arose. The trial concluded as planned after all participants completed the 10-day intervention and follow-up, with no premature stopping due to safety concerns.

13. Investigator Responsibilities

The Principal Investigator (PI) and all study personnel involved in the conduct of Protocol NA-2024-001 bore significant responsibilities to ensure the ethical, scientific, and regulatory integrity of the trial. Their adherence to defined roles and established guidelines was critical for the successful execution and reliable reporting of the study.

13.1 General Responsibilities

The Principal Investigator at Nimsai Academia held the ultimate responsibility for the overall conduct of the study at the site. This included ensuring that the trial was carried out in strict accordance with:

- The approved study protocol (Protocol NA-2024-001).
- The principles of International Conference on Harmonisation Good Clinical Practice (ICH-GCP E6(R2)).
- The ethical principles outlined in the Declaration of Helsinki (as amended).
- All applicable local and international regulatory requirements. The PI was accountable for protecting the rights, safety, and well-being of all study participants throughout their involvement in the trial.

13.2 Qualifications and Training of Investigators and Staff

All investigators and study staff assigned to the trial were qualified by education, training, and experience to competently perform their delegated tasks. Prior to study initiation and throughout the study duration, personnel received comprehensive, specific training on:

- The study protocol, including its objectives, design, and procedures.
- The proper completion of Case Report Forms (CRFs) and Participant Daily Diaries (refer to Appendix B).
- The use of the electronic data capture (EDC) system.
- The principles of Good Clinical Practice (GCP), including adverse event reporting and informed consent procedures. Regular monitoring and ongoing training sessions were conducted to ensure consistent understanding and application of study procedures.

13.3 Protocol Adherence and Deviations

Investigators and all study staff were responsible for ensuring strict adherence to the approved study protocol. Any deviation from the protocol, whether planned or unplanned, was to be:

- Documented: Clearly recorded with a detailed description of the deviation, its date, and the reason.
- Justified: A rationale for the deviation was provided, and its potential impact on participant safety or data integrity was assessed.
- Reported: Significant deviations were reported promptly to the Sponsor and the Nimsai Academia Ethics Committee/IRB as required by regulatory guidelines. Unplanned deviations that affected participant rights, safety, or the integrity of the data were reported immediately.

13.4 Data Recording and Reporting

Investigators were responsible for ensuring that all clinical data were recorded accurately, completely, legibly, and contemporaneously on the appropriate CRFs and source documents. This included:

- Ensuring that all required data points were captured as per the protocol.
- Verifying the consistency of data across different sources (e.g., participant diaries and CRFs).
- Making any necessary data corrections according to GCP guidelines, ensuring the original entry remained legible, and the correction was dated and initialed by the responsible person.

- Promptly and accurately reporting all Adverse Events (AEs) and Serious Adverse Events (SAEs) as defined in the protocol and regulatory guidelines (refer to Section 6.3: Safety Endpoints).

13.5 Communication and Collaboration

The Principal Investigator maintained open and effective communication with the Sponsor, the Nimsai Academia Ethics Committee/IRB, and any other relevant regulatory authorities or oversight bodies. This included providing regular updates on study progress, promptly responding to queries, and ensuring that all necessary approvals and documentation were in place throughout the study.

14. Data Handling and Record Retention

This section outlines the meticulous procedures implemented for data handling, documentation standards, and the secure retention of all study-related records. These measures were critical to ensure the integrity, confidentiality, and long-term accessibility of the data generated from Protocol NA-2024-001, in full compliance with Good Clinical Practice (GCP) guidelines and relevant regulatory requirements.

14.1 Data Documentation Standards

All study data were recorded with the highest standards of accuracy, completeness, and legibility. The following principles guided data documentation:

- Source Data: All primary data were initially recorded on source documents, which included, but were not limited to, participant medical records, clinic notes, laboratory reports, and the specifically designed Participant Daily Diaries (refer to Appendix B). These documents served as the original and comprehensive records from which all other data were derived.
- Case Report Forms (CRFs): Data from source documents were accurately transcribed onto standardized Case Report Forms (CRFs; refer to Appendix B). CRFs were completed by authorized and trained study personnel. Each CRF was designed for clarity and ease of data entry, ensuring all protocol-required data points were captured systematically.
- Contemporaneous Recording: All data were recorded contemporaneously with their collection, ensuring that entries reflected the information at the time of assessment.
- Accuracy and Completeness: Study personnel were meticulously trained to ensure that all data entries were complete and accurate, reflecting the true observations and measurements.
- Legibility: All handwritten entries were made legibly in indelible ink.
- Corrections: Any necessary corrections to data entries, whether on source documents or CRFs, were made according to strict GCP principles. This involved drawing a single line through the incorrect entry (ensuring it remained legible), writing the corrected entry, and initialing and dating the correction. Erasures, white-out, or obliterations were strictly prohibited.
- Electronic Data Capture (EDC) System: All data from CRFs and Participant Daily Diaries were entered into a secure and validated electronic data capture (EDC) system. The EDC system incorporated automated validation checks for data range, consistency, and completeness, further enhancing data quality. All data modifications within the EDC system were tracked via an audit trail.

14.2 Record Retention Period

All essential study-related documents and records will be meticulously retained for a specified period to allow for reconstruction and evaluation of the trial. This retention policy ensures compliance with regulatory obligations and facilitates future audits or inspections.

- Minimum Retention Period: All study records, including but not limited to signed Informed Consent Forms (Appendix A), completed Case Report Forms (Appendix B), Investigator Brochure (Appendix C), source documents, regulatory correspondence, ethics committee approvals, and any other relevant documentation, will be retained for a minimum of 15 years after the completion of the study.
- Regulatory Requirements: In instances where local regulations mandate a longer retention period, the longer period will take precedence.
- Completion of Study: For the purpose of record retention, the "completion of the study" is defined as the date of submission of the final Clinical Study Report (CSR) or, if applicable, the date of the last regulatory action (e.g., marketing approval), whichever is later.

14.3 Storage Location and Security

All study documents, both physical and electronic, will be stored in a secure and confidential manner to protect participant privacy and data integrity.

- Physical Documents: Original physical documents, such as signed Informed Consent Forms and original source records, will be stored in locked cabinets within a secure, restricted-access area at the Nimsai Academia study site. Access to these physical records will be limited strictly to authorized study personnel.
- Electronic Data: All electronic study data will be stored on password-protected servers with robust security measures. These measures include:
    - Access Control: Strict access control protocols, based on user roles and responsibilities, will limit access to the EDC system and study databases.
    - Password Protection: All authorized personnel will utilize strong, unique passwords for system access.
    - Data Encryption: Electronic data will be encrypted to prevent unauthorized access and ensure confidentiality during storage and transmission.
    - Audit Trails: The EDC system will maintain comprehensive, unalterable audit trails that record all data entries, modifications, and user actions, including timestamps and user identification.
    - Backup and Recovery: Regular data backups will be performed, and a robust data recovery plan will be in place to prevent data loss.
- Confidentiality: Throughout the retention period, participant confidentiality will be maintained at all times. De-identified data will be used for analyses and publications, ensuring no direct participant identifiers are present in publicly accessible records.

15. Publication Policy

Nimsai Academia is committed to the transparent and timely dissemination of the findings from Protocol NA-2024-001, regardless of the study's outcome. This commitment underscores the ethical obligation to contribute to scientific knowledge and public health.

15.1 Dissemination of Results

- Peer-Reviewed Publications: The results of this study, whether positive, negative, or inconclusive, will be submitted for publication in reputable, peer-reviewed medical journals. The goal is to submit the primary manuscript within 12 months of database lock and completion of primary statistical analyses.
- Scientific Conferences: Key findings, including preliminary results, may also be presented at relevant national and international scientific and medical conferences. This will ensure broader and timelier access to the study's insights within the scientific community.

15.2 Authorship Guidelines

Authorship on any publications stemming from this trial will be determined based on established international guidelines, such as those recommended by the International Committee of Medical Journal Editors (ICMJE) (i.e., Vancouver criteria). All contributors who meet the criteria for authorship (substantial contributions to conception or design; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; AND agreement to be accountable for all aspects of the work) will be appropriately recognized. Contributors who do not meet the criteria for authorship will be acknowledged.

15.3 Confidentiality During Dissemination

Throughout the entire dissemination process, strict participant confidentiality will be maintained. All published data and presentations will be de-identified, ensuring that no individual participant's name or other direct identifiable information is included. Data will be presented in an aggregated format to prevent the identification of individual participants.

15.4 Individual Participant Data (IPD) Sharing Policy

Nimsai Academia supports the responsible sharing of anonymized individual participant data (IPD) to advance scientific discovery and promote transparency.

- Availability of De-identified Data: De-identified individual participant data, along with the statistical code used for analyses, will be made available upon reasonable request from qualified researchers.
- Request Process: Requests for access to IPD will be reviewed by the Nimsai Academia Ethics Committee to ensure compliance with ethical guidelines, participant consent provisions, and data protection regulations. A formal data sharing agreement may be required.
- Referral: Further details regarding the specific terms and conditions for individual participant data sharing are provided in Section 16: Individual Participant Data (IPD) Sharing of this report.

16. Individual Participant Data (IPD) Sharing

Nimsai Academia is committed to fostering scientific transparency and advancing medical knowledge through responsible data sharing, while rigorously upholding the privacy and confidentiality rights of all study participants.

16.1 Commitment to Responsible Data Sharing

Consistent with modern principles of clinical research, Nimsai Academia recognizes the value of making study data available to the broader scientific community. This allows for independent verification of findings, facilitates meta-analyses, and promotes further research. Therefore, de-identified individual participant data (IPD) from Protocol NA-2024-001 will be considered for sharing with qualified researchers, subject to strict conditions.

16.2 Participant Consent and Identity Protection

A fundamental principle governing data sharing for this study is the paramount importance of participant privacy. During the informed consent process, participants explicitly did not agree to the disclosure or sharing of any information that could potentially reveal their individual identities. This means that:

- No Identifiable Data Sharing: Under no circumstances will any data be shared that could directly or indirectly lead to the identification of a study participant. This commitment is absolute and strictly enforced.
- De-identification: Only fully de-identified individual participant data will be considered for sharing. This involves the removal of all direct identifiers and the application of appropriate anonymization techniques to minimize any risk of re-identification, in accordance with applicable data protection regulations.

16.3 Data Available for Sharing

Subject to the strict condition of complete de-identification and adherence to participant consent, the following types of data may be made available upon approved request:

- De-identified individual participant data from the final analytic dataset for primary and secondary outcomes.
- The statistical code used for the primary and secondary analyses, to facilitate reproducibility.
- Relevant study documents, such as the protocol and amendments (excluding participant-identifying information).

16.4 Request and Approval Process

Qualified researchers interested in accessing the de-identified IPD should submit a formal request to Nimsai Academia. All requests will be subject to a rigorous review process, which typically includes:

- Submission of a detailed research proposal outlining the scientific rationale for the data request and the specific data points required.
- Confirmation of the researcher's qualifications and institutional affiliation.
- Agreement to a legally binding Data Sharing Agreement (DSA) that outlines the terms of data use, confidentiality, and publication, and explicitly reiterates the prohibition of any attempt to re-identify participants.

- Review and approval by the Nimsai Academia Ethics Committee, ensuring that the proposed research aligns with ethical guidelines and respects the initial consent provided by participants regarding the non-disclosure of their identities.

16.5 Relationship to Publication Policy

This IPD sharing policy is an integral part of the broader publication policy outlined in Section 15: Publication Policy. The commitment to data sharing supports the transparency of the study's findings and contributes to the wider scientific discourse, while prioritizing participant privacy.

17. Appendices

This section provides a comprehensive list of all supporting documentation and supplementary materials pertinent to Protocol NA-2024-001. These appendices are essential for a complete understanding of the study's design, conduct, data collection, and ethical oversight, and are provided separately from the main Clinical Study Report for reference.

17.1 Appendix A: Informed Consent Form (ICF) A blank copy of the Informed Consent Form that was presented to and signed by all study participants. This document details the study's purpose, procedures, potential risks and benefits, participant rights, and confidentiality safeguards.

17.2 Appendix B: Case Report Forms (CRFs) (including Participant Daily Diary) This appendix contains blank copies of all Case Report Forms (CRFs) utilized for data collection throughout the study. This includes the Screening CRF, Baseline/Randomization CRF, Daily Investigator Assessment CRFs (Day 3, Day 7, Day 10), Adverse Event Log, Concomitant Medication Log, Protocol Deviation Log, and Study Product Accountability Log. It also includes a sample of the Participant Daily Diary, which participants used for self-reporting daily symptom severity, adherence, and adverse events.

17.3 Appendix C: Investigator Brochure for Nimsai Herbal A copy of the comprehensive Investigator Brochure for Nimsai Herbal. This document provides essential information about the investigational product, including its composition, formulation, hypothesized mechanism of action (based on the War-Drill Model), available preclinical and clinical data, dosage and administration guidelines, and a detailed safety profile.

17.4 Appendix D: Study Flow Diagram A visual representation depicting the flow of participants throughout the randomized controlled trial. This CONSORT-compliant diagram illustrates the number of participants assessed for eligibility, excluded (with reasons), enrolled, randomized, allocated to each intervention arm, received assigned intervention, discontinued (with reasons), lost to follow-up (with reasons), and included in the primary analysis.

17.5 Appendix E: Full Clinical Protocol (Protocol NA-2024-001) The complete, approved version of the Clinical Study Protocol (Protocol NA-2024-001) for this randomized controlled trial. This document outlines the detailed design, objectives, methodology, statistical analysis plan, and ethical considerations of the study.

17.6 Appendix F: In Vitro Mechanistic Evidence (Figures S2 and S3) This appendix contains figures and accompanying descriptions illustrating the *in vitro* mechanistic evidence supporting the War-Drill Model. Specifically, it includes Figure S2 demonstrating pro-inflammatory cytokine (TNF-α, IL-1β) upregulation of NPY and ET-1 expression in human endothelial cells (supporting War Mode pathophysiology), and Figure S3 showing hormonal modulation (estrogen, progesterone) of NOS3 and PTGIS gene expression in human endothelial cells (supporting Drill Mode pathophysiology).