A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER, PARALLEL GROUP PILOT STUDY OF THE SAFETY AND EFFICACY OF HYDROCORTISONE ACETATE SUPPOSITORIES, 25 MG COMPARED TO PLACEBO SUPPOSITORIES IN THE TREATMENT OF SYMPTOMATIC INTERNAL HEMORRHOIDS

CLINICAL STUDY PROTOCOL

Protocol Number: HDCS 1701 (formerly 1-2017)

Protocol Version Number: 4.0

Protocol Version Date: 26Apr2019

Study Sponsor: Nivagen Pharmaceuticals, Inc.

IND: 129039

PROTOCOL APPROVAL:

I am aware of, and agree to comply with, all of the procedures contained within this protocol and requirements of applicable regulatory agencies:

Corporate Information

CONTACT LIST

Sponsor:
Anand Shulka
Vice President, R&D
Nivagen Pharmaceuticals, Inc.
3050 Fite Circle, Suite 100
Sacramento,CA 95827
Office: 916-364-1662
Personal Information
Email: ashukla@nivagen.com

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PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol HDCS 1701 "A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel Group Pilot Study of the Safety and Efficacy of Hydrocortisone Acetate Suppositories, 25 mg Compared to Placebo Suppositories in the Treatment of Symptomatic Internal Hemorrhoids" and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of Subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations.

I will not enroll any Subjects into this protocol until IRB approval and Sponsor approval are obtained.

_____	_____	_____
Principal Investigator	Signature	Date

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CBC	Complete Blood Count
ClinRO	Clinician Reported Outcome
CMP	Complete Metabolic Panel
CRO	Contract Research Organization
DCF	Data Clarification Forms
EC	Ethics Committee
ED	Early Discontinuation
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IGA	Investigator Global Assessment
ICH	International Conference on Harmonization
ID	Identification
IHSSA	Internal Hemorrhoid Sign and Symptom Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
mITT	Modified Intent To Treat
OTC	Over the Counter
PGIS	Patient Global Impression of Severity
PGIC	Patient Global Impression of Change
PP	Per Protocol
PRO	Patient Reported Outcome
RLD	Reference Listed Drug
SAE	Serious Adverse Event
US	United States
UV	Unscheduled Visit

1. TITLE:

A randomized, double-blind, placebo-controlled, multicenter, parallel group pilot study of the safety and efficacy of Hydrocortisone Acetate Suppositories, 25 mg compared to placebo suppositories in the treatment of symptomatic internal hemorrhoids.

2. INTRODUCTION:

Hemorrhoidal disease is common in the United States with at least 15 million people comprising nearly 5% of the population suffering from this condition. Hemorrhoids begin with the enlargement of normal vascular cushions which are present in the anal canal at birth and are themselves a normal part of the human anatomy. However, hemorrhoids may be diagnosed only if symptoms of bleeding, prolapse or thrombosis exist in addition to the presence of enlarged vascular cushions. Hemorrhoids may be internal and/or external. Internal hemorrhoids occur above the dentate line and are covered with colonic mucosa whereas external hemorrhoids occur below the dentate line and are covered with squamous epithelium. The incidence of hemorrhoids peaks in the 65-74-year-old age group with lesser rates for both younger and older age groups.

Current theory attributes the development of hemorrhoids to the dilation of the vascular cushions due to increased anal sphincter pressure which interferes with the drainage of blood from the rich plexus of arterial and venous vessels in these cushions but does not interfere with the in-flow of blood through the arteries. This results in dilation and progressive development of hemorrhoids. A major factor contributing to hemorrhoidal development is the gradual degeneration of the connective tissue in the vascular cushions which leads to further enlargement of the vessels and to their eventual prolapse. This combination of decreased outflow and gradual connective tissue degeneration results in the progressive development of the condition.

Early hemorrhoids are frequently treated with a fiber diet and with lifestyle modifications such as increased exercise and the avoidance of obesity and sedentary occupation which appear to be significant risk factors for the disease. Also, control of diarrhea appears to be a useful option in the prevention of the development of hemorrhoids. However, in more advanced cases acute hemorrhoidal attacks are present with bleeding, inflammation and often thrombosis of the hemorrhoidal veins. Conservative therapy consists of local treatment. Several types of drugs have been used for this purpose. These include local anesthetics, chiefly pramoxine. This is a rapidly acting, local anesthetic which is applied topically as needed up to five times a day. It provides local relief particularly of itching through its anesthetic action. Local application of phenylephrine is also used in the treatment of hemorrhoids to reduce blood flow through the hemorrhoids by utilizing the drug's vasoconstricting action. This produces temporary relief of burning and itching. 5-amino salicylic acid (Mesalamine) is also used off-label as a local anti-inflammatory agent to treat hemorrhoids. It appears to reduce the pain and bleeding of hemorrhoids during acute attacks. Hydrocortisone in various types of vehicles is also a prominent modality of treatment for hemorrhoids as well as other anorectal conditions. Foams, suppositories and locally applied creams have been used as vehicles for the application of hydrocortisone, although none are FDA-approved products for the treatment of hemorrhoids. Hydrocortisone's potent anti-inflammatory action is thought to reduce the inflammation associated with the hemorrhoids and thus improve bleeding, itching and other symptoms of hemorrhoids. Products using these ingredients have a long history of use in the United States and are commonly relied upon for the non-surgical, conservative treatment of hemorrhoids.

3. OBJECTIVE:

a. To determine the effectiveness of Nivagen's Hydrocortisone Acetate Suppositories 25 mg for the relief of symptoms associated with internal hemorrhoids.
b. To determine the safety and tolerability of Nivagen's Hydrocortisone Acetate Suppositories 25 mg.

4. PHASE: 2

5. STUDY DESIGN:

This study will be a randomized, double-blind, placebo-controlled, multicenter, parallel group pilot study of 25 mg hydrocortisone suppositories administered twice daily compared to a vehicle placebo in subjects with symptomatic internal hemorrhoids. Approximately 100 subjects will be randomized in a 1:1 ratio (Test product: placebo).

The study will consist of 3 periods:

a. Screening Period (2 weeks/Days -14 to -1)
b. Treatment Period (2 weeks/ Days 1-14)
c. Follow-up Period (2 weeks/ Days 15-29)

Subjects will use daily paper diaries to record the time and date of each medication application, concomitant medication and adverse events (AEs). The subjects will use electronic diaries to complete the Internal Hemorrhoids Sign and Symptom Assessment (IHSSA) daily for the duration of the study and the Patient Global Impression of Severity (PGIS) and Change (PGIC) at visits.

6. STUDY POPULATION:

Male and female subjects, at least 18 years of age, with a diagnosis of symptomatic internal hemorrhoids will be selected to participate in the study.

7. PRODUCT DESCRIPTION:

Test Product: Hydrocortisone Acetate Suppository, 25 mg (Nivagen Pharmaceuticals Inc.)
Placebo: Vehicle Suppository (Nivagen Pharmaceuticals Inc.)

8. GROUPS:

Two Groups (1:1) Total Subjects: Approximately 100 (50:50)

9. STUDY SCHEDULE:

Visit 1 (Days -14±2; Initiation of Screening)
Visit 2 (Day 1; Start of Treatment)
Visit 3 (Day 8±1, Interim)
Visit 4 (Day 15±2, End of Treatment)
Visit 5 (Day 29±3, Follow-Up/End of Study; UV/ED)

10. STUDY OUTLINE:

Visit Title Visit Number Study Day	Initiation of Screening Visit 1 Day -14±2	Start of Treatment Visit 2 Day 1	Interim Visit 3 Day 8±1	End of Treatment Visit 4 Day 15±2	Follow-up/End of Study UV/ED[8] Visit 5 Day 29±3
Informed Consent	X				
Medical History	X				
Demographics	X				
Concomitant Medication Review	X	X	X	X	X
Physical Exam including Vital Signs	X				
Clinical Laboratory Tests	X[1]		X[2]	X[3]	
Urine Pregnancy Test[4]	X	X	X	X	X
Urine Drug Screen	X				
Breath Alcohol Test	X				
Inclusion/Exclusion Criteria	X	X			
Adverse Events Assessment		X	X	X	X
Anoscopy		X		X	
Assessment of Disease Grade/ Diagnosis		X			
Randomization		X			
Cognitive Interview[5]	X				
Exit Interview[6]				X	
PROMIS Global Health Questionnaire		X		X	
IHSSA daily diary[7] (ePRO)	X	X	X	X	X
Patient Global Impression of Severity (PGIS) (ePRO)		X		X	
Patient Global Impression of Change (PGIC) (ePRO)				X	
Dispense IP Supplies		X			
IP Accountability *Drug will be returned*				X	X as needed
Dispense Diary/Instructions	X	X		X	
Subject Compliance/Diary Review and Collection		X		X	X as needed
Schedule Next Visit	X	X	X		X as needed

[1]Complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis, HIV, Hepatitis B, Hepatitis C
[2]Comprehensive metabolic panel (CMP)
[3]Complete blood count (CBC), comprehensive metabolic panel (CMP)
[4]The urine pregnancy test is to be conducted for women of child-bearing potential. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a urine pregnancy test.
[5]First 5 enrolled subjects at a sponsor selected site
[6]First 25 enrolled subjects who reach Visit 4 and agree to participate in the interview
[7]Internal Hemorrhoids Sign and Symptom Assessment. To be completed daily throughout the study via electronic diary (ePRO).
[8]UV, Unscheduled Visit; ED, Early Discontinuation Visit

11. RANDOMIZATION:

a. Two groups.
b. This is a double-blind study.
c. An independent third party will generate and hold the randomization code throughout the conduct of the study. The Nivagen product and placebo will be similar in appearance and will also be labelled and packaged to be similar in appearance. The Subject and Investigator will be blinded as to the treatment.

12. INCLUSION CRITERIA:

a. Subject reports an average score of 1.5 or greater (on 0-4 scale) on either the IHSSA itch severity or itch frequency items (Section 21.b) during the 2-week screening period
b. Subject reports hemorrhoidal bleeding associated with their bowel movements at least 50% of the days where a bowel movement occurs, as indicated by responses to the IHSSA (Section 21.b) during the 2-week screening period.
c. Have a diagnosis of symptomatic Grade I, II or III internal hemorrhoids (Banov et al. 1985) by history; confirmed by anoscopy.
d. Is a male or female aged 18 years and older.
e. Give voluntary consent to participate in the study following a full explanation of the nature and purpose of the study, by signing the IRB-approved Informed Consent document prior to any study specific evaluations.
f. Is willing to forego the use of non-prescription (OTC) and prescription medication or procedures for the treatment of hemorrhoidal disease and/or pain for the duration of the study.
g. Female Subjects of childbearing potential (excluding women who are or premenarchal, surgically sterilized (by hysterectomy) or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 30 days after the last administration of study drug. For this study, the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. A sterile sexual partner is NOT considered an adequate form of birth control.
h. All male Subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 30 days after the last administration of study drug. Abstinence is an acceptable method of birth control. Female partners should use an acceptable method of birth control as described in the above Item g.
i. Subjects agree to not appreciably change their diet during the study.

13. EXCLUSION CRITERIA:

a. Has a fissure or a fistula-in-ano, abscess, polyps or colorectal adenoma or colorectal cancer, arteriovenous malformations, or any other pathological condition of the anus other than symptomatic internal hemorrhoids which might be a potential cause of hematochezia.
b. Has inflammatory bowel disease.
c. Has Grade IV hemorrhoidal disease (Banov et al. 1985).
d. Has external hemorrhoids.
e. Has had or is receiving pelvic radiation.
f. Is using other OTC, prescription or narcotic medications for treatment of hemorrhoidal disease and/or pain. Washout of 7 days required if medicated treatment used.
g. Has had a sphincterotomy, anal stretch or other procedure that may reduce the resting anal pressure.
h. Endoscopic or surgical treatment of internal hemorrhoids in the past such as IRC, rubber band ligation or injection therapy.
i. Is immunocompromised (e.g. receiving cancer chemotherapy, steroids, HIV positive).
j. Is a pregnant or nursing female.
k. Is known to be allergic to latex, lanolin, white petrolatum, paraffin wax, sorbitan sesquioleate, propylene glycol, hydrocortisone or psyllium.
l. Is not willing to use a finger to insert the suppository even with a finger cot.
m. Has received glucocorticoids (any form) within the last 2 months prior to starting study.
n. Subjects who have unstable medical disorders that are clinically significant or have life-threatening diseases.
o. Subjects who consume excessive amounts of alcohol (greater than two drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine and barbiturates).
p. Positive urine screening for drugs of abuse or positive alcohol breath test.
q. Subjects who have participated in an investigational drug study (i.e., Subjects have been treated with an investigational drug) within 30 days prior to baseline will be excluded from study participation. Subjects who are participating in non-treatment studies such as observational studies or registry studies can be considered for inclusion.
r. Subjects who have been previously enrolled in this study.
s. A subject who has a history of being unresponsive to anal hydrocortisone therapy.
t. Lacks suitability for participation in this study for any reason in the opinion of the Investigator.
u. Clinically significant complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis or positive HIV, Hepatitis B, Hepatitis C.
v. Female subjects with Abnormal Uterine Bleeding (menorrhagia).

14. TREATMENTS:

Suppositories should be stored at room temperature away from moisture and heat. One (1) Hydrocortisone Acetate Suppository, 25 mg or Placebo (Vehicle) Suppository is inserted into the anal canal twice daily (morning and evening) for 2 weeks (14 days). Subjects are to be instructed to wash their hands before and after handling the suppository and to try to empty their bowel and bladder just before inserting suppository. Subjects should clean their rectum with a moist cloth or wipe before using the suppository and gently dry the area by blotting with toilet tissue. The outer wrapper is to be removed from the suppository before inserting and handling of

the suppository too long is to be avoided or it will melt in their hands. To insert the suppository, the subject is to lie on their side with their lower leg straight out and their upper leg bent forward toward their stomach and then lift their upper buttock to expose their rectal area. No more than the specified amount of suppository is to be used and is not to be applied more than twice daily as this will not produce faster results and may increase irritation. To insert one suppository, pointed end first, subject is to use their finger until it passes the muscular sphincter of the rectum, about 1 inch in adults. (If not inserted past the sphincter, the suppository may pop out.). Subject is to hold their buttocks together for five seconds and for best results, to remain lying down for five minutes to avoid having the suppository come out. The suppository will melt quickly once inserted and there should be little or no discomfort while holding it in. Subject is to avoid having a bowel movement for one to three hours after inserting the suppository.

Note that the medication from the suppository may stain fabric. Subjects may experience irritation such as burning, itching, dryness, skin/hair follicle irritation, or changes in skin color around the rectal area. Subjects are to report to the study staff any reactions that make continued application of the study medication difficult. The PI may recommend that the study medication be used less frequently on the irritated areas until the irritation goes away. If subject sees a doctor for any medical problems, they are to be advised to inform the study staff at their next visit. Subject is to record any illness or unwell feelings such as headaches, cold, cramps, etc., on the last page of their diary. Subjects are to record any change in medications since the previous visit (other than study medication) on the last page of the diary. All unused study medication must be returned to the study site at the end of treatment.

15. LABORATORY STUDIES:

Complete blood count (CBC), comprehensive metabolic panel (CMP), blood HIV/Hepatitis B/Hepatitis C testing, urinalysis, urine pregnancy, urine drug screen, breath alcohol tests.

16. DIAGNOSTIC TESTS:
Anoscopy - Classification of Internal Hemorrhoids (Banov et al. 1985).
Video of the procedure will be recorded and sent to the CRO for central reading.

Grade	Description
I	Hemorrhoids are visualized on anoscopy and may bulge into the lumen but do not prolapse below the dentate line
II	Hemorrhoids prolapse out of the anal canal with defecation or with straining but reduce spontaneously
III	Hemorrhoids prolapse out of the anal canal with defecation or straining, and require manual reduction
IV	Hemorrhoids are irreducible and may strangulate

17. RETENTION SAMPLES:
Retention samples will be randomly selected at the study sites from the clinical drug supplies received prior to dispensing to subjects and sent to BRR for long-term storage. Retention samples will not be returned to the sponsor at any time.

18. ADMINISTRATIVE MATTERS:
In addition to recording the time and date of each medication application, the Daily Personal Diaries will be used to record concomitant medication taken and all adverse events experienced. Paper copies of the IHSSA daily electronic diaries will be provided to subjects for use as a backup for missed ePRO questionnaires.

19. STUDY DISCONTINUATION:
Subjects could be discontinued from the study for the following reasons:
a. Pregnancy.
b. Acute illness or clinically significant laboratory result.
c. Significant protocol deviation.
d. Serious adverse experience.
e. Decision by the Subject to leave for any reason.
f. If the Subject's condition has worsened to the degree that the Principal Investigator feels it is unsafe for the Subject to continue in the study.
g. If the Subject's drug code is unblinded.
i. If the Subject is lost to follow-up.
j. If the Subject becomes pregnant.
k. If the Subject becomes a prisoner or become involuntarily incarcerated.
l. Any other reason that may affect the outcome of the study or the safety of Subjects.
m. Termination of the study by the Sponsor.

A significant protocol violation is defined as any Subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy.

The reasons for a Subject discontinuation will be documented. If a Subject is discontinued from the study for any reason, the procedures scheduled for Visit 5 will be completed and any outstanding data and study drug should be collected if possible. Data, in addition to the reason for discontinuation and the date of removal, will be documented on the End of Study eCRF.

Before a Subject is considered lost to follow-up, the Principal Investigator will document all attempts to reach the Subject twice by telephone and will send a certified follow-up letter.

If a Subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a Subject, the Principal Investigator must strive to follow the Subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up. Should a serious adverse event (SAE) be noted, procedures stated in Section 24.d. must be followed.

20. SUBJECT POPULATIONS:

a. The per-protocol (PP) population includes all subjects who meet all inclusion and no exclusion criteria, completed the evaluations for Visit 4 within the designated visit window (+/- 2 days) with no protocol violations that would affect the treatment evaluation. Subjects must take at least 80% but no more than 120% of the required doses. Compliance will be verified using subject diaries.

b. The modified intent-to-treat (mITT) population includes all subjects who meet all inclusion/exclusion criteria, apply at least one (1) dose and return for at least one (1) post-baseline evaluation visit.

c. The safety population (intent-to-treat (ITT)) includes all subjects who meet all inclusion/exclusion criteria and apply at least one (1) dose.

21. ENDPOINTS:

a. Clinician Reported Outcome (ClinRO) - Anoscopy (Visits 2, 4).

Anoscopy – Visual assessment of hemorrhoids (Fukuda et al. 2005; Lunniss and Mann 2004). Video of the procedure will be recorded for blinded central reading and assessment according to the following scale:

Swelling	% Lumen	Score	
	0	None	0
	≤25	Mild	1
	≤50	Moderate	2
	≤75	Severe	3
	>75	Very severe	4

b. Patient Reported Outcome (PRO) – Internal Hemorrhoid Sign and Symptom Assessment (IHSSA) (Daily between Visits 1 and 5).

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system on the patient's own smartphone or personal computer. The IHSSA training materials, post-bowel movement assessment, and end of day assessment are included in **Appendix 1**.

c. Patient Reported Outcome (PRO) – Patient Reported Outcome Measurement Information System (PROMIS) Global Health Questionnaire Version 1.2 (Visits 2 and 4).

The PROMIS Global Health Questionnaire is completed by patients during Visits 2 and 4. It will be completed before any clinical or laboratory tests are administered. The PROMIS Global Health Questionnaire assesses an individual's physical, mental, and social health using 10 items. The measure is generic, rather than disease-specific, and often uses an "In General" item context as it is intended to globally reflect individuals' assessment of their health. The questionnaire produces two scores: Physical Health and Mental Health. Raw scores for both scales are converted to T-scores with a mean of 50 and standard deviation of 10. The items of the PROMIS Global Health Questionnaire are included in **Appendix 2**.

d. Patient Reported Outcome (PRO) – Patient Global Impression of Severity (Visits 2 and 4) and Patient Global Impression of Change (Visit 4) Items

The Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) items are designed to capture the patient's overall perspective on sign and symptom severity. The 8-item PGIS asks patients to rate the severity of their hemorrhoid-related signs and symptoms over the past week. The 9-item PGIC asks patients to rate the direction and magnitude of the change in their signs and symptoms since starting the study medication. The PGIS and PGIC are included in the study to help establish the threshold for clinically relevant change on the IHSSA. Although they address signs and symptoms of internal hemorrhoids, the IHSSA is considered the primary measure of these constructs. The PGIS and PGIC items are included in **Appendix 3**.

Based on the results of the pilot study, primary and secondary endpoints will be selected for future studies.

22. SUBJECT SAFETY:

a. Safety assessment will be conducted on all subjects administered at least one suppository. Adverse drug reactions may include burning and local irritation upon application. Systemic absorption of topical corticosteroids has produced reversible suppression of the HPA axis. Adverse medical events experienced by the subjects will be tabulated. The relationship of adverse events, if any, to the study drug will be assessed by the Investigator (see Section 24).

b. Physical Examination

The investigator, sub-investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, and Registered Nurse as per local regulations) will perform a brief physical examination, prior to the Subject starting study drug.

The physical examination will include, at a minimum, examination of the Subject's general appearance, skin, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities.

Vital signs, including blood pressure, pulse rate, respiratory rate and oral body temperature will be documented at Visit 1. Vital signs will be measured after the Subject has rested in a seated position for at least 5 minutes.

The Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes). Height will be measured without shoes.

c. Concomitant medications

Concomitant medications, including the use of non-drug treatments/therapies, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

d. A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including acetaminophen, should be recorded.

e. Individual subject stopping criteria

Subjects will be withdrawn if they are hypersensitive to the drug product or develop a CTCAE v4.0 (NCI 2009) Grade 3 or higher adverse event (**Appendix 4**). Subjects will be monitored for drug-induced liver injury (DILI) (FDA 2009). Subjects will be withdrawn if:

i. Alanine or aspartate aminotransferase (ALT or AST) >8x upper limit of normal (ULN).
ii. ALT or AST >3x ULN and (total bilirubin (TBL) >2x ULN).
iii. ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Subjects will be re-tested (CMP) within 48-72 hours if ALT or AST >3x ULN and/or TBL >2x ULN. If repeat testing shows ALT or AST >3x ULN, close observation will be initiated to determine whether the abnormalities are improving or worsening.

Close observation includes:

iv. Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
v. Obtaining a more detailed history of symptoms and prior or concurrent diseases.
vi. Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.

vii. Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
viii. Obtaining a history of exposure to environmental chemical agents.
ix. Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
x. Considering gastroenterology or hepatology consultations.

f. Pilot study stopping criteria

The pilot study may be stopped if ≥2 patients on drug develop the same CTCAE v4.0 Grade 3 adverse event or if 1 patient develops a CTCAE v4.0 Grade 4 or higher adverse event (**Appendix 4**).

23. STATISTICAL METHODS:

a. Endpoints

Anoscopy results at Day 15 will be compared to responses at baseline (Day 1). IHSSA scores from Days 1-15 (treatment period) and 16-29 (follow-up period) will be compared to responses from Days -14 to -1 (baseline period). The 95% confidence intervals for the differences between the change from baseline for the hydrocortisone acetate suppository and that for the placebo will be calculated.

b. Safety

The incidence of all AEs reported during the study will be classified based on Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 terminology (system organ classes and preferred terms) and summarized for each treatment group. Incidence of adverse events will be tabulated by system organ class, preferred term, and severity, and by system organ class, preferred term, and relationship to study drug.

24. ADVERSE EVENTS:

a. Definitions

i. Any untoward events occurring during the study will be documented and summarized upon completion of the study.
ii. The term Adverse Event (AE) will cover any untoward medical occurrence in a clinical investigation where a volunteer was administered an investigational product, which does not necessarily have to have causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with use of a medicinal product, whether considered related to the medicinal product. This includes all events both expected and unexpected (the nature or severity of which is not consistent with information in the relevant source document(s)).
iii. In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, an Adverse Drug Reaction (ADR) is defined as follows: all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products, an adverse drug reaction is defined as a response to a drug which is noxious and

unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

iv. A medical event is defined as any unintended sign, symptom, or disease that occurs between the pre-trial evaluation and the first investigational product administration of the clinical study. As no investigational product has been administered yet, those events are not to be considered as adverse events.

v. Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfills the definition of "serious adverse event", it must be recorded as such (see below).

b. An adverse event may be:

i. A new illness.

ii. Worsening of a concomitant illness.

iii. An effect of the study medication including comparator; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the qualified investigator or medical qualified designate considers to be clinically important.

iv. A combination of two or more of these factors.

v. Abnormalities in laboratory tests, in the measurements of vital signs, or in other measurements performed after the drug administration or at the end of the study are to be recorded as adverse events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to study discontinuation and/or fulfilling a seriousness criterion. If asymptomatic, but with a suspected underlying process, the qualified investigator or the qualified medical designate may consider the abnormalities to be medically relevant.

c. Surgical procedures themselves are not adverse events. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

d. A serious adverse event is one that occurs at any dose (including overdose) and that:

i. Results in death.

ii. Is life-threatening.

iii. Requires in-patient hospitalization or prolongation of existing hospitalization.

iv. Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions).

v. Is a congenital anomaly or birth defect.

vi. Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the volunteer or may require intervention to prevent one or the other outcomes listed above (according to medical judgment of the qualified investigator).

e. Classification of Adverse Events

All adverse events will be recorded on an adverse event information sheet and graded as mild, moderate, or severe according to the following definitions:

i. Mild: Causing no limitation of usual activities; the volunteer may experience slight discomfort.

ii. Moderate: Causing some limitation of usual activities; the volunteer may experience annoying discomfort.

iii. Severe: Causing inability to carry out usual activities; the volunteer may experience intolerable discomfort or pain.

f. Relationship to Study Medication

The relationship is characterized as:

i. Not Related: This applies to any AE that is clearly not related to use of the study drug.

ii. Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.

iii. Probable: There is a reasonable temporal relationship between the use of the study drug and the AE. Based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely.

iv. Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the Subject's clinical state, environmental or toxic factors or other modes of therapy administered to the Subject. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the investigational product.

g. Documentation and Reporting of Adverse Events

i. For the purposes of this study, the period of observation of adverse events extends from the start of treatment with the investigational product until the final study visit. During this period, all adverse events spontaneously reported by the volunteer, observed by the Qualified Investigator (or delegates) or elicited by general questioning will be documented in the CRF and will be reported in the final report.

ii. If necessary, every effort will be made to obtain an adequate follow-up of the volunteers. Should any volunteers choose to withdraw early from the study, they will be advised of the safety precautions to be taken.

iii. The volunteers will be questioned on their health status at the beginning of the study and before their departure from the clinical site. An open-ended question will be asked.

iv. It is the qualified investigator's responsibility to record and report all adverse events that occur during the study regardless of their relationship to the study medication. If judged necessary by the qualified investigator, an adverse event will be reported in accordance with the applicable regulatory requirements.

h. Pregnancy in a female volunteer on the study shall be reported to the sponsor or their authorized representative within 24 hours of the knowledge of its occurrence by the qualified investigator that such pregnancy occurs during the Study or right after. Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the volunteer's safety, the pregnancy will be followed up to determine outcome as, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

i. As for an adverse event, the pregnancy will be recorded on a Clinical Trial Pregnancy Form and reported by the qualified investigator to the sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and

any pregnancy outcome. Any SAE experienced during pregnancy will be reported on a SAE Report Form.

j. Any adverse event that is considered serious will be reported to the Institutional Review Board (IRB) and to the Sponsor representative promptly by telephone and in writing within three working days. Any unexpected fatal or life-threatening serious event will be reported to the IRB and to the Sponsor representative promptly by telephone and in writing within one working day. This report will contain a detailed description of the observed symptoms and the contra-active therapy. The qualified investigator will judge the possible causal relationship between the event and the study drug.

25. ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study Subjects are the most important considerations and should prevail over interests of society and science.

i. Informed Consent

The Principal Investigator must ensure that Subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent/assent form must be submitted to the IRB, together with the protocol, for approval. Prior to beginning of the study, the Principal Investigator must have the IRB's written approval of the written informed consent/assent form and any other information to be provided to Subjects.

Subjects 18 years of age or older must provide Institutional Review Board (IRB) approved written informed consent. Subjects under the age of 18 years must have parent or legal guardian provide IRB approved written informed consent. In addition, an assent form for minors must be completed for subjects under the legal age of consent, if applicable, depending on the age range required by state laws.

Each Subject's signed informed consent/assent must be kept on file by the Principal Investigator. A copy of the signed consent/assent form will be given to the Subject or legal guardian. A notation will be made in the Subject's medical record indicating the date the informed consent/assent was obtained. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject to review and sign. Both the consent/assent form and the HIPAA authorization form (if applicable) must be signed by the Subject or legal guardian before any protocol assessments can be undertaken.

ii. Institutional Review Board

Before study initiation, the Principal Investigator must have written and dated approval

from the IRB for the protocol, consent form, Subject recruitment materials and any other written information to be provided to Subjects.

Any changes to the protocol as well as a change of the Principal Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

The Principal Investigator will ensure that an IRB that complies with the regulatory requirements will be responsible for the initial and continuing review and approval of the proposed clinical study.

iii. Subject Confidentiality

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority(ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identity of the Subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the Subject's identity will remain confidential.

26. DOCUMENTATION:

a. Site Regulatory Documents Required for Initiation

The following documents will be received by the CRO prior to the initiation of the study:

i. Current curricula vitae, signed and dated for the Principal Investigator and each Sub-Investigator (current within 2 years)
ii. Current medical licenses of the Principal Investigator and Sub-Investigators
iii. Documentation of IRB approval of this study protocol, Principal Investigator and informed consent form
iv. Current IRB membership list or roster
v. A copy of the protocol agreement page signed by the Principal Investigator
vi. Non-disclosure Agreements for the Principal Investigator and Sub-Investigators
vii. Completed and signed FDA Form 1572
viii. Statement of Non-Debarment
ix. Fully executed Clinical Trial Agreement (CTA)

b. Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent/assent, source documents, as well as eCRFs (paper or electronic files). No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories designed to document all observations and other data pertinent to the investigation on each individual treated with the Investigational Product or entered as a control in the investigation. Data reported on the CRF, which are derived from source documents, must be consistent with the source documents.

c. Data Collection and Reporting

Data for individual Subjects will be collected on eCRF designed by the Contract Research Organization. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for completing the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart are to be maintained separately from the eCRF in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

1. Subject Screening Log – reflecting the reason any Subject screened for the study was found to be ineligible
2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee will be documented
4. Enrollment Log – documenting Subject initials and start and end dates for all Subjects enrolled
5. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site

and received and signed for by the Principal Investigator

6. Drug Accountability Log – reflecting the total amount of Investigational Product dispensed to and returned by each Subject
7. Informed Consent Form – which must be available for each Subject and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the CRO's data management personnel will be answered by site personnel and verified by the monitor.

d. Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the Subject is being studied
- General information supporting the Subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
- Any additional visits during the study
- Any relevant telephone conversations with the Subject regarding the study or possible adverse events
- An original, signed informed consent form for study participation

The Principal Investigator must also retain all Subject specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to validate data in the CRFs against these sources of data.

e. Quality Assurance

Designated personnel from Nivagen Pharmaceuticals Inc. will be responsible to ensure that the trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP, GLP, and the applicable regulatory requirements.

f. Study Monitoring

The study will be monitored by a representative of the Contract Research Organization to assess compliance with the protocol, ICH-GCP and applicable regulations. The Principal Investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol.

The study monitor will review the informed consent forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

g. Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

h. Modifications to the Protocol

The procedures defined in the protocol and in the eCRF will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no violations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB prior to implementation. All amendments to the protocol, which involve substantial changes in study design, procedure or analyses, may be submitted to FDA IND for prior approval (if required).

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

All protocol violations will be reported on the protocol violation log and included in the study reports. A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

i. Completion of Study

The Principal Investigator is required to sign the eCRFs and forward all other relevant data and records to the Contract Research Organization.

The Principal Investigator is expected to submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation. CRO must submit a final report as agreed in the Study Agreement for this study between Sponsor and CRO.

j. Premature Termination or Suspension of a Study

Nivagen Pharmaceuticals Inc. may terminate the study at any time for scientific or corporate reasons. If the trial is prematurely terminated or suspended for any reason, the Qualified Investigator should promptly inform the trial volunteers, should assure appropriate therapy and follow-up for the volunteers and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

k. Adherence to Protocol

Excluding an emergency in which proper treatment is required for the protection, safety and well-being of the study volunteers, the study will be conducted as described in the approved protocol and performed according to ICH/GCP guidelines. Any deviation from the protocol will be recorded and explained. If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

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overview of the importance and value of the interviews so they can relay this information to the subject when the time for scheduling arrives. The interview coordinator will provide the subject with a description of the purpose of the interview and an opportunity to ask any questions before the interview begins. A subject may refuse to move forward with the interview at the time of their visit, and they may refuse during the scheduling process or at any time during the interview. If a subject participates in the cognitive or exit interview, all personal contact information will be destroyed immediately following the interview. Reports generated from the interview data will be in aggregate form only and no subject will be able to be individually identified from any report materials.

28. STUDY VISITS:

1. Visit 1: Initiation of Screening (Day -14±2)

The following procedures will be performed at Visit 1:

1. Written informed consent will be obtained. Subjects must have provided IRB approved written informed consent. Prior to initiating screening for the study, Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. In addition, the Principal Investigator or the Principal Investigator's Designee will provide a HIPAA authorization form (if applicable) for the Subject to review and sign. Both the ICF and the HIPAA authorization form (if applicable) must be signed by the Subject before any protocol assessments can be undertaken.
2. A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure,

kidney disease, and auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

* Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart)

3. Demographics and vital signs (blood pressure, temperature, heart and breathing rates) will be documented. Subjects must remain in a seated position for 5 minutes before vital signs are obtained.
4. A brief physical examination, including height (measured in inches) and weight (measured in pounds), will be performed. At a minimum, the physical examination will include the following: assessment of general appearance, skin, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, extremities as well as a visual rectal exam (to exclude external hemorrhoids).
5. A complete list of current and past (within the previous 30 days) concomitant medications will be obtained and reviewed for each Subject. (See Section 22. Subject Safety)
6. A urine pregnancy test will be conducted for all female Subjects of childbearing potential.
7. Blood and urine samples will be collected for clinical laboratory tests including complete blood count (CBC), comprehensive metabolic panel (CMP), urinalysis, HIV, Hepatitis B, and Hepatitis C, and drug screening (drugs of abuse, prescription).
8. A breath alcohol test will be conducted.
9. When the Subject has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. (See Sections 12 & 13 Inclusion & Exclusion Criteria)
10. The following will be dispensed during Visit 1:
    - A diary card to record Adverse Events and Concomitant Medications along with instructions on how to complete.
    - Backup diary cards to record missed ePRO questionnaires (as needed)
11. Appropriate study personnel will provide training to the Subjects on Internal Hemorrhoids Sign and Symptom Assessment (IHSSA) and ePRO, which will be recorded by the Subjects daily during the study. (See Appendix 1)
12. Cognitive interviews will be conducted with selected Subjects via a third party to discuss IHSSA and internal hemorrhoid signs and symptoms of the Subjects. (See Section 27. Subject Interviews)
13. Visit 2 (Day 1, 14±2 days from Visit 1) will be scheduled and the Subject will be instructed to bring the Subject diary and backup ePRO diary (if applicable) with him or her to this visit.

2. Visit 2: Start of Treatment (Day 1)

The following procedures will be performed at Visit 2:

1. The overall status of the Subject's internal hemorrhoids will be assessed using the PGIS (ePRO). (See Appendix 3)
2. The Subject's symptomatic internal hemorrhoid will be assessed by an anoscopic examination (Grade I, II or III (Banov et al. 1985)). (See Section 16 Diagnostic Tests) To be included in the study, subjects must have a diagnosis of symptomatic Grade I, II or III internal hemorrhoids. Video of the procedure will be recorded for blinded central reading and assessment of swelling as the Clinician Reported Outcome (ClinRO).

3. Appropriate study personnel will review the use of IHSSA with the Subject. (See Appendix 1)
4. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. (See Section 22. Subject Safety)
5. The occurrence of all AEs will be assessed and documented following procedures in Section 24 Adverse Events.
6. A urine pregnancy test will be conducted for all female Subjects of childbearing potential.
7. When the Subject has completed all screening procedures, compliance with the inclusion and exclusion criteria will be reviewed. (See Sections 12 & 13 Inclusion & Exclusion Criteria) After the inclusion and exclusion criteria have been confirmed, the Subject will be randomized to a treatment group. The Subject will be assigned a randomization number (See Section 11. Randomization).
8. The following will be dispensed during Visit 2:
    - The Investigational Product (28 suppositories)
    - A diary card to record IP Use, Adverse Events and Concomitant Medications along with instructions on how to complete.
    - Backup diary cards to record missed ePRO questionnaires (as needed)
9. Randomized Subjects will be instructed on the correct method for the application of the Investigational Product. The first application of the Investigational Product will be performed by the Subject at home. The study restrictions will also be reviewed with the Subject and an instruction sheet will be issued to the Subject. (See Section 14. Treatments)
10. Randomized Subjects will be instructed how and when to complete the diary for Study Medication use. They will be told that they are to document all treatments administered, including the date and all treatments missed. In addition, Subjects will be reminded to document all AEs. Subjects will also be instructed to call the study site if they experience any severe intolerability to Investigational Product.
11. PROMIS Global Health questionnaire will be performed.
12. Study instructions will be reviewed with the Subject, including the procedure for application of the Investigational Product. (See Section 14. Treatments)
13. Visit 3 (Day 8 ± 1 days from the date of Visit 2) will be scheduled and the Subject will be instructed to bring the Subject's diary and backup ePRO diary (if applicable) with him or her to this visit.

3. Visit 3: Interim Visit (Day 8±1)

The following procedures will be performed at Visit 3:

1. Appropriate study personnel will review the use of IHSSA with the Subject. (See Appendix 1)
2. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. (See Section 22. Subject Safety)
3. A urine pregnancy test will be conducted for all female Subjects of childbearing potential.
4. Blood sample will be collected from the Subject for clinical laboratory tests: comprehensive metabolic panel (CMP).
5. The occurrence of all AEs will be assessed and documented following procedures in Section 24 Adverse Events.

6. Study instructions will be reviewed with the Subject, including the procedure for application of the Investigational Product. (See Section 14. Treatments)
7. Visit 4 (Day 15 ± 2 days from the date of Visit 2) will be scheduled and the Subject will be instructed to bring all unused Investigational Product (if applicable) and the Subject diary and backup ePRO diary (if applicable) with him or her to this visit.

4. Visit 4: End of Treatment Visit (Day 15±2)

The following procedures will be performed at Visit 4:

1. The Subject's symptomatic internal hemorrhoid will be assessed by an anoscopic examination. Video of the procedure will be recorded for blinded central reading and assessment of swelling as the Clinician Reported Outcome (ClinRO).
2. Appropriate study personnel will review the use of IHSSA with the Subject. (See Appendix 1)
3. The overall status of the Subject's internal hemorrhoids will be assessed using the PGIS and PGIC (ePRO). (See Appendix 3)
4. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. (See Section 22. Subject Safety)
5. A urine pregnancy test will be conducted for all female Subjects of childbearing potential.
6. Blood sample will be collected from the Subject for clinical laboratory tests: complete blood count (CBC), and comprehensive metabolic panel (CMP).
7. The occurrence of all AEs will be assessed and documented following procedures in Section 24 Adverse Events.
8. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject's diary and backup ePRO diary (if applicable) will be collected and reviewed for completion.
9. The following will be dispensed during Visit 4:
    - A diary card to record AE/CM from Visit 4 to Visit 5
    - Backup diary cards to record missed ePRO questionnaire (if applicable)
10. Visit 5 (Day 29 ± 3 days from the date of Visit 2) will be scheduled and the Subject will be instructed to bring the Subject diary and backup ePRO diary (if applicable) with him or her to this visit.
11. PROMIS Global Health questionnaire will be performed.
12. The Subject's unused Investigational Product will be returned to the site. (See Section 14. Treatments)
13. Exit interviews will be conducted with the first 25 enrolled Subjects who reach Visit 4 and agree to participate in the interview. (See Section 27. Subject Interviews)

5. Visit 5: Follow-Up/End of Study Visit (Day 29±3)

The following procedures will be performed at Visit 5:

1. Appropriate study personnel will review the use of IHSSA with the Subject. (See Appendix 1)
2. The use of concomitant medications since the previous study visit will be documented and assessed for each Subject. (See Section 22. Subject Safety)
3. A urine pregnancy test will be conducted for all female Subjects of childbearing potential.
4. The occurrence of all AEs will be assessed and documented following procedures in Section 24 Adverse Events.

5. The Subject's compliance with the study protocol, including use and application of Investigational Product, will be assessed. The Subject diary and backup ePRO diary (if applicable) will be collected and reviewed for completion.

6. Unscheduled Visits (UV) and Early Discontinuation (ED) Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion, it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for Visit 5 will be performed. If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the Subject will continue to take part in the study), then all procedures scheduled for that interim visit will be performed, with the exception of the collection of Investigational Product and Subject diaries from Subjects. If the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

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II. APPENDIX 2: PROMIS Global Health Questionnaire Version 1.2

PROMIS Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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PROMIS Scale v1.2 – Global Health

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
GlobalR10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
GlobalR09r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

GlobalR07r	How would you rate your pain on average?	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

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III. APPENDIX 3: Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) Items

Item Text	**Response Scale**
Patient Global Impression of Change Items **(To be administered at the End of Treatment visit)**	
Instructions: The following questions ask you about the overall **change in your hemorrhoid-related symptoms since you started taking the study medication**. Please choose the response that best describes your experience. There are no right or wrong answers. Please answer all of the questions.	
	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
Corporate Information	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
	Very Much Better Much Better A Little Better The same (no change) A Little Worse

	Much Worse Very Much Worse
S h	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
S **c** o	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
S **h**	Very Much Better Much Better A Little Better The same (no change) A Little Worse Much Worse Very Much Worse
Patient Global Impression of Severity Items **(To be administered at the Randomization and End of Treatment Visits)**	
Instructions: The following questions ask you about **your hemorrhoid-related symptoms over the past week**. Please choose the response that best describes your experience. There are no right or wrong answers. Please answer all of the questions.	
	No bleeding Mild bleeding Moderate bleeding Severe bleeding Very severe bleeding
	No itching Mild itching Moderate itching Severe itching Very severe itching
	No pain Mild pain Moderate pain Severe pain Very severe pain
	No swelling Mild swelling Moderate swelling Severe swelling Very severe swelling
Please choose the response that best describes your hemorrhoid-related **pressure (pressure or feeling of**	No pressure Mild pressure

Corporate Information

Corporate Information	Moderate pressure Severe pressure Very severe pressure
	No burning Mild burning Moderate burning Severe burning Very severe burning
	No discomfort Mild discomfort Moderate discomfort Severe discomfort Very severe discomfort
	I am not able to complete any daily activities I am able to complete some daily activities I am able to complete many daily activities I am able to complete most daily activities I am able to complete all daily activities

IV. APPENDIX 4: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (NCI, 2009)

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline. A Semi-colon indicates 'or' within the description of the grade. A single dash (-) indicates a grade is not available.

Grade	Clinical description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection. Grade 5 Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL):
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

V. APPENDIX 5: Cognitive Interview Guide

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COGNITIVE INTERVIEW

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[Interviewer: Have the patient look at Instructions for Patient Training]

INSTRUCTIONS:
Let's start with the instructions across the top of the page.

Actual Instruction Text:

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Going back now to the answer you selected (__) What amount of improvement in bleeding would be meaningful to you?

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DISCUSSION ITEM # 4: Episodic Assessment of Internal Hemorrhoid Symptoms

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meaningful to you?

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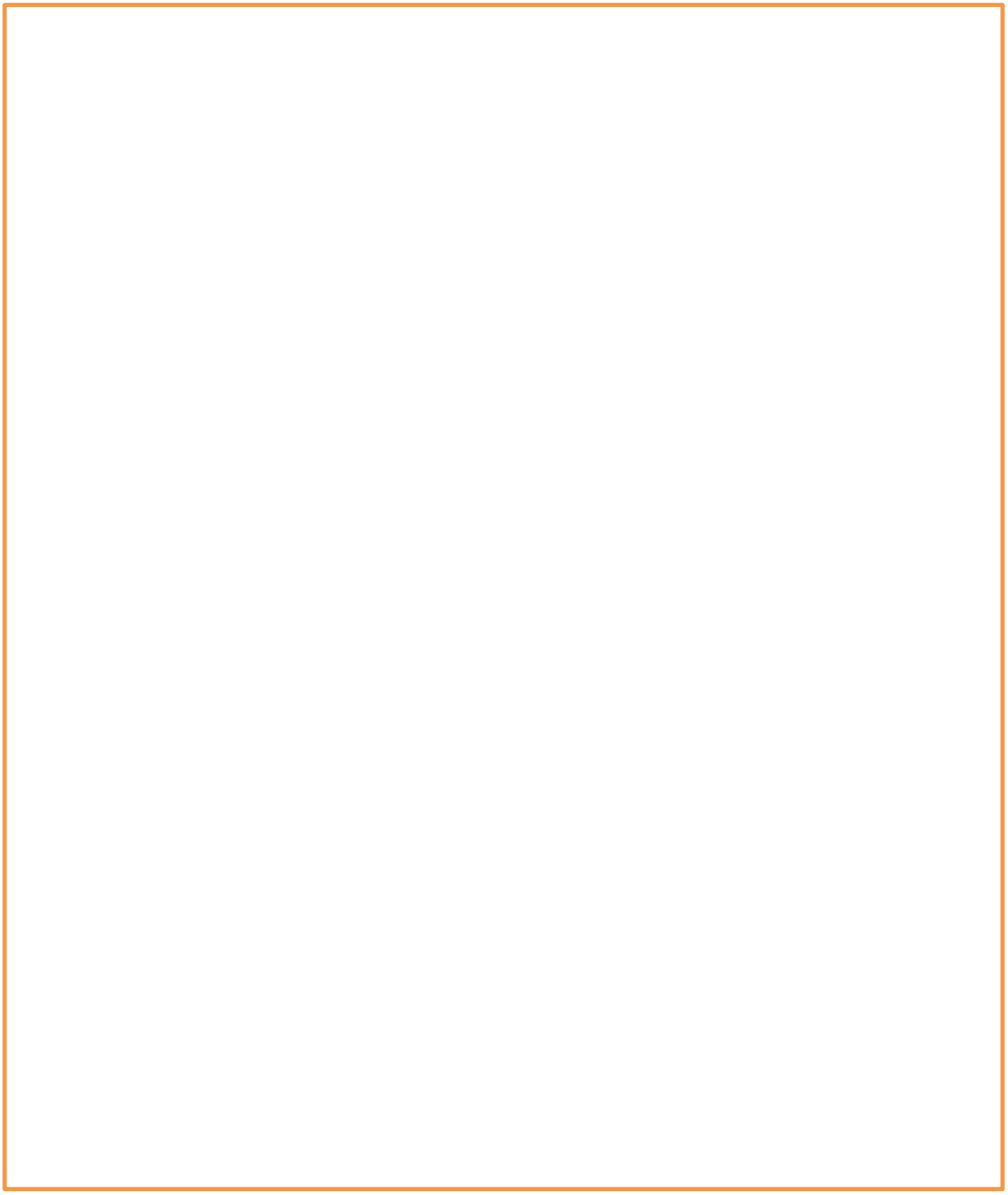
V. APPENDIX 6: Exit Interview Guide



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DISCUSSION ITEM #9: Study Treatment – Importance

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Thank you for participating in this interview today!

VI. APPENDIX 7: Revision History

Version #	Affected Sections
Final 1.0 (12Sep2017)	N/A (new)
Final 2.0 (04Nov2018)	• Protocol version number and date updated • Title Page and Contacts List updated • Principal Investigator Agreement signature page added • Vital Signs in Physical Exam added • IHSSA added • Multiple and various wording changes/additions/edits made to comply with CRO SOPs • Updated and added Appendices
Final 3.0 (15Mar2019)	• Protocol version number and date updated • Inclusion criteria a & b revised
Final 4.0 (26Apr2019)	• Protocol version number and date updated • Inclusion criteria a & b revised • Visual rectal exam added to Visit 1 Physical Exam