TITLE PAGE

Atopic Dermatitis Treatment

Protocol Number: SAN007-02

A Double-Blind, Randomized, Placebo-Controlled, Safety, Tolerability, and Efficacy Trial of a Novel Botanical Drug Product, Containing East Indian Sandalwood Oil (EISO) For the Treatment of Atopic Dermatitis

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Signature Page

Product: SAN007 - Atopic Dermatitis Treatment Regimen

Protocol number: SAN007-02

The signatures of the representatives below constitute their approval of this protocol, and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

Approved by the following:

Sponsor representative (Santalis):

Somer Baburek Study Manager	Somer Baburek Signature	3-Nov-2017 Date

Signature Page for Principal Investigator

Product: SAN007 - Atopic Dermatitis Treatment

Protocol number: SAN007-02

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with 21 CFR Part 50, ICH GCP guidelines, and the Declaration of Helsinki.

Principal Investigator Name	Signature	Date

Title	A Double-blind, Randomized, Placebo-controlled, Safety, Tolerability and Efficacy Trial of a Novel Botanical Drug Product containing East Indian Sandalwood Oil (EISO) for the Treatment of Atopic Dermatitis
Setting and Trial Center(s)	This trial will be conducted at approximately five study centers in the United States.
Number of Subjects	Up to 100 subjects will be enrolled to ensure at least 90 subjects complete the treatment period of the study on the study drug reformulation included in this amendment.
Objectives	The objectives of this trial are: • To evaluate the safety of SAN007 when administered to subjects with atopic dermatitis • To evaluate the tolerability of SAN007 when administered to subjects with atopic dermatitis. • To evaluate the preliminary efficacy of SAN007 when administered to subjects with atopic dermatitis
Trial Design and Subject Population	This trial will be a double-blind, randomized, placebo-controlled, safety, tolerability, and efficacy trial of SAN007 treatment regimen when administered daily for up to 28 days to subjects at least 18 years of age, with atopic dermatitis. Subjects will enter the Screening Period once the informed consent and photographic consent process has been completed. Subjects with a total body surface area (BSA) of ≥2% and ≤ 15% atopic dermatitis involvement in the treatable areas, and who meet all of the inclusion, and none of the exclusion criteria, will be enrolled. Once subject eligibility is confirmed, and the screening procedures completed, the subject will start the Treatment Period of the study. All enrolled subjects will receive either 5% SAN007 cream or placebo cream (randomized in a 2:1 ratio) OR 10% SAN007 cream or placebo cream (randomized in a 2:1 ratio) with the first dose applied at Visit 1 Baseline. Subjects will be instructed on how to apply the study medication twice daily, ≥ 8 hours between applications, for 28 days. Subjects will return to the clinic on Study Days 7,14, and 28 for study-related assessments. Subjects will receive a telephone call from the site on Study Days 21 and 35.

Inclusion Criteria	Subjects will be included in the trial if they meet all of the following criteria: 1. Are at least 18 years of age. 2. Have atopic dermatitis, as determined by an EASI score of ≥2 and ≤50 (Hanifin, 2001). 3. Total treatment area(s) of atopic dermatitis involvement ≥2% and ≤15% body surface area (BSA). 4. Have atopic dermatitis that has been clinically stable for ≥ 1 month prior to the Screening Visit. 5. Are able to obtain written informed consent in a manner approved by the Institutional Review Board and comply with the requirements of the study. 6. Are willing to refrain from using any lotions, moisturizer, cleansers, cosmetics or creams, other than those issued as part of the study, on the target treatment areas during the treatment period. 7. Are free of any systemic or dermatologic disorder, which, in the opinion of the investigator, would interfere with the study results or increase the risk of adverse events. 8. Are willing to refrain from exposure to artificial ultraviolet radiation for the duration of the study. 9. Are willing to cover target treatment areas to avoid exposure to natural ultraviolet radiation for the duration of the study. 10. If female is of childbearing potential, they must be willing to practice an acceptable form of birth control for the duration of the study. (i.e. oral contraceptive, barrier method or intrauterine device.) 11. Are willing to avoid participation in any other clinical trial for the duration of this study. 12. Are willing to refrain from treating areas that are not the defined treatment area(s), which will be excluded from the IGA assessments and BSA calculation. These areas are as follows: head, neck, soles of feet, palms of hands, axillae, or intertriginous areas.
Exclusion Criteria	Subjects will be excluded from the trial if they meet any of the following criteria:

	1. Have a sibling or immediate family member already participating in this trial. 2. Currently requires and/or, in the past month, has required topical use of a medium or high potency steroid. 3. Atopic dermatitis that, in the opinion of the investigator, is likely to stem from an allergic reaction. (i.e. contact dermatitis). 4. Have <2% or >15% total BSA of atopic dermatitis involvement 5. Have participated in any interventional clinical trial in the previous 30 days to the screening visit. 6. Have a known sensitivity to any of the constituents of the test product including sensitivities to sandalwood oil, fragrances or any member of the Compositae family of vascular plants (e.g., sunflowers, daisies, dahlias, etc.). 7. Have received phototherapy within the last two months prior to enrollment. 8. Have received any systemic medication for atopic dermatitis in the past two months that would interfere with the evaluation of atopic dermatitis (excluding antihistamines or leukotriene inhibitors). 9. Have a present condition or abnormality, that in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data. 10. Are pregnant, breast-feeding, or plan to become pregnant at any point, for the duration of the trial. 11. Are not willing to practice an approved form of birth control while on the study drug for the duration of the trial. (i.e. oral contraceptive, barrier method or intrauterine device). 12. Have been treated, with prescription medication for atopic dermatitis, within 60 days prior to the Screening Visit. 13. Have any evidence of systemic cancer, squamous cell carcinoma, or basal cell carcinoma, in the last five years, or any other confounding skin condition. 14. Have undergone treatments with topical atopic dermatitis drug products, other than retinoids or corticosteroids, within 14 days prior to the Baseline Visit, and for therapy containing corticosteroids or retinoids within 28 days prior to Baseline Visit. 15. Have open sores, or open lesions, in the treatment area(s).

	16. Have a history of alcohol or illegal drug/substance abuse, or suspected alcohol or illegal drug/substance abuse in the past two years. 17. Require greater than 2.0 mg/day inhaled or intranasal corticosteroids. 18. Have an active infection of any kind at Visit 1, Baseline. 19. Have an occupation that requires ≥50% of time be spent outdoors, where prolonged exposure to ultraviolet radiation is unavoidable.
Screening-Baseline	**<u>Screening Visit (Day - 7)</u>** Eligible subjects will be asked to read and sign an informed consent and photograph consent form. No study procedures will be conducted until the informed consent and photograph consent form is signed. At the Screening Visit, the following procedures will be performed: • Conduct the informed/photography consent process. • Record Demographics to include age, sex, and race. • Review the inclusion/exclusion criteria. • Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements taken 60-days prior to Screening. • Perform a full physical examination including height (cm) and weight (kg). • Record pertinent medical history, to include tobacco, illegal substance(s), and alcohol history, along with current use. • Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA) and BSA. • Administer the Eczema Area Severity Index (EASI). If more than seven days is required in order for the subject to qualify for the study, then the subject must be screen failed, re-screened and all Screening Procedures repeated.

Treatment Period	**Visit 1 Baseline (Day 1)** The following procedures will be completed at Visit 1 Baseline. It is possible for the subject to be Screened and complete the Visit 1 Baseline procedures on the same day. o Review inclusion and exclusion criteria to ensure the subject qualifies for the study. o If this visit is NOT combined with the screening visit: o Perform an abbreviated physical examination including height (cm) and weight (kg), o Update concomitant medications including all prescription drugs, non-prescription drugs and nutritional supplements o Review and update the subject's pertinent medical history. o Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA) and BSA. o Administer the Eczema Area Severity Index (EASI). o Using calculated BSA, calculate Subject Dose using 0.5gm per 1% BSA (i.e. 2% BSA= 2 x 0.5gm= 1gm per application) o If subject is a female of childbearing potential, collect a urine sample and perform a β-human chorionic gonadotropin pregnancy test. o Weigh full tube of SAN007 study medication, with cap on, and record weight. o Photograph the treatment area prior to first dose. o Instruct the subject on proper washing of the target treatment area(s), (using only study-approved cleanser) and self-application of SAN007 study medication, subject to apply first dose in the office. o Assess Tolerability immediately following study drug application. o Weigh tube of SAN007, with cap on, immediately following

	first application and record weight. The difference between this weight, and the pre-application weight, is to be used as the expected estimated usage per application. (i.e. pre-application weight - post-application weight = expected usage per application (EUA) o Instruct the subject when bathing, to refrain from using any body wash, lotion, or moisturizer other than that which has been provided on the target treatment areas, during the treatment period. o Instruct the subject to return with the study drug in one week for the next study visit.
	Visit 2 (Day 7 ± 2), Visit 3 (Day 14 ± 2) The following procedures will be performed during Treatment Visit 2 and Visit 3: • Query for adverse events. • Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA), Tolerability and BSA. • Administer the Eczema Area Severity Index (EASI). • Update concomitant medications, including all prescription drugs, nonprescription drugs, and nutritional supplements. • Query for treatment regimen compliance. • Weigh and record the weight of the study medication, re-dispense existing, or dispense a new tube of study medication • Calculate compliance. (i.e. Visit Day x 2 (applications per day) x EUA= expected usage). If Subject's actual compliance is ≤80% of expected compliance, re-educate and document in source. • Photograph the treatment area(s). • Review the directions for use of the study medication with the subject, and re-educate, if applicable. • (Visit 2 [Day 7 ± 2] only). Instruct the subject to return in one week for the next study visit with study drug. • (Visit 3 [Day 14 ± 2] only). Remind the subject that there will be a follow up telephone call for Visit 4 (Day 21 ± 2)

	Visit 4 (Day 21 ± 2) Telephone Contact • Query for adverse events. • Update concomitant medications, to include all prescription drugs, nonprescription drugs, and nutritional supplements. • Query for treatment regimen compliance. • Instruct subject to return to the clinic for Visit 5 Final Visit on Day 28, with the study drug.
Final Visit	**(Day 28 ± 2) Visit 5 Final Visit** • Query for adverse events. • Update concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements. • Query for treatment regimen compliance. • Collect and weigh the study medication, and record the weight. • Calculate compliance. (i.e. Visit Day x 2 (applications per day) x EUA= expected usage) If Subject's actual compliance is ≤80% of expected compliance, re-educate and document in source. • If subject is a female of childbearing potential, collect a urine sample and perform a □-human chorionic gonadotropin pregnancy test. • Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA), Tolerability and BSA. • Administer the Eczema Area Severity Index (EASI). • Photograph the treatment area(s). • Instruct Subject to return to the clinic for another Study Visit **only** if study-related adverse events persist, or, in the Investigator's opinion, an additional Study Visit is warranted to ensure the subject's safety.
Follow-up Phone Contact	**Day 35 (± 2 days) Telephone Contact** • Query for status of AD since discontinuation of study

	medication o E.g. Has your condition been stable, improved, or worsened, since the discontinuation of study treatment?
Duration of Treatment and Trial Participation	The maximum duration of trial participation for each subject is up to 35 days: • 7-day Screening Period (Day - 7) • 28 ± 2 days Treatment (Visits 2 through 5) • Follow-up Call (Day 35) Phone contact on Visit 4 (Day 21) and follow-up call (Day 35,) will be made with the subject. If the subject's treatment is interrupted by illness or other circumstances, every attempt will be made to have the subject return to the clinic for a final visit. If the subject has remained compliant with the study medication, as determined by subject, and confirmed by product weight, if necessary, the subject will be allowed to continue the trial.
Trial Drug, Dose and Mode of Administration	SAN007 treatment products will be provided by Santalis Pharmaceuticals, and the treatment regimen administered to the subject and explained to the LAR, if applicable. The following treatment products will be provided to the subjects: • Cetaphil Daily Facial Cleanser- to be used on the face when washing. • Cetaphil Gentle Skin Cleanser- to be used on the body when showering. AND STUDY DRUG LABELED WITH ONE OF THE FOLLOWING: • 5% SAN007 Cream - to be used morning and night, ≥ 8 hours between applications OR • Placebo - to be used morning and night, ≥ 8 hours between applications OR • 10% SAN007 Cream - to be used morning and night, ≥ 8 hours between applications OR • Placebo - to be used morning and night, ≥ 8 hours between applications

	The first treatment of SAN007 will be applied at the Visit 1 Baseline, then, the subject will be instructed on the procedure for self-administration at home.
Trial Population	Up to 100 subjects, from the time of this amendment, at least 18 years of age, with a clinical diagnosis of atopic dermatitis meeting the criteria of an EASI score between 2-50 (Hanifin, 2001) with a BSA involvement of atopic dermatitis between 2%-15%, in the permitted treatment areas.
Criteria for Evaluation	Subjects that receive one application of study medication will be included in the safety and tolerability analysis. Subjects that complete at least 90% of treatments, as determined by product usage, will be included in the efficacy analysis. Missing efficacy data will be imputed using the last observation carried forward. No imputations will be made for missing safety data.
Safety Evaluations	**Safety** The primary purpose of this study is to determine the safety profile of SAN007. Safety will be assessed by evaluating adverse events (AEs) with respect to severity, duration, and relationship to study drug.
Tolerability Evaluation	**Tolerability** The number and percentage of subjects reporting discomfort, either during or immediately following the application of SAN007. This will also be recorded as an AE. The study restricted treatment areas are not to be included in this evaluation. (see #12 under Inclusion Criteria)
Preliminary Efficacy Evaluation	**Preliminary Efficacy Endpoints** Preliminary efficacy will be evaluated by the following: ▪ Percentage of subjects who have a ≥ 25% reduction in the Eczema Area and Severity Index (EASI) score at any point during the trial. ▪ Number of subjects achieving an Investigator Global Assessment (IGA) of "clear" or "almost clear" at any time point during the 28 days of therapy. The study restricted treatment areas are not to be included in this evaluation. (see #12 under Inclusion Criteria) ▪ Percentage of subjects who have a ≥50% reduction in the Eczema Area Severity Index (EASI) score at any point during the trial. ▪ Percentage of subjects achieving at least a 1-grade

	improvement in IGA score ▪ Percentage of subjects who have at least a 20% reduction in BSA affected by atopic dermatitis. Additional secondary and exploratory endpoints may be outlined in the statistical analysis plan.
Data Analysis	**Safety** The number and percentage of subjects reporting at least one occurrence of an AE for each unique System Organ Class and Preferred Term will also be tabulated by severity, and by the relationship to trial drug. All AEs will be presented in a data listing. **Tolerability** Tolerability will be based on the number of subjects reporting discomfort during, or immediately following, application of SAN007, this will also be recorded as an AE. The study exclusion areas are not to be used in this evaluation. **Preliminary Efficacy Endpoints** ▪ Percentage of subjects who have a ≥ 25% reduction in the Eczema Area and Severity Index (EASI) score at any point during the trial. • Number of subjects achieving an Investigator Global Assessment (IGA) of "clear" or "almost clear" at any time point during the 28 days of therapy. The study restricted treatment areas are not to be included in this evaluation. (see #12 under Inclusion Criteria) • Percentage of subjects who have a ≥50% reduction in the Eczema Area Severity Index (EASI) score at any point during the trial. • Percentage of subjects achieving at least a 1-grade improvement in IGA score ▪ Percentage of subjects who have at least a 20% reduction in BSA affected by atopic dermatitis.
Planned Dates of Study	August 2017- January 2018
Manufacturer of Investigational Products	Pam Lewis & Associates Boerne, TX USA
Regulatory	This study will be conducted under a US IND, and in accordance with 21 CFR Part 50, ICH GCP guidelines, and the Declaration of Helsinki.

Trial Contacts		
Name	**Affiliation / Address**	**Responsibility**
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Table of Contents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AD	Atopic Dermatitis
ADR	Adverse Drug Reaction
AE	Adverse Event
ARTG	Australian Registry of Therapeutic Goods
BID	Bis in diem/twice a day
BSA	Body Surface Area
CFR	Code of Federal Regulations
	Electronic Case Report Form
CRO	Contract Research Organization
EASI	Eczema Area Severity Index
E.g.	For example
EISO	East Indian Sandalwood Oil
ERB	Ethical Review Board
FAS	Full analysis set
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers' Association
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
GRAS	Generally recognized as safe
HIPPA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IGA	Investigators Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent To Treat
JECFA	Joint Food and Agricultural Organization of the United Nations/ World Health Organization Expert Committee on Food Additives
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-The-Counter
PP	Per Protocol
QA	Quality Assurance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SPF	Sun Protection Factor
UPT	Urine Pregnancy Test
W/w	Weight/weight
WHO	World Health Organization

1. INTRODUCTION

1.1 ATOPIC DERMATITIS

Atopic dermatitis (eczema) is the most common skin condition in children, and is estimated to affect more than 20% of children.[1] Atopic Dermatitis is often associated with high levels of IgG and co-exists with other conditions, such as asthma and rhinitis.[2] Of great concern to clinicians is the rapid increase in the incidence of Atopic Dermatitis and the early onset of the disease with over 90% of children presenting with the condition before the age of 4.[3] For unknown reasons, Atopic Dermatitis seems to improve with age but half of all children with Atopic Dermatitis will have symptoms as adults.[6]

Atopic Dermatitis will present differently in infants, children, and adults. Infants with Atopic Dermatitis will typically present suddenly as a rash that makes the skin dry, scaly, and itchy. The rash forms on the scalp and face, is most notable on the cheeks, and can bubble up and ooze fluid.[4] While Pruritus is a hallmark of the condition, erythema, edema, xerosis, erosions/excoriations oozing, crusting and lichenification can all contribute to the disease burden.

The rash usually appears in the creases of the elbows or knees. Additionally, other common areas can include the neck, wrist, ankles, and creases between the buttocks and legs. The rash is itchy and scaly patches also appear. Over time, the areas affected by Atopic Dermatitis can become bumpy, change color, and thicken as a result of constant scratching.[4]

The cause of Atopic Dermatitis is unknown, but it is not contagious and a strong genetic relationship has been found with children whose parents have Atopic Dermatitis, asthma or hay fever.[5]

There is no known cure for Atopic Dermatitis, and treatment is limited to controlling the condition by relieving the pain and itching. Treatment may include corticosteroids, anti-histamines, antibiotics, other immunomodulators and phototherapy.

Both the wood (in powder form), and the oil of the East Indian Sandalwood tree, have been used to treat a variety of conditions. In traditional Indian (Ayurvedic) medicine, East Indian Sandalwood Oil (EISO) was used as a treatment for inflammatory and eruptive skin diseases.[7, 8] Traditional Chinese medicine also lists sandalwood as a treatment for gonorrhea,[9] as well as for epigastric pain and chest pain.[10] In Europe, sandalwood has been used to treat fever and pain.

According to the British Pharmaceutical Codex, EISO was formerly used to treat the subacute stages of cystitis and gonorrhea based on its antiseptic and diuretic actions. Treatment was administered orally in capsules or as an emulsion at doses of between 0.3 and 1 mL (0.3 gm and 1 gm).[11] The Martindale Complete Drug Reference includes EISO as a treatment for infections of the lower urinary tract due to its antibacterial and antispasmodic activities.[12] Multi-agent and/or homeopathic preparations are marketed in Austria (as Brady's Magentropfen), Switzerland (as Kernosan Eau Dentifrice), and France (as Santalum Complexe No. 30). The neat oil is recommended to be taken orally, between 0.5 gm to 1.5 gm daily, for up to six weeks (total dose: 21 gm to 63 gm). In Germany, EISO is included as a Commission E herbal product for oral use (0.5 gm to 1.5 gm per day for 6 weeks) for the treatment of urinary tract infections.[13]

According to the Australian Government, Department of Health and Aging, Therapeutic Goods Administration (TGA), EISO (Santalum album) may be used without restriction as both a topical active and excipient in medicines listed on the Australian Register of Therapeutic Goods (ARTG) for supply in Australia.[14] The safety of complementary medicine substances for use in Listed Medicines is established through an evaluation process that aims to ensure that any substance approved for use in Listed Products is low risk. Listed Medicines are restricted to indication and claims relating to health maintenance, health enhancement or non-serious, self-limiting conditions.

Sandalwood oil and santalols are commonly used in the food/flavor and fragrance industries.[6] Sandalwood oil has been approved by The Flavor and Extract Manufacturers' Association (FEMA No. 3005) as "generally recognized as safe" (GRAS) for use as a flavoring ingredient in foods.[15] The US Food and Drug Administration (FDA) has approved sandalwood oil as a natural flavoring substance and as a natural substance used in conjunction with flavors.[16] In addition, the FDA has approved santalol, the major constituent of sandalwood oil, as a synthetic flavoring substance.[17] The Joint Food and Agricultural Organization of the United Nations/World Health Organization Expert Committee on Food Additives (JECFA) concluded that, based on current use levels of the compounds in foods, santalols posed no safety concerns.[18] Sandalwood oil is reported as registered by the Council of Europe and its use has been "deemed admissible with a possible limitation of the active principle in the final products."[6]

Several individual cases have been described where patch testing was used to determine sensitivity to sandalwood.[22-25] Of the 4 separate cases reported, the only positive patch tests were seen in Subjects with pigmented forms of dermatitis.

Ten studies were conducted between 1977 and 2005 and included from 50 to more than 5500 Subjects with contact dermatitis, eczema, photosensitivity disorders, or Subjects with suspected contact or fragrance allergies.[26-35] Subjects were exposed to sandalwood oil (2% to 10% when specified) and then underwent patch testing. Positive reactions to sandalwood oil occurred in less than 0.1% to up to 6.6% of Subjects. To date, Santalis, or its sister company, ViroXis Corporation, has initiated three clinical studies of EISO preparations under IND 108,458 for the treatment of the viral skin conditions Verruca vulgaris (Study No. VIR001-01) and Molluscum contagiosum (VIR003-01). East Indian Sandalwood Oil is also being investigated as the active ingredient in a mouth rinse to be tested as a preventative therapy or treatment option for Subjects with oral mucositis inducted by radiation therapy (Study No. SAN005-01).

A total of 183 Subjects completed Study No. VIR001-01. Subjects received EISO in a cream formulation at concentrations of 10%, 20%, or 30%. Preparation of the clinical study report is ongoing, but preliminary results indicate that Subjects in the 10% EISO arm experienced the highest response rates (clearance of warts and reduction in total wart area). Overall, treatment was well tolerated in all study arms. Four Subjects experienced AEs considered probably or definitely related to study drug treatment (irritation at application site). There were no severe drug-related AEs, serious adverse events (SAEs), or deaths reported on study. Only a single Subject discontinued the study as a result of a drug-related AE.

As of 02 February 2016, enrollment in Study No. VIR003-01 is ongoing, with a total of three Subjects having received EISO in an ointment formation at a concentration of 10%. The first Subject returned for the Day 14 visit and the second and third Subjects received study drug, but had not yet returned for their Day 7 visit. No adverse events, SAEs, or deaths have been reported.

1.2 PROPOSED MECHANISM OF ACTION

Nonclinical studies have shown sandalwood oil to have anti-inflammatory, anti-proliferative, anti-carcinogenic, anti-fungal, anti-viral and bactericidal activities. Ongoing programs are focused on the evaluation and/or development of assays to assess the activity of SAN007 against various inflammatory markers, as well as analyze its anti-proliferative activity to supplement the clinical programs. EISO has shown specific anti-proliferative cytotoxicity against UV and oncogenically transformed cell lines while leaving normally dividing cells unaffected at the same doses. Sandalwood oils have been shown to mimic ibuprofen non-steroidal anti-inflammatory drugs that act by inhibiting cyclooxygenases suggesting a possible

mechanism for the observed anti-inflammatory properties of topically applied sandalwood oils and providing a rationale for use in products requiring anti-inflammatory effects [Ref Sharma 2014].

2. OBJECTIVES

The objectives of this trial are:

- To evaluate the safety of SAN007 when administered to subjects with mild to moderate atopic dermatitis.
- To evaluate the tolerability of SAN007 when administered to subjects with mild to moderate atopic dermatitis.
- To evaluate the preliminary efficacy of SAN007 when administered to subjects with mild to moderate atopic dermatitis.

3. STUDY PLAN

3.1 OVERALL STUDY DESIGN

This trial will be a double-blind, randomized, placebo-controlled, safety, tolerability and efficacy trial of SAN007 treatment regimen when administered daily for up to 28 days to subjects at least 18 years of age, with atopic dermatitis.

Subjects will enter the Screening Period once the informed consent and photographic consent process has been completed. Subjects with a total body surface area (BSA) of ≥2% and ≤ 15% atopic dermatitis involvement, in the treatable areas, and who meet all of the inclusion, and none of the exclusion criteria, will be enrolled.

Once subject eligibility is confirmed and the screening procedures completed, the subject will start the Treatment Period of the study. All enrolled subjects will receive either 5% SAN007 or placebo cream (randomized in a 2:1 ratio) OR 10% SAN007 or placebo cream (randomized in a 2:1 ratio) with the first dose applied at Visit 1 Baseline. Subjects will be instructed on how to apply the study medication twice daily, ≥8 hours between application, for 28 days. Subjects will return to the clinic on Study Days 7,14, and 28 for study-related assessments. Subjects will receive a telephone contact from the site, on Study Days 21 and 35.

Safety will be assessed by evaluating adverse events (AEs) with respect to severity, duration, and relationship to study drug.

In addition, cutaneous tolerability will be evaluated at each visit. Tolerability evaluation will be based on subjects reporting discomfort during or immediately following application of SAN007. This will also be recorded as an AE. The study exclusion areas are not to be used in this evaluation.

Efficacy will be assessed at each study visit through the completion of the IGA, EASI,and BSA calculation.

During the active treatment period, Subjects will return to the study site, according to the study schedule, for interim assessments and recording of concomitant medication(s) and adverse events (AEs).

Figure 4-1 Study Design

Screening	Baseline	← Treatment →				Follow-Up
Day –7 to 0	Day 1	Day 7 (±2 days)	Day 14 (±2 days)	Day 21 (±2 days)	Day 28 (±2 days)	Day 35 (±2 days)
	Visit 1	Visit 2	Visit 3	Visit 4 (Telephone Call)	Visit 5	(Telephone Call)

3.2 STUDY ENDPOINTS

The primary purpose of this study is to determine the safety profile of SAN007. Safety will be assessed by evaluating adverse events (AEs) with respect to severity, duration, and relationship to study drug.

Tolerability will be based on the number of subjects reporting discomfort during, or immediately, following application of SAN007. This will also be recorded as an AE. The study exclusion areas are not to be used in this evaluation.

Preliminary Efficacy will be evaluated using the following:

- The preliminary efficacy endpoint will be the percentage of subjects who have a ≥ 25% reduction in the Eczema Area and Severity Index (EASI) score at any point during the trial.
- Number of subjects achieving an Investigator Global Assessment (IGA) of "clear" or "almost clear" at any time point during the 28 days of therapy.
- Percentage of subjects who have a ≥50% reduction in the Eczema Area Severity Index (EASI) score at any point during the trial.
- Percentage of subjects achieving at least a 1-grade improvement in IGA score

- Percentage of subjects who have at least a 20% reduction in BSA affected by atopic dermatitis

Additional secondary and exploratory endpoints may be outlined in the statistical analysis plan.

3.3 DISCUSSION OF DESIGN

This Phase 2 study is designed to determine the safety profile of SAN007. In addition, the study may potentially provide estimates of improvement rates resulting from the topical application of SAN007. Based on the safety profile of EISO in this population and improvement rates, it is anticipated that confirmatory Phase 3 studies with appropriate sample sizes can be developed.

4. SELECTION OF STUDY POPULATION

4.1 NUMBER OF SUBJECTS REQUIRED

Up to 100 subjects, from the time of this amendment, at least 18 years of age, with a diagnosis of mild to moderate atopic dermatitis will be enrolled in this study to ensure up to 90 subjects complete the study.

4.2 INCLUSION CRITERIA

Subjects will be included in the trial if they meet all the following criteria:

1. Are at least 18 years of age.
2. Have atopic dermatitis, as determined by an EASI score of ≥2 and ≤50 (Hanifin, 2001).
3. Total body surface area (BSA) of atopic dermatitis involvement ≥2% and ≤15%, excluding restricted treatment areas from the calculation.
4. Have atopic dermatitis that has been clinically stable for ≥ 1 month prior to the Screening Visit.
5. Are able to obtain written informed consent in a manner approved by the Institutional Review Board and comply with the requirements of the study.
6. Are willing to refrain from using any lotions, moisturizer, cleansers, cosmetics or creams, other than those issued as part of the study, on the target treatment areas during the treatment period.
7. Are free of any systemic or dermatologic disorder, which, in the opinion of the investigator, would interfere with the study results or increase the risk of adverse events.

8. Are willing to refrain from exposure to artificial ultraviolet radiation for the duration of the study.

9. Are willing to cover target treatment areas to avoid exposure to natural ultraviolet radiation for the duration of the study.

10. If female of childbearing potential, must be willing to practice an acceptable form of birth control for the duration of the study. i.e. oral contraceptive, barrier method or intrauterine device.

11. Are willing to avoid participation in any other clinical trial for the duration of this study.

12. Are willing to refrain from treating restricted areas, which will be excluded from IGA assessments and BSA calculation. These areas are as follows: head, neck, soles of feet, palms of hands, axillae, or intertriginous areas.

4.3 EXCLUSION CRITERIA

Subjects will be excluded from the trial if they meet any of the following criteria:

1. Have a sibling or immediate family member already participating in this trial.

2. Currently requires and/or, in the past month, has required topical use of a medium or high potency steroid.

3. Atopic dermatitis that, in the opinion of the investigator, is likely to stem from an allergic reaction. (i.e. contact dermatitis)

4. Have <2% or >15% total BSA of atopic dermatitis involvement.

5. Have participated in any interventional clinical trial in the previous 30 days to the screening visit.

6. Have a known sensitivity to any of the constituents of the test product including sensitivities to sandalwood oil, fragrances or any member of the Compositae family of vascular plants (e.g., sunflowers, daisies, dahlias, etc.).

7. Have received phototherapy within the last two months prior to enrollment.

8. Have received any systemic medication for atopic dermatitis in the past two months that would interfere with the evaluation of atopic dermatitis (excluding antihistamines or leukotriene inhibitors).

9. Have a present condition or abnormality that, in the opinion of the Investigator, would compromise the safety of the subject or the quality of the data.

10. Are pregnant, breast-feeding or plan to become pregnant at any point for the duration of the trial.

11. Are not willing to practice an approved form of birth control while on the study drug for the duration of the trial. i.e. oral contraceptive, barrier method or intrauterine device.

12. Have been treated, with prescription medication for atopic dermatitis, within 60 days prior to the Baseline visit.

13. Have any evidence of systemic cancer, squamous cell carcinoma, basal cell carcinoma, in the last 5 years or any other confounding skin condition.

14. Have undergone treatments with topical atopic dermatitis drug products, other than retinoids or corticosteroids, within 14 days prior to the Baseline Visit, and for therapy containing corticosteroids or retinoids within 28 days prior to Baseline Visit.

15. Have open sores or open lesions in the treatment area(s).

16. Have a history of alcohol or illegal drug/substance abuse, or suspected alcohol or illegal drug/substance abuse in the past 2 years.

17. Require ≥ 2.0 mg/day inhaled or intranasal corticosteroids.

18. Have an active infection of any kind at Visit 1 Baseline.

19. Have an occupation that requires ≥50% of time be spent outdoors, where prolonged exposure to ultraviolet radiation is unavoidable.

4.4 SUBJECT ENROLLMENT

The Investigator will maintain a log of pre-screened subjects and an enrollment log of all subjects enrolled in the study indicating their assigned study number.

Each potential subject will sign and date an informed consent and a photography consent form before any study procedures are performed.

Once a potential subject is determined to be eligible for inclusion in the study, site personnel will conduct the study visit procedures and dispense study medication.

5. VISIT SCHEDULE AND ASSESSMENTS

5.1 STUDY PROCEDURES

The visit schedule and assessments are summarized in Table 5-1. A subject will have 5 visits: Screening Visit, Baseline Visit (Day 1), Treatment Visit 2 (Day 7), Treatment Visit 3 (Day 14), Telephone Call Visit 4 (Day 21) and a Final Visit 5 (Day 28) at the end of the study treatment. On Study Day 35, the subject will receive a follow-up phone call and be queried for condition status since going off study.

Source documents will be completed at each subject's visit, and the data captured in the source documents will be subsequently entered into the electronic case report forms (eCRFs) by the Investigator or designee. In addition, two Telephone Visits, Visit 4 (Day 21± 2) and the Follow-Up (Day 35 ± 2) phone call will be conducted.

Table 5-1 Time and Events

Procedure	Screening Period	Treatment Period					Follow-Up
	Day-7 to 0	Visit 1- Day 1	Visit 2- Day 7 (± 2 days)	Visit 3- Day 14 (± 2 days)	Visit 4- Day 21 (± 2 days)	Final Visit 5- Day 28 (± 2 days)	Follow-up Call- Day 35 (± 2 days)
Conduct informed consent and photography consent[1]	X						
Record demographics	X						
Review inclusion/exclusion criteria	X	X					
Record/update all concomitant medications	X	X	X	X	X	X	
Perform a full physical examination	X						
Record/update pertinent medical history[2]	X	X	X	X	X	X	
Administer IGA and EASI	X	X	X	X		X	
Calculate the BSA of treatment area	X	X	X	X		X	
Tolerability Assessment		X	X	X		X	
Perform an abbreviated physical examination[3]		X					
If subject is female, collect urine sample and perform a β-human chorionic gonadotropin pregnancy test[4]		X				X	
Weight study medication and record weight[5]		X	X	X		X	
Calculate Expected Use per application		X					
Calculate Dose		X					
Calculate compliance			X	X		X	
Dispense/re-dispense study drug[6]		X					
Subject apply medication		X					
Instruct the subject on proper washing or the treatment area and self-application of study medication		X					
Photograph treatment area(s)		X	X	X		X	
Instruct subject to return for next study visit		X	X		X		
Query for adverse events[7]			X	X	X	X	
Query for treatment regimen compliance			X	X	X	X	
Inform subject next contact will be by telephone				X		X	
Collect study medication						X	
Query for status of condition since study completion							X

Footnotes to Table 5-1: Time and Events

1- Site staff will follow the requirements of the IRB or Ethics Review Board to obtain informed consent from the Subjects
2- Only pertinent medical history will be recorded for each Subject

3- Only complete if Screening and Baseline visit are not done together
4- A urine pregnancy test will be completed for all subjects of child-bearing potential at the designated study visits, or at any visit if there is suspicion of pregnancy during the treatment period.
5- This should be done twice at Baseline Visit, before, and after application
6- Additional study drug may be dispensed at each visit depending on usage
7- Adverse events (AE) will be collected after the Subject's first treatment at Visit 1 and throughout the trial. Record only study medication related AE at Visit 5. If AE persists after the follow-up visit, the Subject may be required to return to assess the AE.

5.2 Study Visits and Procedures

- **Screening Period (-7 Days)**

Eligible subjects will be asked to read and sign an informed consent and photograph consent form. No study procedures will be conducted until the informed consent and photograph consent form is signed.

At the Screening Visit, the following procedures will be performed:

- Conduct the informed consent and photography consent process.
- Record Demographics to include age, sex, and race.
- Review the inclusion/exclusion criteria.
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements.
- Perform a full physical examination including height (cm) and weight (kg).
- Record pertinent medical history including tobacco, illegal substance and alcohol history and current use.
- Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA) and BSA.
- Administer the Eczema Area Severity Index (EASI).

If more than 7 days is required for the subject to qualify for the study, then the subject must be screen failed, rescreened and all screening procedures repeated.

- **Visit 1 Baseline (Day 1)**

The following procedures will be completed at Visit 1 Baseline. It is possible for the subject to be screened and complete the Visit 1 Baseline procedures on the same day.

- Review inclusion and exclusion criteria to ensure the subject qualifies for the study.
- If this visit is not combined with the screening visit:
- Perform an abbreviated physical examination including height (cm) and weight (kg)

- Update concomitant medications including all prescription drugs, non-prescription drugs and nutritional supplements
- Review and update the subject's pertinent medical history.
- Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA) and BSA.
- Administer the Eczema Area Severity Index (EASI).
- Using calculated BSA, calculate Subject dose using 0.5gm per 1% BSA (i.e. 2% BSA= 2 x 0.5gm= 1gm per application)
- If subject is a female of childbearing potential, collect a urine sample and perform a β-human chorionic gonadotropin pregnancy test.
- Weigh full tube of SAN007 study medication, with cap on, and record weight prior to first dose.
- Instruct the subject on proper washing of the target treatment area(s) (using only study-approved cleanser) and self-application of SAN007 study medication, subject to apply first dose in the office.
- Assess Tolerability immediately following study drug application.
- Weigh tube of SAN007, with cap on, immediately following first application and record weight prior to for dose. The difference between this weight and the pre-application weight is to be used as the expected estimated usage per application. (i.e. pre-application weight- post-application weight = expected usage per application (EUA)
- Photograph the treatment area(s).
- Instruct the subject, when bathing, to refrain from using any body wash, lotion or moisturizer, other than that which has been provided for the treatment areas during the treatment period.
- Instruct the subject to return with the study drug in one week for the next study visit.

- **Visits 2 (Day 7 [±2 days]) and 3 (Day 14 [±2 days])**

The following procedures will be performed during Treatment Visit 2 and Visit 3:

- Query for adverse events.
- Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA), Tolerability and BSA.

- Administer the Eczema Area Severity Index (EASI).
- Update concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements.
- Query for treatment regimen compliance.
- Weigh and record the weight of the study medication, then re-dispense existing, or dispense a new, tube of study medication
- Calculate compliance. (i.e. visit day x 2 (applications per day) x EUA= expected usage) If Subject's actual compliance is ≤80% of expected compliance, re-educate and document in source.
- Photograph the treatment area(s).
- Review the directions for use of the study medication with the subject, and re-educate if applicable.
- (Visit 2 [Day 7 ± 2] only) Instruct the subject to return in one week for the next study visit, with their study drug.
- (Visit 3 [Day 14 ± 2] only) Remind the subject that the next visit will be a telephone follow-up Visit 4 (Day 21 ± 2)

- **Visit 4 Telephone Call (Day 21 [±2 days])**

The following information will be collected from the subject during the Visit 4 telephone call:

- Query for adverse events.
- Update concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements.
- Query for treatment regimen compliance.
- Instruct subject to return to the clinic for Visit 5 Final Visit (Day 28 ±2), with the study drug.

- **Visit 5 Final Visit (Day 28 [±2 days])**

The following procedures will be performed during the Final Study Visit:

- Query for adverse events.
- Update concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements.
- Query for treatment regimen compliance.

- Collect and weigh the study medication and record the weight.
- Calculate compliance. (i.e. Visit Day x 2 (applications per day) x EUA= expected usage) If Subject's actual compliance is ≤80% of expected compliance, re-educate and document in source.
- If subject is a female of childbearing potential, collect a urine sample and perform a β-human chorionic gonadotropin pregnancy test.
- Administer the following assessments, in which only the treatment area(s) are to be evaluated: Investigator's Global Assessment (IGA), Tolerability and BSA.
- Administer the Eczema Area Severity Index (EASI).
- Photograph the treatment area(s).
- Instruct the to return to the clinic for another study visit **only** if study-related adverse events persist or, in the Investigator's opinion, an additional study visit is warranted to ensure the subject's safety.

- **Follow-up Call (Day 35 [±2 days])**

The following will be asked of the subject during the follow up telephone call:

- Query for status of AD since discontinuation of study medication
    - E.g. Has your condition been stable, improved or worsened, since discontinuing study medication?

6. EVALUATION SCALES

6.1 ECZEMA AREA AND SEVERITY INDEX (EASI)

The Eczema Area and Severity Index (EASI) score is used to measure the severity and extent of eczema.

6.1.1 EASI Body Regions

The index is applied to four body regions:

- Head and neck
- Upper limbs
- Trunk
- Lower limbs

6.1.2 EASI Intensity

The intensity of eczema, and the percentage of the affected area, are calculated for each region. The intensity of eczema is rated on a four-point scale of 0-3 (none, mild, moderate, severe):

- Redness (erythema)
- Thickness (induration, population edema)
- Scratching (excoriation)
- Lichenification (lined skin)

6.1.3 EASI Subtotal of Intensity of Each Body Region

The four intensity scores are added up for each of the four regions to give subtotal (A1, A2, A3, A4). Each subtotal is multiplied by the body surface area represented by that region:

- A1 x 0.1 gives B1 (in children 0-7 years, A1 x 0/2 gives B1)
- A2 x 0.2 gives B2
- A3 x 0.3 gives B3
- A4 x 0.4 gives B4 (in children 0-7 years, A1 x 0.3 gives B1)

6.1.4 EASI Percentage Area

The percentage area affected by eczema is evaluated in the four regions of the body. In each region, the area is expressed as:

- 0- 0 to <1%
- 1-1% to 9%
- 2- 10% to 29%
- 3- 30% to 49%
- 4- 50% to 69%
- 5- 70% to 89%
- 6- 90% to 100%

6.1.5 EASI Calculations of Area

Each of the body area scores are multiplied by the area affected:

- B1 x (0-6) = C1
- B2 x (0-6) = C2
- B3 x (0-6) = C3

  B4 x (0-6) = C4

6.1.6 EASI Total Score

The final EASI score is:

EASI= C1 + C2 + C3 + C4.

An increase in EASI score, from Baseline, during study participation, will be recorded as an AE. A new adverse event will be opened only if the PI assesses an increase in severity from initial AE. Otherwise, the initial adverse event will remain open until resolution or study completion.

6.2 INVESTIGATOR GLOBAL ASSESSMENT

The Investigator Global Assessment (IGA) should be administered by the same Investigator, or designee, for any given Subject at all study visits. Any increase in IGA grade will be recorded as an AE. It will be used to measure efficacy according to the following scale:

Grade	Score	Description
Clear	0	No inflammatory signs of AD
Almost Clear	1	Just perceptible erythema and just perceptible population/infiltration
Mild	2	Mild erythema and mild population/infiltration
Moderate	3	Moderate erythema and moderate population/infiltration
Severe	4	Severe erythema and severe population/infiltration

6.3 URINE PREGNANCY TESTS

Females of childbearing potential will undergo a urine pregnancy test (UPT) at Visit 1 (Day 1) and at Visit 5 (Day 28 ±2). If the urine pregnancy test is positive at Visit 1, the subject will not be permitted to enroll in the study. Any subject who becomes pregnant during the trial must be discontinued from further treatment. If there is a suspicion of pregnancy at any time during the Treatment Period, a urine sample will be obtained and tested. All pregnancies should be immediately reported to the sponsor and medical monitor within 24 hours of awareness and followed through to resolution.

6.4 INTERRUPTION OR DISCONTINUATION OF TREATMENT

Every subject has the right to refuse further participation in the study at any time and without providing reasons (see also Section 9.1.2). A subject's participation is to be terminated immediately upon request. The investigator should seek to obtain the reason and record this on the electronic case report form (eCRF).

Should the subject, during the course of the study, develop conditions, which would have prevented his/her entry into the study according to the safety related medical exclusion criteria, he/she must be withdrawn immediately.

The subject may be withdrawn from the study at any time at the discretion of the investigator for medical reasons and/or due to non-adherence to the treatment

scheme and other duties stipulated in the study protocol. The reasons are to be fully documented on the eCRF.

In addition, the sponsor and the investigator reserve the right to end or suspend the study at any time (see Section 9.2.3).

6.5 WITHDRAWALS

The following medical and other reasons justify a premature termination, by subject or investigator, of any of the study products:

- Adverse event (including any SAE, clinically significant AE, intercurrent illness, or other medical condition that indicates to the investigator that continued participation is not in the best interest of the subject);
- Death;
- Lost to follow-up;
- Noncompliance with study medication dosing regimen, protocol requirements, or study-related procedures;
- Investigator discretion in case of occurrence of any medication condition, requirement for prohibited concomitant medication or treatment, or circumstances that would not allow the subject to adhere to protocol requirements;
- Pregnancy;
- Study terminated by Sponsor;
- Withdrawal of consent;

If a subject withdraws from the study, all efforts will be made to complete a final evaluation. subjects discontinued due to an AE will be followed until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate eCRF. All subjects who are withdrawn should complete protocol-specified withdrawal procedures.

6.6 WITHDRAWAL PROCEDURES

Protocol-specified withdrawal procedures are the same as those to be performed at the last study visit (Section 5.2.4).

6.7 SUBJECT REPLACEMENT

Subjects who prematurely discontinue the study may be replaced until 90 subjects have completed the study, or a total of 100 subjects have been enrolled, from the time of this amendment.

6.8 SUBJECT RE-SCREENING

Subjects previously denied entry into the study may be re-screened for eligibility once all enrollment criteria are met and issued a new subject number.

7. STUDY TREATMENT

7.1 DRUG PRODUCT (SAN007)

7.1.1 Formulation

The active ingredient under investigation in this study is East Indian Sandalwood Oil (EISO) in a cream for topical administration.

Formulation information for the investigational products is presented in Tables 7-1 and 7-2.

Table 7-1: Study Drug Information

Active ingredient	East Indian sandalwood oil (EISO) (5%, based on w/w)
Inactive ingredients	Purified water, Potassium Phosphate, Monobasic (USP), Sodium Hydroxide (NF), Sodium Lauryl Sulfate (NF/USP), Methylparaben (NF), Cetyl Alcohol (USP), Stearyl Alcohol (USP), Propolene Glycol (USP), t-Butyl Hydroquinone (TBHQ) (FCC), Propylparaben (NF).
Dosing schedule	Twice daily (bid) for 28 days. Topically.
Manufacturer	Pam Lewis & Associates Boerne, TX, USA
Packaging	60 gram (50 gram fill) white aluminum tube w/ internal liner
Storage requirements	Store at controlled room temperature[a] (20°C to 25°C [68°F to 77°F])

a: Excursions are allowed between 15°C and 30°C (59°F and 86°F)

Table 7-2: Study Drug Information

Active ingredient	East Indian sandalwood oil (EISO) (10%, based on w/w)
Inactive ingredients	Purified water, Potassium Phosphate, Monobasic (USP), Sodium Hydroxide (NF), Sodium Lauryl Sulfate (NF/USP), Propolene Glycol (USP), Methylparaben (NF), Cetyl Alcohol (USP), Stearyl Alcohol (USP), Isopropyl Palmitate, NF, White Petrolatam, USP, Light Mineral Oil, NF, t-Butyl Hydroquinone (TBHQ) (FCC), Propylparaben (NF).
Dosing schedule	Twice daily (bid) for 28 days. Topically.
Manufacturer	Pam Lewis & Associates Boerne, TX, USA
Packaging	60 gram (50 gram fill) white aluminum tube w/ internal liner
Storage requirements	Store at controlled room temperature[a] (20°C to 25°C [68°F to 77°F])

a: Excursions are allowed between 15°C and 30°C (59°F and 86°F)

Table 7-3: Placebo Information

Active ingredient	None
Inactive ingredients	Purified water, Potassium Phosphate, Monobasic (USP), Sodium Hydroxide (NF), Sodium Lauryl Sulfate (NF/USP), Propolene Glycol (USP), Methylparaben (NF), Cetyl Alcohol (USP), Stearyl Alcohol (USP), Isopropyl Palmitate, NF, White Petrolatam, USP, Light Mineral Oil, NF, t-Butyl Hydroquinone (TBHQ) (FCC), Propylparaben (NF).
Dosing schedule	Twice daily (bid) for 28 days. Topically.
Manufacturer	Pam Lewis & Associates Boerne, TX, USA
Packaging	60 gram (50 gram fill) white aluminum tube w/ internal liner
Storage requirements	Store at controlled room temperature[a] (20°C to 25°C [68°F to 77°F])

a: Excursions are allowed between 15°C and 30°C (59°F and 86°F)

7.1.2 Packaging and Labeling

The study product labels will contain, at minimum, the following information:

- Sponsor name and address;
- Protocol number;
- Kit Number;
- Subject number (may be hand printed on the label);
- Product description;
- Lot number;
- Storage conditions;
- Investigator name (may be hand printed on the label);

- Expiry or retest date, if applicable;
- "Investigational use only. Keep out of reach of children"
- For topical application only. Apply only to atopic dermatitis, in treatment areas twice daily, morning and evening.

Study product will be provided individually. Only one study product container will be dispensed at one time to the subject, with additional tubes dispensed as needed.

7.1.3 Dosing Regimen

Subjects are to self-administer the treatment regimen according to the following schedule and order:

- Step 1. Thoroughly wash the treatment area with study-issued cleanser, tepid water, and a clean washcloth.
- Step 2. After gently patting the skin dry, apply the study medication to the target treatment area(s) as directed by the study staff. Study medication dosing is as follows: approximately 0.5 gm (approximately one fingertip, from the first knuckle to the tip of the finger) per 1% body surface area involvement (approximately the size of the palm of one's hand) should be applied to the treatment area. Be sure to apply the study medication morning and night, ≥ 8 hours in between doses, and wait until the area feels dry to the touch before covering with clothes.
- Step 3. Wash hands thoroughly to remove any traces of study medication and to prevent the accidental contact of study medication with non-treatment areas.

The site staff will be responsible for instructing subjects on the procedures for self-administration at home, with subjects applying first dose at Visit 1 Baseline. Subjects achieving complete symptom resolution will continue to apply study medication for the entire 28-day treatment period. Dose administration should be ≥ 8 hours between doses.

7.1.4 Dose Modification

In the event the subject experiences a rash, or any other health issue in the treatment area during the study, the subject should be examined by the investigator. All AEs should be recorded in the electronic case report forms (eCRFs) and local skin reactions must be reported to the study coordinator and/or investigator.

If a subject experiences a new or worsening localized rash in the treatment area or generalized rash, the subject should contact the study site, cease study treatment, and report to the study center for examination.

Upon resolution of any rashes (localized or generalized), the subject may be re-challenged with study treatment under medical supervision by study personnel. The investigator or designee must stress the importance of applying the treatment regimen according to the instructions provided. In the absence of further rashes/skin irritations, study treatment may resume. If a rash or skin condition reappears, treatment should be stopped, subjects should report to the study physician, and they will be discontinued from the study.

Although there have been rare (<1%) reported instances of anaphylaxis in the literature, anaphylactic reaction is possible. If a subject suspects that he/she may be experiencing a severe, acute reaction, the subject should report to the nearest hospital Emergency Room, Urgent Care center, or call 911 or 000 for immediate treatment and stabilization. At that point, the subject should have final study assessments performed (if reasonable) and should be discontinued from the study.

Definition of Dose Limiting Toxicity
For this study, a dose-limiting toxicity is defined as any one or more of the following:

- Any instance of anaphylaxis during treatment.
- Any instance of angioedema during treatment.
- Second instance of an allergic reaction following re-challenge by subjects who had only minimal redness or reaction during study treatment

Subjects should NOT be re-challenged if they experienced a generalized allergic reaction or a severe local reaction (e.g., severe erythema, blistering or swelling at the site of application).

7.1.5 Assignment to Treatment

7.1.5.1 Subject Numbering

Each subject who signs informed consent and photograph consent documents and successfully completes the screening procedures will be enrolled into the study. Each subject will be assigned a unique subject number that will be used on all eCRFs.

7.1.5.2 Prior and Concomitant Therapy

All medications, including all prescription drugs, nonprescription drugs, and nutritional supplements, taken within 60 days prior to the start of the study will be recorded at the Screening Visit and updated as necessary at each subsequent visit.

Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the Subject's eCRF.

Concomitant therapies that are not permitted at any time during the Subject's participation in the trial include, but are not limited to, isotretinoin, corticosteroids or retinoids (oral or topical), all immunosuppressive or immunomodulary medications (biologics), any medication being used off-label for the treatment of atopic dermatitis, and all other anti-atopic dermatitis medications.

In addition, no other treatments to the target treatment area(s) should occur during study participation.

7.2 TREATMENT COMPLIANCE

At each study visit, subjects will be questioned about compliance with the treatment schedule. Subjects who are consistently noncompliant (i.e., < 90% of required doses) will be counseled and may be withdrawn from the study.

Records of study product used will be kept. The products will be weighed prior to dispensation and at each study visit. Subjects will be asked to return all used, partially used, and empty products to the study site at the end of the study.

7.3 EFFICACY ASSESSMENT

At each study visit, the Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), and BSA calculation will be completed and documented on the source documents and eCRF. Efficacy, via EASI, IGA, and BSA improvement should always be compared to status of condition at Visit 1 Baseline.

If possible, the same investigator who assessed the subject at Visit 1 Baseline should assess the subject at subsequent study visits. The investigator who performs the IGA and EASI should be proficient with this measure and routinely perform these evaluations.

7.3.1 Treatment of New Lesions

During the Treatment Period, new lesion(s) that appear are permitted to be treated as long as they are not in a study exclusion area; however, these lesions should not be included in the EASI, IGA, or BSA assessments. Any changes in tolerability between old lesions and new should be recorded and clearly differentiated in the source records and eCRF.

7.3.2 Photograph of Treatment Area

Photographs will be taken of the affected area(s) for informational purposes only. Camera, instructions on taking the photographs, and related items for photography will be provided by the study Sponsor. Should the subject have >4 lesions to be

photographed, the PI should choose four lesions that are representative of the overall severity of the disease and photograph these same four lesions at each study visit.

7.4 SAFETY REPORTING

7.4.1 Definitions

Adverse event - An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, without judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Adverse reaction - An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

Suspected adverse reaction - Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition (of suspected adverse reaction), and in the requirement to report them is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event.

Unexpected Adverse Event - An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure

Serious - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the outcomes listed in Section 7.6.

Life-threatening - An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject or subject at immediate risk of death. It does not include an

adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

If either the sponsor or investigator believes that the event meets the definition of life-threatening, it must be considered life-threatening.

7.5 ADVERSE EVENTS

Information about all AEs, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, or other means, will be collected and recorded on the Adverse Events page of the eCRF and followed as appropriate. Adverse events will be coded using an internationally recognized dictionary.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (i.e., any procedures specified in the protocol). Adverse events occurring before starting study treatment, but after signing the informed consent form, are recorded on the Medical History/Current Medical Conditions page of the eCRF.

As far as possible, each AE will also be described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study product (definitely, probably, possibly, unlikely, or not related),
4. the action(s) taken, and,
5. the outcome, as relevant.

Severity of adverse events

The investigator is to classify the severity of an AE according to the following definitions:

Mild:	The Subject is aware of the signs or symptoms, which are easily tolerated.
Moderate:	The signs and symptoms are sufficient to restrict, but not prevent usual activity.
Severe:	The Subject is unable to perform usual activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed considering the possible range of intensity of the symptom(s).

Relationship of adverse event to study treatment

The investigator is to classify the relationship of the AE to the investigational product according to the definitions outlined in Table 7-6.

The following study measurements will be reported as an AE:

1. Any increase in the subjects' EASI score or IGA during study participation.
2. A negative change in Tolerability, during or immediately after study drug application.

Table 7-6: Terms for Defining Relationship of Adverse Event to Study Product

Association	Definition
Not related	(1) the existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site) or (2) non-plausibility, e.g., the subject is struck by an automobile or develops cancer a few days after product administration.
Unlikely related	A clinical event, including laboratory test abnormality (if applicable), with an improbable time sequence to product administration and in which other drugs, chemicals for underlying disease provide plausible explanations.
Possibly related	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably related	A clinical event, including laboratory test abnormality (if applicable), with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Definitely related	A clinical event, including laboratory test abnormality (if applicable), with an established temporal or other association (e.g., re-challenge) and the event is not reasonably explained by the Subject's known clinical state or any other factor, based on available information.

7.6 SERIOUS ADVERSE EVENTS

An AE can be severe, but not necessarily serious. A serious adverse event (SAE) or suspected adverse reaction is 'serious' if, in the view of either the investigator or sponsor, results in any of the following outcomes:

1. death;
2. a life-threatening adverse event
3. in-subject hospitalization or prolongation of existing hospitalization;
4. a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
5. a congenital anomaly or a birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical

judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious AEs are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen; and/or
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

If either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor.

Information about all SAEs will be collected and recorded on the Serious Adverse Event Report Form. To ensure subject safety each SAE must also be reported to the sponsor within 24 hours of learning of its occurrence and if applicable to the responsible Institutional Review Board (IRB) according to their reporting requirements.

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(Must state: "ATTENTION:")

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Sponsor: Santalis Pharmaceuticals

Pregnancy, although not itself an SAE, should also be reported on a Serious Adverse Event Report Form.

A death occurring during the study, or which comes to the attention of the investigator within four weeks after stopping treatment, must be reported.

Any serious adverse event occurring in a subject after providing informed consent, and until four weeks after stopping study drug treatment must be reported.

7.7 APPROPRIATENESS MEASUREMENTS

Standardized and most widely accepted methods for evaluating safety and preliminary efficacy will be used for assessments in this study.

8. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

8.1 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

- Up to 100 subjects will be enrolled in this study to ensure 90 subjects complete the study, from the time of this amendment. The primary endpoint of this study is to determine the safety profile of SAN007 by evaluating AEs, with respect to severity, duration, and relationship to the study drug, as well as tolerability by subjects reporting discomfort during or immediately following an application of SAN007. The preliminary efficacy analysis of the study will be evaluated using the following:
- Percentage of subjects who have a ≥ 25% reduction in the Eczema Area and Severity Index (EASI) score at any point during the trial.
- Number of subjects achieving an Investigator Global Assessment (IGA) of "clear" or "almost clear" at any time point during the 28 days of therapy. The study restricted treatment areas are not to be included in this evaluation. (see #12 under Inclusion Criteria)
- Percentage of subjects who have a ≥50% reduction in the Eczema Area Severity Index (EASI) score at any point during the trial.
- Percentage of subjects achieving at least a 1-grade improvement in IGA score
- Percentage of subjects who have at least a 20% reduction in BSA affected by atopic dermatitis.

No interim or subgroup analyses are planned.

8.2 SAMPLE SIZE AND POWER CONSIDERATIONS

This is the first study of the investigational product in the proposed indication. Therefore, the choice of sample size is not based on statistical considerations or expected to yield statistically significant results.

8.3 ANALYSIS POPULATIONS

8.3.1 Intent-to-Treat Analysis Set

The Intent-to-treat (ITT) Analysis Set is defined as all subjects enrolled and randomized into the study.

8.3.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized subjects who applied at least one administration of the investigative study drug, and who had at least one post-baseline efficacy assessment.

The FAS will be the primary population used for efficacy analysis.

8.3.3 Per Protocol Set

The Per Protocol Analysis Set (PP) is defined as all subjects in the FAS who do not have any major protocol violations, including:

- Violations of inclusion/exclusion criteria;
- Use of prohibited concomitant medications;
- Noncompliance (i.e., <90% compliant with study treatment);
- Failure to provide a clinical observation at Day 28;

The PP Analysis Set will be a secondary population used for supportive analysis of efficacy variables and will be analyzed according to the study treatment actually received.

8.3.4 Safety Analysis Set

The Safety Analysis Set is defined as all subjects enrolled and randomized who received at least one application of study treatment.

8.4 PLANNED METHODS OF ANALYSIS

8.4.1 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, and race) and background characteristics for the enrolled subject population. Past/coexistent medical history information for all subjects will be presented in a by-patient listing.

8.4.2 Study Product/Visit Compliance

The number and percentage of subjects attending each study visit will be presented. Compliance with study treatment and extent of exposure will be summarized by descriptive statistics of total number of applications received, total weight of product used, and average weight per application of product. The number and percentage of subjects who received fewer than 90% of prescribed applications will be presented.

8.4.3 Prior and Concomitant Therapy

Prior and concomitant medication information for all treated subjects will be presented in a by-patient listing.

8.4.4 Preliminary Efficacy Analysis

The primary data analysis set for preliminary efficacy analyses will be the FAS population defined in Section 8.3.3. The preliminary efficacy analysis will be evaluated by the following:

- Percentage of subjects who have a ≥ 25% reduction in the Eczema Area and Severity Index (EASI) score at any point during the trial.
- Number of subjects achieving an Investigator Global Assessment (IGA) of "clear" or "almost clear" at any time point during the 28 days of therapy. The study restricted treatment areas are not to be included in this evaluation. (see #12 under Inclusion Criteria)
- Percentage of subjects who have a ≥50% reduction in the Eczema Area Severity Index (EASI) score at any point during the trial.
- Percentage of subjects achieving at least a 1-grade improvement in IGA score
- Percentage of subjects who have at least a 20% reduction in BSA affected by atopic dermatitis.

The efficacy endpoints analysis will be summarized using standard statistical methods. In general, categorical endpoints (e.g., Investigators Global Assessment and EASI) will be tabulated by number and percentage. Continuous endpoints (i.e., mean change from baseline and percent change from baseline) will be summarized using descriptive statistics (N, mean, median, standard deviation, and range).

8.4.5 Safety Evaluations

8.4.5.1 Adverse Events

The assessment of safety will be based mainly on the frequency of AEs.

Adverse events may be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Adverse events will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each body system and having each individual AE. Any other information collected (e.g., severity or relatedness to study medication) will be listed as appropriate.

8.4.5.2 Tolerability Evaluations

The number and percentage of subjects reporting intolerance to study drug during or immediately following application.

8.4.5.3 Interim Analyses

No interim analyses are anticipated.

8.4.5.4 Special Methods

Not applicable.

9. ADMINISTRATIVE PROCEDURES

9.1 ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol, and in accordance with standard operating procedures of Santalis and the CRO, if applicable. These are designed to ensure adherence to Good Clinical Practices guidelines, as described in:

- International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- (If Applicable) Australian Therapeutic Goods Administration (TGA) Act 1989, and the Therapeutic Goods Regulations 1990.
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects; Helsinki 1964 and amendments).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.1.1 Human Research Ethics Committee (HREC), Ethics Review Board (ERB) or Institutional Review Board (IRB)

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects must be reviewed by a properly constituted Human Research Ethics Committee (HREC), Institutional Review Board (IRB) or Ethics Review Board (ERB). A signed and dated statement that the protocol and informed consent and photographic consent have been approved by the HREC, IRB or ERB must be received before study initiation. The name and occupation of the chairman, and the members of the HREC, IRB, or ERB must also be received. This committee must also approve any amendments to the protocol, other than administrative ones, and a signed and dated statement of approval must be received prior to initiation of the amendment procedures.

9.1.2 Subject Information and Consent

The investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent

medical treatment or relationship with the treating physician. All reasonable efforts will be made to protect the subject's identity in study photography.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and he/she should be given a copy of the signed document. No subject can enter the study before informed consent and photographic consent have been obtained from him or her.

9.1.3 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document it must be obliterated before a copy of the document is supplied to the sponsor. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that subject confidentiality will be maintained at all times.

9.2 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.2.1 Protocol Amendments

With the exception of administrative changes, any changes or additions to this clinical study protocol require a written protocol amendment that must be approved by the Sponsor and the investigator before implementation.

9.2.2 Other Changes in Study Conduct

Deviations from the planned study conduct are not permitted. Any unforeseen changes in study conduct must be reported within 5 days to the Sponsor.

9.2.3 Termination or Suspension of Study

The Sponsor reserves the right to terminate or suspend the study at any time. If applicable, appropriate regulatory authorities will be notified of the termination/suspension and the reason(s).

9.3 DATA HANDLING AND RECORD KEEPING

9.3.1 Recording of Data

eCase Report Forms will be designed to identify each subject by number and subject's initials, the protocol number, and the results observed. Data on subjects

collected on eCRFs during the study will be documented in an anonymous fashion, and the subject will only be identified by the subject number, and by his/her initials. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both the study sponsor, and the investigator are bound to keep this information confidential.

All subjects who have signed the ICF and randomized into the trial will be entered into the eCRF. Clinical source documents must support all data recorded on eCRFs. The eCRF cannot act as the source document for any of the data submitted to the sponsor. All data must have a separate identifiable source. Only trained and delegated site staff may complete the eCRF or change the data. After each subject's visit, data will be entered into the appropriate eCRF within 72 hours.

In addition to the eCRFs, individual subject source documents will be maintained. These documents may include the visit dates, the clinical study number, the name or initials of the subject, medical history or previous physical examinations, demographic and medical information, including, concomitant medications/treatments, etc, any AEs encountered, and other notes, as appropriate. All information on eCRFs must be traceable to the source documents kept in the subject's file, including reasons for corrections on the eCRF or source documents. These reasons must be initialed and dated by the individual who made the correction. Data without a written or electronic record will be defined before the start of the study and will be recorded directly on the eCRFs by the investigator or his/her designee, which will be documented as being the source data.

The lead investigator at the site must sign the designated page(s) of the eCRFs, thereby stating that he/she takes responsibility for the accuracy of the data in the entire case record book. All records will be kept in conformance to applicable country laws and regulations.

The original signed informed consent form will be attached to each subject's file. When the study treatment is completed, the informed consent form will be in the appropriate file folder; otherwise a note indicating where the records can be located will be made.

9.3.2 Retention of Documents

Essential documents, as listed below, must be retained in a secure place by the investigator for a minimum of five years from completion of the study (and must inform the Sponsor prior to destruction), or as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The investigator agrees to

adhere to the document retention procedures by signing the protocol. Essential documents include:

- the study protocol and any amendments;
- IRB/HREC/IEC approvals for the study protocol and all amendments;
- all source documents;
- eCRF originals or copies;
- Subjects' informed consent forms including photographic consent forms (with study number);
- product inventory
- any other pertinent study document (e.g., investigator's brochure, correspondence, study reports, etc.).

9.3.3 Database Management

Data may be entered into an acceptable database for review and analysis.

9.3.4 Coding of Concomitant Medications and Adverse Events

Concomitant medications entered into the database may be coded using the World Health Organization (WHO) Drug Reference List, which classifies the medications according to the Anatomic Therapeutic Chemical classification system. Coexistent diseases and AEs may be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

9.4 PRODUCT HANDLING AND ACCOUNTABILITY

Study drug is to be used only for this clinical study and not for any other purpose. Study drug must be kept in an appropriate, secure area (e.g., locked cabinet) and stored according to the conditions specified on the product labels.

The investigator site must maintain a full record of the shipment and dispensing of study product in a product accountability ledger. This log must be kept current and should contain the following information:

- identification of the subject to whom the study product was dispensed,
- date(s) and quantity of the study product dispensed to the subject,
- date(s) and quantity of the study product returned by the subject (if applicable), and
- initials of the study site representative(s) dispensing and receiving returned study product.

The inventory must be available for inspection by the study monitor. Any discrepancy and/or deficiency must be accounted for.

The investigator must not destroy any product labels, or any partly used or unused product supply. At the conclusion of the study and, as appropriate, during the course of the study, all study product supplies, including partially used or empty containers, must be returned or destroyed according to the designation of the sponsor. Any missing supplies will be indicated on the inventory.

If requested in writing by the sponsor, unused product supplies may be destroyed by the Principal Investigator provided such disposition does not expose humans to risks from the drug. **Records shall be maintained by the principal investigator of any such alternative disposition of the investigational product.** These records must show the identification and quantity of each unit disposed of, the method of destruction (taking into account the requirements of local law), and the person who disposed of the products. Such records will be retained in the principal investigator's records for this clinical study and copies will be submitted to the sponsor.

9.5 QUALITY CONTROL AND QUALITY ASSURANCE

9.5.1 Monitoring Procedures

During the study, a study monitor will visit the study site(s) regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, adherence to the protocol and to the principals of ICH-GCP guidelines, the progress of enrollment, and to ensure that study product is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the study monitor during these visits.

The data required by the protocol must be recorded on the appropriate eCRFs. The eCRFs and any source documents will be available to the study monitor who will perform a 100% data check (comparison of the data recorded in the eCRF with those in the source documents). The eCRFs and source data will also be available for an audit by the sponsor, or sponsor representative, at any time.

The investigator must give the monitor and auditor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the Subjects will leave the study site(s). Additional checks on the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. The completed eCRFs and all other records will be kept on file as outlined above (see Section 9.3.2 on retention of documents).

9.5.2 Auditing Procedures

In addition to the routine monitoring procedures, a study center may be audited in depth for study quality assurance by the sponsor, an external auditor on behalf of the sponsor, and/or by regulatory authorities. This audit may include a review of all source documents, drug records, and original eCRFs at some or all of the study sites used in the study. Subject confidentiality will be maintained at all times and consent will be obtained before enrollment of any subject into the clinical trial (see Section 9.1.2 on informed consent). If a regulatory authority requests an inspection, the investigator must immediately inform the study sponsor that this request has been made.

9.6 STUDY FUNDING

The costs necessary to perform the study will be agreed with the investigator and/or the management of the study center, and will be documented in a separate financial agreement that will be signed by the investigator and the sponsor, or designee.

9.7 CONFIDENTIALITY AND PUBLICATION POLICIES

9.7.1 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB/HREB/IEC. Study documents provided by the study sponsor (i.e., protocols, investigators' brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

9.7.2 Communication and Publication of Results

Any formal presentation or publication of data from this study will be considered as a joint publication by the investigator(s) and appropriate sponsor personnel. Authorship will be determined by mutual agreement. The sponsor must receive copies of any intended communication in advance of publication (at least 30 working days for an abstract or oral presentation and 60 working days for a journal submission). The sponsor will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

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