CLINICAL STUDY PROTOCOL

A Phase 3, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Natroba™ (spinosad) for the Treatment of Scabies

Investigational Product: Natroba™ (spinosad) Topical Suspension, 0.9%

IND No.: 66,657

Phase: 3

Protocol Number: SPN-304-15

Document Dates

Original Protocol:	11 March 2015
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Amendment No. 6:	23 March 2018

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Confidentiality Statement

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A Phase 3, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Natroba™ (spinosad) for the Treatment of Scabies

Protocol Number: SPN-304-15

By my signature below, I attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in this protocol (including appendices). I will not initiate this study without approval from the appropriate Institutional Review Board (IRB) and I understand that any changes in the protocol must be approved in writing by the ParaPRO LLC and the IRB before they can be implemented, except where necessary to eliminate immediate hazards to the subject.

Approval Signature

Principal Investigator: _____ Date _____
Signature

_____
Printed Name

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Name of Facility

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Address

_____
City, State, Zip Code

_____
Phone Number

_____
Fax Number

_____
Email Address

CLIENT COMPANY SIGNATURE SHEET

A Phase 3, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Natroba™ (spinosad) for the Treatment of Scabies

Protocol Number: SPN-304-15

By my signature below, I approve this protocol (including appendices).

Approval Signatures

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PROTOCOL SYNOPSIS

TITLE: A Phase 3, Randomized, Double Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Natroba™ (spinosad) for the Treatment of Scabies	
PROTOCOL NUMBER: SPN-304-15	
INVESTIGATIONAL PRODUCT: Natroba™ (spinosad) Topical Suspension, 0.9%	**U.S. IND No.** 66,657
PHASE: 3	
INDICATION: Treatment of scabies	
OBJECTIVES: The primary objective is to assess the safety and efficacy of topical Natroba™ (spinosad) versus Placebo for the complete cure of scabies after a single treatment.	
ENDPOINTS: The primary efficacy endpoint is the proportion of "index" subjects completely cured of scabies by Day 28. The "index" subject is defined as the youngest infested household member (≥4 years). Complete cure is defined as demonstration of both clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermatoscopy for burrows. Safety endpoints include the evaluation of adverse events, general skin and eye irritation, clinical laboratory assessments, vital signs, and use of prior and concomitant medications.	
POPULATION: Approximately 360 subjects will be enrolled in the study. The approximate 360 total is based on: 120 households, each with an "index" subject and approximately 2 additional subjects per household (infested or not) for 360 total. The 120 "index" subjects with confirmed scabies infestation will comprise the primary efficacy population in order to achieve, with attrition, 48 subjects completed per treatment group (Natroba™ versus Placebo). In this study, "index" subjects will be defined as the youngest infested household member (≥4 years). All household members of the "index" subject will be randomized to the same treatment.	
STUDY DESIGN AND DURATION: This is a double blind, two-arm, 28-day, placebo-controlled study with approximately 120 infested "index" subjects randomized 1:1 to Natroba™ or Placebo. All members of a household (no more than 6 individuals) with a suspected "index" subject must be screened at the first visit. In this study, "index" subjects are defined as the youngest infested household member (≥4 years). If the members have an active scabies infestation and meet all other criteria, they must agree to participate in the study. Household members who do not present with scabies at the screening visit must also agree to apply the same blinded investigational product (IP) as household members who present with scabies (see Table 6-1 Schedule of Procedures for status assessment). All infested household members must agree to participate in the study or none will be enrolled. Screening procedures include informed consent, medication and medical history, urine pregnancy test for females of childbearing potential, scabies assessment (visual evidence of burrows, inflammatory/non-inflammatory lesions and pruritus),	

microscopic examination of skin scraping, or dermatoscopy, to demonstrate the presence of mites, eggs, and/or scybala (dermatoscopy must confirm burrows), vital signs, general skin and eye assessment, randomization, and IP dispensing and instruction.

After screening on Day 1, all randomized subjects will be dispensed IP (Natroba™ or Placebo) to apply at home later the same day as a single treatment over the entire body from the neck down to the toes (including the soles of the feet) and to the scalp (if balding) or hairline, temples and forehead on the same day. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver. Subjects will rub the treatment into the skin followed by a 10-minute wait period before getting dressed. Showering or bathing must not occur earlier than 6 hours after treatment and no later than at least 1 hour prior to Day 2 visit.

On Day 2 (Visit 2), all household members will return for general skin and eye assessments of possible irritation, and to confirm that all IP was left on for a minimum of 6 hours before bathing or showering. If a subject reports an adverse event assessed as related by the PI on Day 2 (Visit 2) then a follow-up visit with the investigator must be scheduled within 7 days of visit. All household members will receive a well-being phone call on Day 14 to continue to emphasize instructions to prevent re-infestation, determine if any concomitant medications have been used, and check for adverse events. If a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call, then a follow-up visit with the investigator must be scheduled within 7 days of phone call. .

On Day 28 (Visit 3), all household members will return to the clinic for safety and efficacy assessments. The primary endpoint of complete cure will be assessed in the "index" subject and any infested household members. If the infested subject is completely cured at Day 28, he or she will have completed the study and termination procedures will be conducted. If the subject is not completely cured at Day 28 (with Natroba™ or Placebo), the subject will receive 5% Permethrin and will be directed to their primary care physician for follow-up.

Safety assessments will be made for all household members and will include monitoring of adverse events (AEs) throughout the study, vital signs recording (Days 1 and 28), clinical laboratory analyses (Days 1 and 28), and general skin and eye irritation assessments (Days 1, 2, and 28). The Day 28 procedures will also be completed for early termination (ET) except subjects will not receive rescue Permethrin but will be directed to follow-up with their primary care physician.

The trial design is presented in the Study Flow Diagram (Figure 3-1) and the visit assessments are described in the Schedule of Procedures (Table 6-1).

INCLUSION CRITERIA:

All household members who have provided written informed consent and an authorization for disclosure of protected health information must meet all the following criteria:

1. Male or female, age 4 years and upward.
2. At least one household member must have active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic examination of skin scraping, or dermatoscopy, to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.
3. Generally in good health based on medical history and clinical assessments.
4. Normal-appearing skin in noninfested areas.
5. No history of chronic or recurrent dermatologic disease.

6. Willingness to comply with the study procedures including application of study treatment at home as instructed.
7. Willing and able to practice an acceptable measure of contraception during the study, if female of childbearing potential. Examples of acceptable contraceptive methods include abstinence, intrauterine device (IUD), double barrier method, oral or implantable or injectable contraceptives. Must have been using systemic (oral, injectable, or implantable) contraceptives for at least 3 months. If abstinent and planning to become sexually active must agree to use a double barrier method.
8. Subject agrees to inform their sexual partners to seek an examination for scabies and treatment if, and when, symptoms present.
9. Household members must be 6 or fewer and all members must be willing to attend clinic visits and be randomized to treatment (blinded, but same for all).

EXCLUSION CRITERIA:

All household members must be excluded if any of the following conditions are met:

1. Household has greater than 6 residents.
2. Has a household member(s) who is not willing or not eligible to enroll.
3. Presence of scabies on the scalp.
4. Presence of crusted scabies (Norwegian scabies).
5. Allergies or intolerance to ingredients in the IPs.
6. Current pregnancy (as assessed by urine pregnancy test) or currently nursing.
7. The household has sexually active subjects who do not agree to restrict prolonged skin to skin contact with non-household members during the trial period.
8. Known renal or hepatic impairment.
9. Treatment with scabicide within the prior 4 weeks.
10. Immunodeficiency (including HIV infection) as reported by the subject in Medical History.
11. Signs or symptoms of systemic infection.
12. Administration of any systemic therapy for infectious disease within the prior 2 weeks.
13. Receipt of any other investigational product (IP) within the prior 4 weeks.
14. Any other conditions that, at the investigator's discretion, may interfere with the study conduct, or which might confound the interpretation of the study results, or which may put the subject at undue risk.
15. Does not have a known household affiliation with their household members (stays in one household inconsistently, i.e., sleeps at one place several nights and then other places on other nights).
16. Household member is unwilling to treat scabies.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Natroba™ or Placebo applied in a single topical application to the entire body from the neck down to the toes (including the soles of the feet) and to the scalp (if balding) and/or hairline, temples, and forehead.

EFFICACY VARIABLES:

The primary efficacy assessment is the proportion of "index" subjects completely cured of scabies by Day 28. Complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritis) and microscopic or dermatoscopic cure demonstrating the absence of mites, eggs, and/or scybala, and negative dermatoscopy for burrows.

SAFETY ASSESSMENTS:
Safety assessments include monitoring of AEs on study Days 1, 2, 14 (phone call) and 28, general skin and eye irritation assessments on Days 1, 2 and 28, vital signs on Days 1 and 28, laboratory assessments on Days 1 and 28, prior medications on Day 1 and concomitant medications on Days 2 and Day 28. For early termination (ET), the Day 28 procedures will also be completed.

STATISTICAL ANALYSES:
The primary efficacy endpoint is the proportion of "index" subjects completely cured of scabies by Day 28. The primary analysis set will be the "index" intent-to-treat (ITT) population which is defined as all randomized "index" subjects regardless of whether they have had any post-baseline assessments and the primary efficacy endpoint will be the proportion of "index" subjects completely cured of scabies by Day 28. The number and percentage of "index" subjects who exhibit complete cure (Yes or No) by Day 28 will be presented by treatment group. A Cochran-Mantel-Haenszel general association test stratified by study site (possibly pooled) will be used to compare the complete cure rates between the two treatment groups. The primary analysis will be performed at a significance level of 0.05.

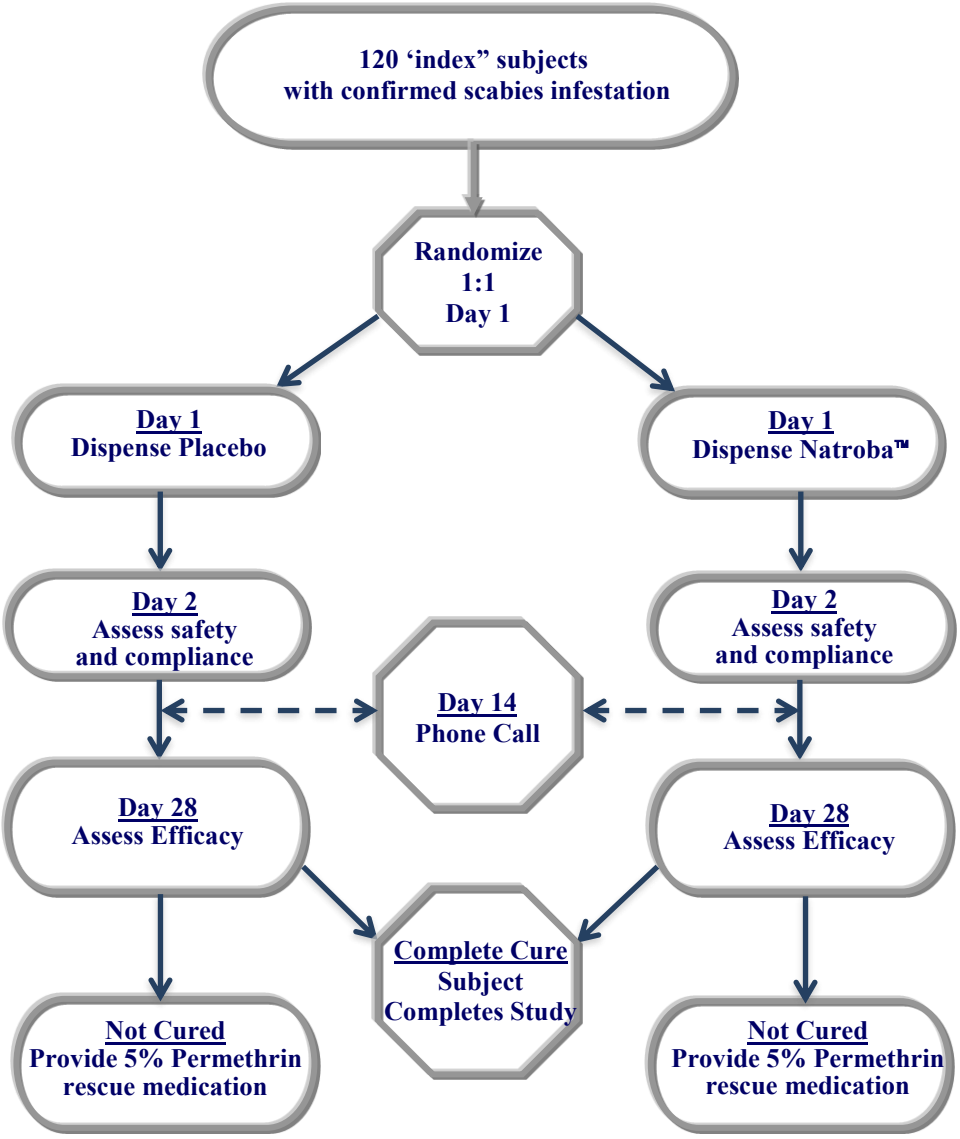
The safety endpoints include the evaluation of adverse events, general skin and eye irritation assessments, vital signs, and use of prior and concomitant medications. Additionally, the descriptive changes from baseline (pre-dose) to final assessment (Day 28) will be calculated for applicable parameters.

SAMPLE SIZE DETERMINATION:
For the primary efficacy analysis, approximately 120 "index" subjects will be enrolled (including possible 20% attrition) from 120 households and randomized 1:1 to each of Natroba™ (spinosad) and Placebo control. The index subject will be the youngest infested member of a household (≥4 years). Referencing to the Sponsor's Proof of Concept (POC) study (SPN-401-12) and published literature,[5-10] out of 60 completed subjects, the cure rate is 70% for Natroba™ and 30% for Placebo control. Based upon a reasonable assumption of 60% cure rate for Natroba™ and 30% for placebo, a sample size of 48 study-completed "index" subjects per group will provide 80% power to declare the non-equivalency using a delta of 30% and Type I error rate of 0.05. Fisher exact test was used to calculate the sample size and the specified power in the following Table 8-1 (PASS 14; 2015, NCSS, LLC., Kaysville, Utah, USA. www.ncss.com).

SITES:
This study will be conducted at approximately 5-10 sites in the United States.

SPONSOR:
ParaPRO LLC

STUDY FLOW DIAGRAM



SCHEDULE OF PROCEDURES AND ASSESSMENTS

Period	**Screening, Randomization and Treatment**	**Treatment/Follow-up**				
Visit	**1**	**2**	**AE follow-up**	**Phone Call**	**AE follow-up**	**3**
Day ±	1	2	3+6	14 ± 2	14 +7[12]	28 ± 2/ET
Informed consent	X					
Prior medications	X					
Medical history	X					
Urine pregnancy test[1]	X					X
Scabies diagnosis[2]	X					
Efficacy assessments[3]						X
Vital signs[4]	X					X
General skin assessment[5]	X	X				X
Eye irritation assessment[5]	X	X				X
Review eligibility criteria	X					
Randomization	X					
Weigh and dispense IP bottle; provide application instructions[6]	X[8]					
Instruct on waiting ≥6 hrs post-treatment (IP) before showering[6]	X					
Collect and weigh used IP bottle		X				X[8]
Review subject compliance[7]		X				
Instructions to prevent re-infestation	X	X		X		
Concomitant medications		X		X		X
Adverse events[9]		X	X[11]	X	X[11]	X
5% Permethrin dispensed to subjects not completely cured at Day 28						X[10]

ET = Early Termination; IP = investigational product.

1. Only for females of childbearing potential.
2. Scabies diagnosis (Inclusion #2) – At least one household member with active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic examination of skin scraping or dermatoscopy to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.
3. Primary Endpoint – Complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including inflammatory/non-inflammatory lesions and pruritus) and microscopic

or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows.

4. Vital signs – height (only Visit 1), weight, blood pressure (BP), and heart rate.
5. Assessment at Visit 1 for eligibility (skin) and eye for baseline, Visit 2 for skin and eye irritation assessments and to confirm IP was washed off, and Visit 3/ET (if applicable) for skin and eye irritation. See Section 7.7 for rating eye irritation.
6. IP Treatment – dispense IP and instruct subject to administer single topical application of IP over entire body from the neck down to the toes (including soles of the feet) and on the scalp/hairline, temples and forehead while at home. Subjects will not shower for at least 6 hours after application and no later than at least 1 hour before Day 2 visit. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver.
7. Confirm that all IP was left on for a minimum of 6 hours before bathing or showering and washed off at least 1 hour before Day 2 visit. Instruct/re-instruct subjects how to prevent re-infestation, to stay in one household, as well as to follow all study procedures and expectations.
8. Collect and weigh used bottle if not collected at Visit 2.
9. Assessed starting post-treatment. Investigators will follow all AEs until the final study visit (Day 28). All SAEs, and all AEs deemed by the Investigator to be related to IP or treatment, will be followed until the event has resolved (even if beyond Day 28).
10. Subjects who are not completely cured at this visit (Day 28) will be provided with 5% Permethrin as rescue medication. Subjects who terminated early will not receive rescue medication. All subjects will be directed to their primary care physician for follow-up.
11. If a subject reports an adverse event assessed as related by the PI on Day 2 (Visit 2) then a follow-up visit with the investigator must be scheduled within 7 days of visit. If a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call, then a follow-up visit with the investigator must be scheduled within 7 days of phone call.
12. It is intended for the AE follow-up to occur within 7 days of the day 14 call. The Day 14 call may occur between study day 12 and 16.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/Term	Definition
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BP	Blood Pressure
C	Celsius
CDC	Center for Disease Control
CGMP	Current Good Manufacturing Practices
CRA	Clinical Research Associate
CRF	Case Report Form
CFR	Code of Federal Regulations
EMEA	European Medicines Agency
ET	Early Termination
F	Fahrenheit
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDPE	High Density Polyethylene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigators' Brochure
IC	Informed Consent
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IP	Investigational Product (Natroba™ or Placebo)
IRB	Institutional Review Board or Independent Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PI	Principal Investigator
POC	Proof of Concept
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation/Term	Definition
SOC	System Organ Class
TEAE	Treatment-emergent AE
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WOCF	Worst Observation Carried Forward

1 BACKGROUND AND RATIONALE

1.1 Background

Human scabies is caused by an infestation of the skin by the human itch mite (Sarcoptes scabiei var. hominis). The microscopic scabies mite burrows into the upper layer of the skin where it lives and lays its eggs. The most common symptoms of scabies are intense itching and a pimple-like skin rash. The itching and rash each may affect much of the body or be limited to common sites such as the wrist, elbow, armpit, webbing between the fingers, nipple, penis, waist, belt-line, and buttocks. The rash also can include tiny blisters (vesicles) and scales. Scratching the rash can cause skin sores; sometimes these sores become infected by bacteria. Tiny burrows sometimes are seen on the skin which are caused by the female scabies mite tunneling just beneath the surface of the skin. These burrows appear as tiny raised and crooked (serpiginous) grayish-white or skin- colored lines on the skin surface. Mites are often few in numbers (only 10-15 mites per person) and the burrows may be difficult to find. The burrows are found most often in the webbing between the fingers, in the skin folds on the wrist, elbow, or knee, and on the penis, breast, or shoulder blades. The head, face, neck, palms, and soles often are involved in infants and very young children, but usually not adults and older children.[1,2]

The scabies mite is usually spread by direct, prolonged, skin-to-skin contact with a person who has scabies. Scabies occurs worldwide and affects people of all races and social classes. Worldwide prevalence has been estimated at about 300 million cases yearly.[2] Scabies can spread rapidly under crowded conditions where close body contact is frequent. Institutions such as nursing homes, extended-care facilities, and prisons are often sites of scabies outbreaks. Current treatment recommended by Centers for Disease Control (CDC) is a single overnight topical application of 5% Permethrin.[1]

Natroba™ (spinosad) Topical Suspension, 0.9% has been approved by the Food and Drug Administration for the treatment of head lice in patients 6 months of age and older.[3] Spinosad is derived from the fermentation of a soil actinimycete bacterium, and acts by causing neuronal excitation in insects. After periods of hyperexcitation, the lice become paralyzed and die. This same mode of action applies to the scabies mite. After topical application in infested pediatric subjects, spinosad levels in plasma were below the limits of quantitation. Preclinical testing for carcinogenesis, mutagenesis and impairment of fertility were negative. Clinical studies with subjects infested with head lice showed Natroba™ (spinosad) Topical Suspension, 0.9% to be more effective than Permethrin 14 days after treatment.[3]

1.2 Rationale

ParaPRO conducted a proof-of-concept trial that was a double-blinded, two-arm 28-day placebo controlled study of subjects randomly assigned 3:1 to Natroba™ or Placebo.[4] Subjects applied a single treatment over the entire body from the neck down to the toes (including the soles of the feet) in-clinic on Day 1, rubbing the investigational product (IP) into the skin and waiting 10 minutes before getting dressed. Showering or bathing was to occur no earlier than 6 hours after treatment. Efficacy assessments included visual skin assessment of scabies infestation (visual assessment of burrows, lesion counts, and presence of new lesions), skin scraping for microscopic examination (for evidence of mites) and a pruritus score by a subjective scale. The scabies scores were changed by -1.4 with Natroba (p=0.0020), compared to -1.0 with Placebo (p=0.2500). The count of lesions was significantly decreased with Natroba (-28.1, p=0.0020), however, not with Placebo (-9.8, p=0.6250). Microscopy showed significant improvement, 13/15 negative with Natroba (p=0.0074), compared to 3/5 with Placebo (p=1.000).

The design for the current Phase 3 trial is similar to the phase 3 trials evaluating efficacy of Natroba™ Topical Suspension for treatment of head lice, although subjects in this trial received only one application of the Natroba™ Topical Suspension.[3] In the two phase 3 studies of individuals with lice, all subjects who were treated on Day 0 returned for efficacy evaluation at Day 7. Subjects with live lice present at Day 7 received a second treatment. Subjects who were lice free on Day 7 were to return on Day 14 for evaluation. Subjects with live lice and who received a second treatment on Day 7 were to return on Days 14 and 21 for evaluation. Efficacy was assessed as the proportion of primary subjects who were free of live lice 14 days after the initial/final treatment.

Based on the safety and efficacy of Natroba™ (spinosad) Topical Suspension, 0.9% in the treatment of head lice,[3] the present study is designed to evaluate pivotal phase 3 data on the safety and efficacy of the topical suspension against scabies, an infestation by *Sarcoptes scabiei var. hominis*. The effect of the Natroba™ (spinosad) Topical Suspension, 0.9% will be compared to that of a Placebo control.

2 OBJECTIVES

2.1 Primary

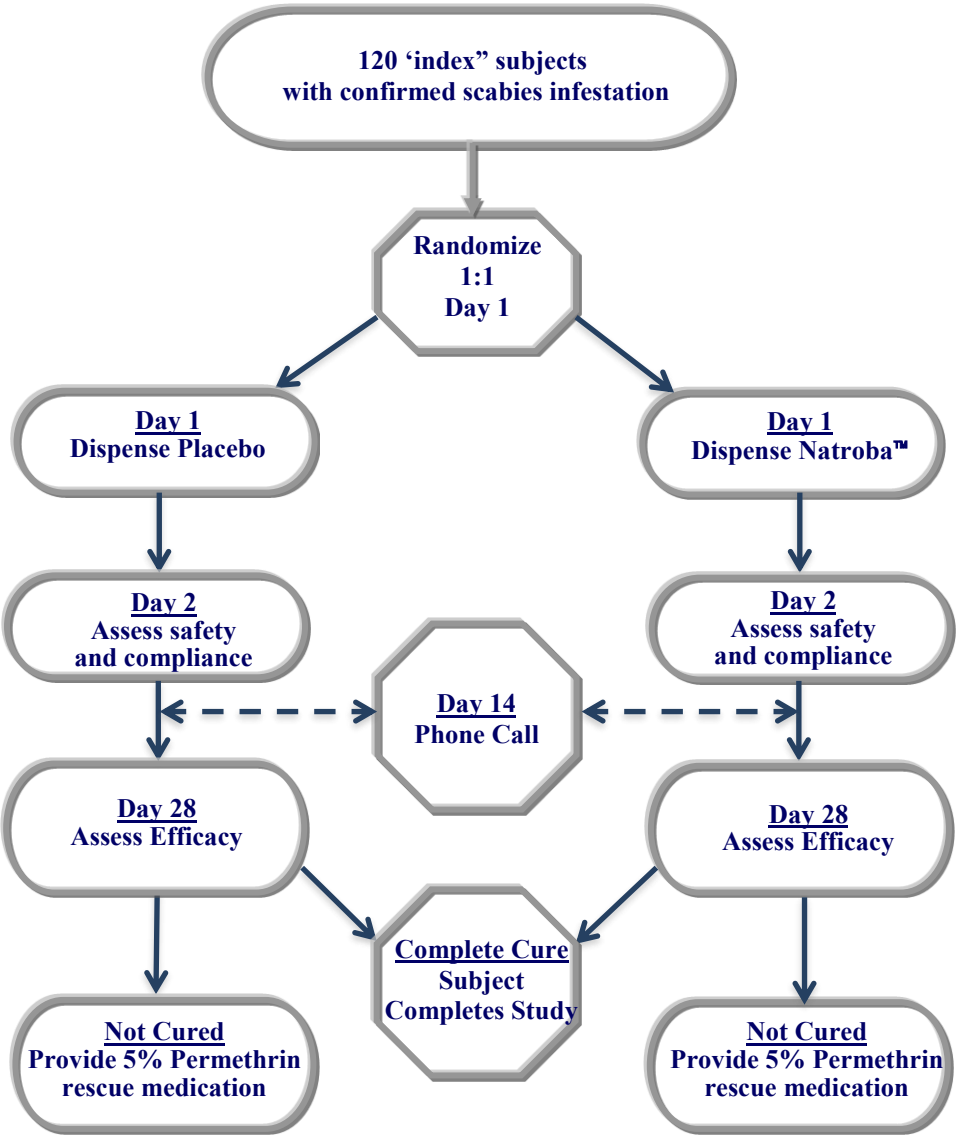
The primary objective is to assess the safety and efficacy of topical Natroba™ (spinosad) versus Placebo for the complete cure of scabies after a single treatment.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

The study is a double blind, two-arm, 28-day, placebo-controlled study randomizing approximately 120 infested "index" subjects 1:1 to Natroba™ or Placebo in order to have at least 96 subjects completed (Figure 3-1).

Figure 3-1: FLOW DIAGRAM



All members of a household (no more than 6 individuals) with a suspected "index" subject must be screened at the first visit. In this study, "index" subjects are defined as the youngest infested household member (≥4 years). If the household has at least one member with active scabies infestation and meet all other criteria, they must all agree to participate in the study. Household members who do not present with scabies at the screening visit must also agree to apply the same blinded investigational product (IP) as household members who present with scabies (see Table 6-1 Schedule of Procedures for status assessment). All household members must agree to participate in the study or none will be enrolled. Screening procedures include informed consent, medication and medical history, urine pregnancy test for females of childbearing potential, scabies assessment (visual evidence of burrows, inflammatory/non-inflammatory lesions and pruritus), microscopic examination of skin scraping or dermoscopy to demonstrate the presence of mites, eggs, and/or scybala (dermatoscopy must confirm burrows), vital signs, general skin and eye assessment, randomization, and IP dispensing and instruction.

After screening on Day 1, all randomized subjects will be dispensed IP (Natroba™ or Placebo) to apply at home later the same day as a single treatment over the entire body from the neck down to the toes (including the soles of the feet) and to the scalp (if balding) or hairline, temples and forehead on the same day. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver. Subjects will rub the treatment into the skin followed by a 10-minute wait period before getting dressed. Showering or bathing must not occur earlier than 6 hours after treatment and no later than at least 1 hour prior to Day 2 visit.

On Day 2 (Visit 2), all household members will return for general skin and eye assessments of possible irritation, and to confirm that all IP was left on for a minimum of 6 hours before bathing or showering. If a subject reports an adverse event assessed as related by the PI on Day 2 (Visit 2) then a follow-up visit with the investigator must be scheduled within 7 days of visit. All household members will receive a well-being phone call on Day 14 to continue to emphasize instructions to prevent re-infestation, determine if any concomitant medications have been used, and check for adverse events. If a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call, then a follow-up visit with the investigator must be scheduled within 7 days of phone call.

On Day 28 (Visit 3), all household members will return to the clinic for safety and efficacy assessments. The primary endpoint of complete cure as well as the key secondary endpoint to determine improvement based on lesion count will be assessed in the "index" subject and any infested household members. If the infested subject is completely cured at Day 28, he or she will have completed the study and termination procedures will be conducted. If the subject is not completely cured at Day 28 (with Natroba™ or Placebo), the subject will receive 5% Permethrin and will be directed to their primary care physician for follow-up.

Safety assessments will be made for all household members and will include monitoring of adverse events (AEs) throughout the study, vital signs recording (Days 1 and 28), and general skin and eye irritation assessments (Days 1, 2, and 28).

The Day 28 procedures will also be completed for early termination (ET) except subjects will not receive rescue Permethrin but will be directed to follow-up with their primary care physician.

The trial design is presented in the Study Flow Diagram (Figure 3-1) and the visit assessments are described in the Schedule of Procedures (Table 6-1).

3.2 Discussion of Study Design

The phase 3 study design is a generally accepted clinical approach to provide sufficient pivotal results for the evaluation of safety and efficacy. The design for this trial is similar to the phase 3 trials evaluating efficacy of Natroba™ Topical Suspension for treatment of head lice except that in this study the subjects will receive only one application of Natroba™ Topical Suspension.[3] In the two phase 3 studies of individuals with lice, all subjects who were treated on Day 0 returned for efficacy evaluation at Day 7. Subjects with live lice present at Day 7 received a second treatment. Subjects who were lice free on Day 7 were to return on Day 14 for evaluation. Subjects with live lice and who received a second treatment on Day 7 were to return on Days 14 and 21 for evaluation. Efficacy was assessed as the proportion of primary subjects who were free of live lice 14 days after the initial and/or final treatment.

The primary efficacy endpoint will be the proportion of "index" subjects completely cured of scabies by Day 28 after a single application of IP on Day 1. In households where efficacy results are likely to be correlated, selecting one subject ("index" subject) from each unit provides for efficacy results that are more independent. These subjects are selected according to a consistent criterion; in this study "index" subjects will be defined as the youngest (≥4 years) infested member of the household. Thus the primary analysis population will be the "index" intent-to-treat (I-ITT) population which is defined as all randomized "index" subjects regardless of whether they have had any post-baseline assessments and the primary efficacy endpoint will be the proportion of "index" subjects completely cured of scabies by Day 28.

A large open-label, randomized, comparative, parallel clinical trial conducted in 315 patients with uncomplicated scabies assessed the efficacy and safety of topical Permethrin, oral ivermectin, and topical ivermectin.[5] The first group received Permethrin 5% cream as single application, second group received tablet ivermectin 200 mcg/kg as single dose, and third group received ivermectin 1% lotion as single application. All the patients received anti-histaminic for pruritus. The patients were followed up at intervals of 1, 2, 3, and 4 weeks. Primary efficacy variable was clinical cure of lesions. Statistical analysis was done by chi square test and one-way

ANOVA test. At the end of first week, cure rate was 74.8% in Permethrin group, 30% in oral ivermectin group, and 69.3% in topical ivermectin group ($P < 0.05$). At the end of second week, cure rate was 99% in Permethrin group, 63% in oral ivermectin group, and 100% in topical ivermectin group ($P < 0.05$). At the end of third week, 100% cure rate was observed in Permethrin and topical ivermectin group while 99% in oral ivermectin group ($P = 0.367$). While oral ivermectin was found to be significantly less effective than the 2 topical treatments, there was no difference in effectiveness of topical Permethrin and topical ivermectin, each achieving a faster cure rate than oral ivermectin with one treatment.

Based on the safety and efficacy of Natroba™ (spinosad) Topical Suspension (0.9%) in the treatment of head lice,[3] and published trials of other scabicides,[6,7,8] the present study is designed to evaluate pivotal phase 3 data on the safety and efficacy of a single topical application of Natroba™. The effectiveness of Natroba™ (spinosad) will be compared to that of a Placebo control at 28 days. If complete cure is not attained at 28 days, 5% Permethrin will be administered to those subjects and the subjects will be directed to their primary care physician for follow up.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

The study will enroll approximately 120 "index" subjects to ensure that at least 96 subjects complete the study. Subjects will be recruited from the general population, meeting criteria as described below. All subjects from a single household may be enrolled provided there are 6 or fewer members and all enrolled members meet the criteria below. All household members/parents/guardians will be asked to attend Visit 1 and to sign appropriate Informed Consent forms (IC).

4.1 Inclusion Criteria

All household members who have provided written informed consent and an authorization for disclosure of protected health information must meet all of the following criteria to qualify for entry into the study:

1. Male or female, age 4 years and upward.
2. At least one household member must have active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic examination of skin scraping or dermatoscopy to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.
3. Generally in good health based on medical history and clinical assessments.
4. Normal-appearing skin in noninfested areas.
5. No history of chronic or recurrent dermatologic disease.
6. Willingness to comply with the study procedures including application of study treatment at home as instructed.
7. Willing and able to practice an acceptable measure of contraception during the study, if female of childbearing potential. Examples of acceptable contraceptive methods include abstinence, intrauterine device (IUD), double barrier method, oral or implantable or injectable contraceptives. Must have been using systemic (oral, injectable, or implantable) contraceptives for at least 3 months. If abstinent and planning to become sexually active must agree to use a double barrier method.
8. Subject agrees to inform their sexual partners to seek an examination for scabies and treatment if, and when, symptoms present.

9. Household residents must be 6 or fewer and all residents must be willing to attend clinic visits and be randomized to treatment (blinded, but same for all).

4.2 Exclusion Criteria

All household members must be excluded if any of the following conditions are met:

1. Household has greater than 6 residents.
2. Has a household member(s) who is not willing or not eligible to enroll.
3. Presence of scabies on the scalp.
4. Presence of crusted scabies (Norwegian scabies).
5. Allergies or intolerance to ingredients in the investigational product (IPs).
6. Current pregnancy (as assessed by urine pregnancy test) or currently nursing.
7. The household has sexually active subjects who do not agree to restrict prolonged skin to skin contact with non-household members during the trial period.
8. Known renal or hepatic impairment.
9. Treatment with scabicide within the prior 4 weeks.
10. Immunodeficiency (including HIV infection) as reported by the subject in Medical History.
11. Signs or symptoms of systemic infection.
12. Administration of systemic therapy for infectious disease within the prior 2 weeks.
13. Receipt of any IP within the prior 4 weeks.
14. Any other conditions that, at the investigator's discretion, may interfere with the study conduct, or which might confound the interpretation of the study results, or which may put the subject at undue risk.
15. Does not have a known household affiliation with their household members (stays in one household inconsistently, i.e., sleeps at one place several nights and then other places on other nights).
16. Household member is unwilling to treat scabies.

4.3 Subject Withdrawal Criteria

Subjects may be removed from the study for reasons including the following:

1. Significant protocol violation on the part of the Investigator or subject.

2. Significant noncompliance on the part of the subject as determined by the Investigator in consultation with the Medical Monitor.
3. Subject withdrawal of consent.
4. During the study, subject has the need for medications, supplements, or other products that are excluded (see Section 7.4, "Prohibited Medications").
5. Occurrence of any AE or condition that could, in the Investigator's opinion, interfere with the evaluation of the treatment effect or put the subject at undue risk.

5 STUDY TREATMENTS

5.1 Identity of Investigational Products

The IPs for the study are Natroba™ (spinosad) Topical Suspension (0.9%) and Placebo control. Both of the IPs will be manufactured by Ei LLC, Kannapolis, NC and provided by ParaPRO LLC, Carmel, IN.

Clinical packaging will be a 4-oz. High Density Polyethylene (HDPE) bottle with an orifice reducing plug and a screw on cap with liner.

Natroba™ Topical Suspension contains 9 mg spinosad per gram in a viscous, slightly opaque, light orange colored vehicle consisting of water, isopropyl alcohol, benzyl alcohol, hexylene glycol, propylene glycol, cetearyl alcohol, stearalkonium chloride, ceteareth-20, hydroxyethyl cellulose, butylated hydroxytoluene, FD&C Yellow #6. The vehicle (Placebo) lacks spinosad.

The methods used in, and the facilities and controls used for the manufacturing, processing, packaging, and holding of this drug substance conform with Current Good Manufacturing Practices (cGMP) in accordance with 21 CFR Parts 210 and 211. ParaPRO LLC will maintain certificates of analysis for each ingredient, documenting its purity and potency, and will provide Concentrics Research with Certificates of Analysis for both test and control products.

The following will be printed on the product label (Appendix 1):

SHAKE WELL BEFORE USE

XX

Protocol: SPN-304-15
INVESTIGATIONAL PRODUCT FOR THE TREATMENT OF SCABIES

Site # ____ / Screen # ____ / Subject Initials: _____

Date Dispensed: _____

Caution – New Drug: Limited by Federal (U.S.) Law to Investigational Use

Store at Room Temperature 15° C – 30 ° C (59° F – 86° F)

5.2 Investigational Product Storage and Accountability

Investigational product will be stored at room temperature 15 °C – 30 °C (59 °F – 86 °F) in a locked area with limited access.

All IP will be shipped to the study site(s). The Principal Investigator or designee will inventory and acknowledge receipt of all shipments of IP. The Principal Investigator or designee must keep accurate records of IP via the master IP accountability logs and the subject IP accountability logs. The PI or designee must also maintain a record of all IP supplied to all subjects. The PI or designee must also maintain a record of 5% Permethrin supplied to household members for use as a rescue medication. Supplies of IP will be checked and accountability records will be reviewed by the Clinical Research Associate (CRA) at monitoring visits. The original, completed accountability logs will be collected by the CRA at the close of the study. At the end of the study, all unused, partially used, empty or unopened kits or bottles will be returned to ParaPRO LLC or its designee for destruction. A written explanation will be required for any missing product.

Investigational supplies are to be used only in accordance with this protocol and under supervision of the Principal Investigator. All records must be available for inspection by Concentrics Research and ParaPRO LLC personnel or their designees, and are subject to inspections by the regulatory authorities (e.g., FDA) at any time.

5.3 Methods of Assigning Subjects to Treatment Groups

As "index" subjects and other infested or non-infested household members become eligible for randomization at Visit 1 (Day 1), the site will locally assign a unique subject number to each of the qualified household members that combines a 3-digit site number (xxx), a 2-digit household number (yy), and a 2-digit household member number (zz). For example, the first subject of the first household at site 101 would be randomized to subject number 101-01-01, the second member to 101-01-02, the third member to 101-01-03, and so on. Since all household members receive the same treatment, each household is randomized to either Natroba™ (spinosad) or Placebo control. Non-infested household members will be assigned the same IP treatment as the infested members and will be assigned a subject number and randomization number. The assigned subject numbers to each household will correspond to unique bottle numbers on a scheme that unblinded site personnel will assign and distribute to ensure approximately equal randomization of households to either treatment. Subject numbers must not be re-used once assigned, even if the subject does not take the IP.

5.4 Administration of Investigational Product

For both treatment groups, the blinded Natroba™ (spinosad) or Placebo control will be administered by the subject on Day 1 at the subject's home. All "index" and other infested and non-infested household members will be assigned the same IP treatment, either blinded Natroba™ (spinosad) or Placebo control. The "index" subjects and all household members will be instructed to apply the IP over entire body from the neck down to the toes (including the soles

of the feet) and to the scalp (if balding) or hairline, temples, and forehead. Subjects should not shower for at least 6 hours after application. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver.

If complete cure is not achieved by Day 28 visit, 5% Permethrin will be dispensed to all uncured subjects and they will be directed to their primary care physician for follow up. All uncured subjects will be instructed to apply the 5% Permethrin as per manufacturer's instructions. Subjects who early terminate (ET) will not receive 5% Permethrin and will be directed to their primary care physician for follow up.

5.5 Treatment Accountability and Compliance

At Visit 1, each subject's bottle of IP will be weighed and recorded (application instructions provided) as well as the height and weight of the subject before each subject takes the IP home. All household members will be provided with the same blinded study treatment. The IP will be applied at the subject's home.

Each subject's bottle will be returned the next day at Visit 2. An accounting of the amount of IP used by the subject (by weight) will be documented by the clinic staff. At Visit 2, subjects will be asked to confirm that IP was applied from neck down and to the scalp (if balding) or hairline, temples, and forehead and washed/rinsed off no earlier than 6 hours after application, and no later than at least 1 hour before Visit 2. The used IP bottle will be collected at Visit 3 if not returned at Visit 2.

If subjects are not completely cured by Visit 3 (Day 28), the 5% Permethrin and application instructions will be provided at this visit and subjects will be directed to follow-up with their primary care physician.

5.6 Blinding and Unblinding Method

Eligible households will be assigned to either Natroba™ (spinosad) or Placebo control, by pre-specified un-blinded site personnel. The un-blinded site personnel will assign all eligible members from the same household to the same treatment group. While the treatment bottles for each household will have unique numbers, the numbers for that household will correspond to a specific treatment, Natroba™ (spinosad) or Placebo control. Un-blinded site staff will maintain the randomization scheme with treatment code and associated bottle numbers, and will not reveal the information to the subjects, blinded study personnel or ParaPRO LLC until after the database lock.

In an emergency, the study blind may be broken only if:

- in the opinion of the investigator and/or the Medical Monitor, it is in the subject's best interest to do so;
- knowledge of the treatment will alter the clinical management of the subject;
- approval has been granted by the Medical Monitor and/or ParaPRO LLC.

Whenever possible, the Medical Monitor should be notified prior to unblinding a treatment assignment. In the event that unblinding is necessary for the medical management of the subject, the pre-specified un-blinded site personnel will access the randomization code by a treatment code list provided by Concentrics Research to each site. If a treatment assignment is unblinded, the date and reason for the unblinding must be recorded on the subject's source document, and the Medical Monitor notified within 24 hours. The emergency contact telephone number for the Medical Monitor, Dr. William Miller, is (800) 210-5734. If Dr. Miller's phone is not answered at the time of your call, PLEASE leave a message so Dr. Miller can return your call immediately.

For those subjects not completely cured by Day 28, 5% Permethrin will be dispensed and the subjects will be directed to their primary care physician for follow up.

6 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Table 6.1 represents the schedule of procedures and assessments at each of the scheduled visits. Details of each visit are provided in Sections 6.1 through 6.5.

Table 6-1 SCHEDULE OF PROCEDURES AND ASSESSMENTS

Period	**Screening, Randomization and Treatment**	**Treatment/Follow-up**				
Visit	**1**	**2**	**AE follow-up**	**Phone Call**	**AE follow-up**	**3**
Day ±	1	2	3+6	14 ± 2	14 +7[12]	28 ± 2/ET
Informed consent	X					
Prior medications	X					
Medical history	X					
Urine pregnancy test[1]	X					X
Scabies diagnosis[2]	X					
Efficacy assessments[3]						X
Vital signs[4]	X					X
General skin assessment[5]	X	X				X
Eye irritation assessment[5]	X	X				X
Review eligibility criteria	X					
Randomization	X					
Weigh and dispense IP bottle; provide application instructions[6]	X[8]					
Instruct on waiting ≥6 hrs post-treatment (IP) before showering[6]	X					
Collect and weigh used IP bottle		X				
Review subject compliance[7]		X				X[8]
Instructions to prevent re-infestation	X	X		X		
Concomitant medications		X		X		X
Adverse events[9]		X	X[11]	X	X[11]	X
5% Permethrin dispensed to subjects not completely cured at Day 28						X[10]

ET = Early Termination; IP = investigational product.

1. Only for females of childbearing potential.
2. Scabies diagnosis (Inclusion #2) – At least one household member with active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic examination of skin scraping or dermatoscopy

to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.

3. Primary Endpoint – Complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows.
4. Vital signs – height (only Visit 1), weight, blood pressure (BP), and heart rate.
5. Assessment at Visit 1 for eligibility (skin) and eye for baseline, Visit 2 for skin and eye irritation assessments and to confirm IP was washed off, and Visit 3/ET (if applicable) for skin and eye irritation. See Section 7.7 for rating eye irritation.
6. IP Treatment – dispense IP and instruct subject to administer single topical application of IP over entire body from the neck down to the toes (including soles of the feet) and on the scalp/hairline, temples and forehead while at home. Subjects will not shower for at least 6 hours after application and no later than at least 1 hour before Day 2 visit. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver.
7. Confirm that all IP was left on for a minimum of 6 hours before bathing or showering and washed off at least 1 hour before Day 2 visit. Instruct/re-instruct subjects how to prevent re-infestation, to stay in one household, as well as to follow all study procedures and expectations.
8. Collect and weigh used bottle if not collected at Visit 2.
9. Assessed starting post-treatment. Investigators will follow all AEs until the final study visit (Day 28). All SAEs, and all AEs deemed by the Investigator to be related to IP or treatment, will be followed until the event has resolved (even if beyond Day 28).
10. Subjects who are not completely cured at this visit (Day 28) will be provided with 5% Permethrin as rescue medication. Subjects who terminated early will not receive rescue medication. All subjects will be directed to their primary care physician for follow-up.
11. If a subject reports an adverse event assessed as related by the PI on Day 2 (Visit 2) then a follow-up visit with the investigator must be scheduled within 7 days of visit. If a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call, then a follow-up visit with the investigator must be scheduled within 7 days of phone call.
12. It is intended for the AE follow-up to occur within 7 days of the day 14 call. The Day 14 call may occur between study day 12 and 16.

6.1 Screening, Randomization and Treatment (Visit 1; Day 1)

Procedures as identified in Table 6-1:

- Informed consent
- Prior medications
- Medical history
- Urine pregnancy test (females of child-bearing potential only)
- Scabies assessment
- Vital signs (height at Visit 1 only)
- General skin assessment for eligibility
- Eye assessment
- Review eligibility criteria
- Randomization
- Weigh, dispense and instruct on IP application at home the same day*
- Instruct on showering ≥6 hours post-treatment and at least 1 hour prior to Visit 2
- Instructions to prevent re-infestation
- Concomitant medications

*Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver.

6.2 Follow-up Safety Assessment Visit (Visit 2, Day 2)

- General skin and eye assessments for irritation and wash-off confirmation
- Collect and weigh used IP bottle
- Confirm compliance
- Instructions to prevent re-infestation
- Concomitant medications
- Adverse events

6.3 AE Follow-up Visit (Day 3 + 6 days; conducted only if a subject reports an adverse event assessed as related by the PI on Day 2)

- PI assessment of reported AE

6.4 Phone Call (Day 14 +/- 2 days)

- Instructions to prevent re-infestation
- Concomitant medications
- Adverse events

6.5 AE Follow-up Visit (Day 14 + 7 days; conducted only if a subject reports an adverse event assessed as related by the PI on the Day 14 well-being phone call)

- PI assessment of reported AE

6.6 Final Visit (Visit 3/ET, Day 28 + 2 days)

- Urine Pregnancy Test (females of child bearing potential)
- Efficacy assessments
- Vital signs
- General skin and eye assessments for irritation
- Review subject compliance
- Concomitant medications
- Adverse events
- If subjects are not completely cured at this visit (Day 28), those subjects will be provided 5% Permethrin as rescue medication.
- For those subjects with an ET visit, 5% Permethrin will not be dispensed and the PI will refer the subject to their primary care physician for follow-up.

6.7 Early Termination Procedures

The term "Early Termination" refers to a subject's non-completion of a study whether by his or her own choice or the investigator's decision or due to discontinuation of the study by ParaPRO LLC. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Investigator to keep the subject in the study. Should the subject decide to withdraw, an early termination visit should be conducted, which will include all procedures

normally done at Visit 3. The ET subject will not be dispensed 5% Permethrin and the PI will refer the subject to their primary care physician for follow-up.

The primary reason for a subject withdrawing prematurely should be selected from the following categories:

***Adverse Event or Serious Adverse Event*—**events that are associated with discontinuation.

***Noncompliance with protocol*—**the subject failed to adhere to the protocol requirements. The deviation necessitated premature termination from the study.

***Withdrawal of Consent*—**subject desires to withdraw from further participation in the study in the absence of an adverse event or a medical need to withdraw.

***Lost to Follow-up*—**the subject did not return for one or more follow-up visit(s) following dispensing of test drug. The reason was unknown and appropriate due diligence was exerted by the investigator to contact the subject and encourage their return.

***Other*—**causes of premature termination from the study other than the above, such as theft or loss of IP, termination of study by ParaPRO LLC, etc. The details of the premature termination in this "other" category should be documented fully.

The investigator should notify Concentrics Research promptly when a subject is withdrawn, or if the study is stopped at his/her site by the IRB or if the investigator elects to stop the study.

6.8 Subject Completion Criteria

Successful completion of the study by "index" subjects will occur at Day 28 (Visit 3) if the "index" subject is completely cured of scabies. Other household members will complete the study at Day 28 after safety assessments are completed.

6.9 Protocol Deviations

This study is intended to be conducted as described in this protocol. Any changes/deviations to the protocol must be reported to the IRB (Schulman IRB Cincinnati, OH 45242). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must also notify the Medical Monitor within 24 hours from when the deviation was identified.

7 DETAILED DESCRIPTION OF ASSESSMENTS

7.1 Informed Consent

Written informed consent will be obtained from subjects who are 12 years of age and older as well as the parent or legal guardian of subjects who are 4-17 years of age before any study procedures are performed. In addition to the parent or legal guardian signing the informed consent, verbal and written assent will be obtained from subjects who are between the ages of 7-11 years of age. Assent is not required for subjects 4-6 years of age; however, the parent or legal guardian must sign consent. All potential subjects for the study (or their legal guardians) will be given a copy of the Institutional Review Board (IRB)-approved informed consent form to read. The IRB is Schulman IRB (Cincinnati, OH 45242).

The assent and/or consent forms will be discussed in detail with each potentially eligible subject and the parent or legal guardian of subjects 4-17 years of age, if applicable. The PI or qualified designee will explain all aspects of the study in lay language and answer all the subject's questions regarding the study. The PI or designee will inform the subject as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his or her medical records may be reviewed. The PI or designee will also explain that the subject is completely free to refuse to enter the study or to withdraw from it at any time. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

No study procedures will be performed nor IPs released to any subject who has not signed the assent or IC form or whose parent or legal guardian has not signed the IC form.

7.2 Medical History

A complete medical history will be obtained at Screening (Visit 1).

7.3 Prior Medications and Concomitant Medications

Investigator’s need to be aware that patients often have severe pruritus and will be prescribed medications as well as take OTC medications to treat this condition. The PI needs to inform the subject of prohibited topical medications used for itching or other indication, including over-the-counter (OTC) cortisone products, as these may interfere with efficacy evaluations. Non-medicated lotions are allowed after IP is washed off (e.g., non-scented, hypoallergenic, etc.). Subjects will be instructed not to take any oral prescription medications without prior consultation with the Investigator unless their primary physician otherwise instructs. Oral Benadryl® (diphenhydramine) and other oral OTC anti-pruritics are allowed for itch relief. Subjects will be instructed to tell their primary physician of their participation in this study if they consult their physician during the study. Any therapy taken by the subject in the 4 weeks before randomization (Visit 1) will be reported as prior medication. Any therapy started or

stopped by the subject during the study after randomization will be regarded as concomitant therapy.

All prior and concomitant medications including topical treatments (prescription and over the counter, vitamins, and mineral supplements, and/or herbs) will be documented and must include the following information:

- Medication name
- Indication
- Start date
- Stop date or "Ongoing"

7.4 Prohibited Medications

Subjects should not use any scabicide within 4 weeks before Visit 1, or use any scabicide, or rescue Permethrin, prescription or OTC medicated lotions, other than the IP during the study, through Day 28. There will be no washout of prohibited medications, subjects will be excluded or withdrawn from the study for use of prohibited medications.

7.5 Pregnancy and Contraceptive Use

Urine pregnancy tests will be conducted on women of childbearing potential at screening (Visit 1) and end of study (Visit 3/ET). Such subjects should be willing and able to practice an acceptable method of contraception during the study. Examples of acceptable contraceptive methods include abstinence, intrauterine device (IUD), double barrier method, oral or implantable or injectable contraceptives. Must have been using systemic (oral, injectable, or implantable) contraceptives for at least 3 months. If abstinence is their primary method of birth control they should be instructed to use a double barrier method if they become sexually active with another household member.

7.6 Scabies Assessment

Skin will be examined at Visits 1 and 3/ET to establish positive or negative evidence of active scabies infestation.

- Scabies diagnosis – active scabies infestation confirmed by clinical signs and symptoms (evidence of burrows or presence of scabies inflammatory/non-inflammatory lesions and pruritus) as well as by microscopic examination of skin scraping or dermatoscopy to demonstrate the presence of mites, eggs, and/or scybala. If dermatoscopy is used it should also confirm there are burrows on the skin.

- Primary Efficacy Endpoint – complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows.

7.7 General Skin and Eye Assessments

At Visit 1, the skin will be assessed to determine eligibility – no evidence of crusted scabies, normal skin in non-infested areas. At Visits 1, and 2, the skin and eye assessments will include documentation of presence or absence of irritation, and verbal subject-reported verification that the treatment topical suspension remained on for at least 6 hours before being washed off. At Visit 3/ET, skin and eye assessments will include evidence of irritation.

Eye irritation will be rated:

0 no irritation

1 mild scleral, lid and/or conjunctiva injection

2 moderate scleral and or lid injection with conjunctival erythema

3 severe scleral and/or lid injection with conjunctival erythema and purulent drainage

7.8 Application of IP

The bottle will be weighed before and after application. One bottle of IP (blinded Natroba™ [spinosad] or Placebo control) contains 4-oz. of treatment product. The subject should use as much of one bottle as needed. The subject should apply a thin layer of IP from the neck down to the toes (including soles of the feet) and to the scalp (if balding) or hairline, temples, and forehead at their home on the same day it is dispensed on Visit 1. The IP should be allowed to soak into the skin or dry for 10 minutes before getting dressed. Subjects less than 12 years of age should be assisted with administration by a parent, guardian or caregiver. Showering or bathing should occur no earlier than 6 hours after treatment and no later than at least 1 hour before Visit 2.

7.9 Vital Signs

Height (Visit 1 only), weight, resting blood pressure (BP) and heart rate will be measured at Visits 1 and 3/ET.

7.10 Eligibility Review

Eligibility criteria will be reviewed at Visit 1 prior to randomization, and the subject should qualify prior to randomization.

Screen Failure: A screen failure is defined as a subject who consented but who has not been randomized. Screen failures may re-screen after review and approval by the sponsor. Re-screening may also be necessary due to timing/scheduling or washout of other treatments (except scabicides which exclude the subject) that may have occurred within the prior 4 weeks.

7.11 Randomization and Treatment Assignment

Eligible subjects will be assigned to either treatment group, Natroba™ (spinosad) or Placebo control, by pre-specified un-blinded site personnel that may perform no other study specific duties. The un-blinded site personnel will assign all members from the same household to the same treatment group. The assigned subject numbers in each household will correspond to unique bottle numbers on a scheme that unblinded site personnel will assign and distribute to ensure approximately equal randomization of households to either treatment. Subjects, blinded site personnel and ParaPRO LLC will remain blinded to the treatment until after database lock. Randomization will be stratified by study site.

7.12 Counseling to Prevent Re-Infestation

Subjects should be informed about methods to minimize risk of re-infestation: including avoiding skin contact with others who are infested and avoiding bedding or linens of an infested person, and simultaneous treatment of all household contacts. The following information from the Centers for Disease Control and Prevention may be used as reference:

“When a person is infested with scabies mites the first time, symptoms may not appear for up to two months after being infested. However, an infested person can transmit scabies, even if they do not have symptoms. Scabies usually is passed by direct, prolonged skin-to-skin contact with an infested person. However, a person with crusted (Norwegian) scabies can spread the infestation by brief skin-to-skin contact or by exposure to bedding, clothing, or even furniture that he/she has used.

Scabies is prevented by avoiding direct skin-to-skin contact with an infested person or with items such as clothing or bedding used by an infested person. Bedding and clothing worn or used next to the skin anytime during the 3 days before treatment should be machine washed and dried using the hot water and hot dryer cycles or be dry-cleaned. Items that cannot be dry-cleaned or laundered can be disinfested by storing in a closed plastic bag for several days to a week. Scabies mites generally do not survive more than 2 to 3 days away from human skin. Children and adults usually can return to child care, school, or work the day after treatment.”

7.13 Prophylactic and Rescue 5% Permethrin

All household members that are not infested at the screening visit will be given the same blinded study treatment as household members that are infested. Subjects not cured at Day 28 will be provided with 5% Permethrin as rescue medication, which is the recommended treatment per the current standard of care, and will be directed to their primary care physician for follow-up. Subjects with an ET visit will not receive rescue medication and will be directed to their primary care physician for follow-up.

7.14 Study Compliance

Study compliance will be confirmed at Visit 2.

8 STATISTICAL METHODS

8.1 Sample Size Determination

Approximately 120 "index" subjects will be enrolled (including possible 20% attrition) from 120 households and randomized 1:1 to each of Natroba™ (spinosad) and Placebo control. The index subject will be the youngest infested member of a household (≥4 years). Referencing to the Sponsor's Proof of Concept (POC) study (SPN-401-12) and published literature,[5-10] out of 60 completed subjects, the cure rate is 70% for Natroba™ and 30% for Placebo control. Based upon a reasonable assumption of 60% cure rate for Natroba™ and 30% for placebo, a sample size of 48 study-completed "index" subjects per group will provide 80% power to declare the non-equivalency using a delta of 30% and Type I error rate of 0.05. Fisher exact test was used to calculate the sample size and the specified power in the following Table 8-1 (PASS 14; 2015, NCSS, LLC., Kaysville, Utah, USA. www.ncss.com).

Table 8-1 SAMPLE SIZE NEEDED TO DECLARE NON-EQUIVALENCY WITH RESPECT TO THE PROPORTION OF SUBJECTS ACHIEVING COMPLETE CURE WITH A TYPE I ERROR RATE=0.05 AND SPECIFIED POWER

Proportion in			Required Sample Size per Group	Power
Natroba ™	Placebo	Difference vs. Placebo		
55%	30%	25%	69	80.4%
60%	30%	30%	48	80.0%
65%	30%	35%	37	80.6%

Assuming a drop-out rate could be at most 20%, 120 subjects should guarantee at least 48 evaluable subjects for each treatment group at Day 28 assessment.

8.2 Randomization

This study will investigate 2 treatment groups: Natroba™ (spinosad) Topical Suspension, 0.9% or Placebo control. A randomization scheme will be used locally at each site (stratified by study site) to obtain a balanced allocation of treatments (approximately 1:1) to the households.

8.3 Analysis Populations

Safety Population

The safety population will comprise all subjects who received one dose of IP. Subjects will be analyzed as treated. The safety population includes the "index" subjects along with any household members enrolled in the study. All safety analyses will utilize the safety population.

Intent-to-Treat Population

The intent-to-treat (ITT) population will comprise all subjects who were randomized regardless of whether they have post-baseline assessments. Subjects will be analyzed as randomized. This population includes the "index" subjects along with any household members enrolled in the study.

Index Intent-to-Treat Population

The "index" intent-to-treat (I-ITT) population will comprise all index subjects who were randomized. Subjects will be analyzed as randomized. The index subject will be the youngest infested member of a household (≥4 years). This analysis population will be used for the efficacy analysis.

Index Per Protocol Population

The "index" Per Protocol (I-PP) population is a subset of the I-ITT population. Index subjects will be excluded from the I-PP population for the following reasons:

1. Protocol deviations that would be in violation with the established Inclusion or Exclusion Criteria.
2. Protocol deviations that could confound the evaluation of efficacy outcomes:
    - Scabies assessment not performed (i.e. burrows, lesions, pruritis, skin scraping).
    - Subject received the wrong treatment.
    - Discontinuation prior to acquisition of Visit 3 (Day 28) efficacy measurements.
3. Protocol deviations that are a result of subject non-compliance:
    - Missed Day 2 appointment.
    - Use of another scabicide during the study.
    - Use of prescription or OTC medicated lotions during the study.

Prior to database lock, a memo will be generated identifying any subjects that were excluded from the I-PP population along with the reason why they were excluded.

8.4 Missing Values

There will be no imputation for missing events and assessments in handling safety data.

If a subject has observed data for complete cure at Day 28, the observed cases (OC) will be used at Day 28. If a subject discontinues the study before Day 28, the imputation method for complete cure at Day 28 depends on the reasons of missing, i.e. informative or non-informative missing. Please refer to the SAP for more details.

For other missing efficacy data at Day 28 (e.g., clinical cure, microscopic cure, new lesions and total lesions), Last Observation Carried Forward (LOCF) imputation will be used.

Details of imputation rules for efficacy analyses and other missing data handling conventions will be included in the SAP.

8.5 Statistical Analyses

A statistical analysis plan (SAP), in addition to this section of the study protocol, will describe statistical methodology for analyses and data reporting. A version of the SAP will be prepared at the same time as the protocol is finalized. However, the primary and secondary efficacy endpoints and analyses on them will not be altered unless agreed upon with the FDA. SAP will be finalized before the database is unblinded.

Data collected in this study will be presented using summary tables, figures, and subject data listings. Summary tables will present data by treatment group and, if applicable, by scheduled time of data collection. Continuous variables will be summarized using descriptive statistics, presenting the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. Figures may be used to support the presentation of certain data.

For efficacy analyses, small study sites may be pooled together. Details on the pooling algorithms are provided in Section 8.5.3.3.

All statistical tests and confidence intervals will be 2-sided at an alpha level of 0.05.

8.5.1 Subject Disposition

The tabulation of number of subjects in each treatment group and overall will be displayed for all subjects who are screened, randomized, and in each analysis population.

The number and percent of subjects who completed or discontinued the study will be displayed for each treatment group and overall together with reasons for early termination. Percentages will be based on the total number of randomized subjects in each treatment group and overall.

8.5.2 Demographics and Baseline Characteristics

Descriptive statistics will be provided for demographic and baseline characteristics (gender, age, race/ethnicity, baseline assessments of scabies infestation, previous infestations, and microscopic results).

8.5.3 Efficacy Analyses

8.5.3.1 Primary Efficacy

The primary efficacy endpoint is the proportion of index subjects completely cured of scabies by Day 28. Complete cure is defined as demonstration of clinical cure (all signs and symptoms have completely resolved, including burrows, inflammatory/non-inflammatory lesions and pruritus) and microscopic or dermatoscopic cure with demonstration of the absence of mites, eggs, and/or scybala, and dermatoscopy negative for burrows.

The primary analysis will be based on the data by Day 28 from the I-ITT population. The number and percentage of index subjects who exhibit complete cure (Yes or No) at Day 28 will be summarized by treatment group. A Cochran-Mantel-Haenszel general association test adjusted by study site (small sites pooled) stratification will be performed to compare the complete cure rates between the two treatment groups.

Sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results using different methods of analysis.

A logistic regression analysis will be used assessing the treatment group differences. The model will include clinical site and treatment group as factors, and possibly additional baseline characteristics or a covariate, if appropriate.

Other additional sensitivity analyses include repeating the above analyses on I-PP population and ITT population.

8.5.3.2 Exploratory Efficacy

All exploratory efficacy endpoints will be summarized by the treatment group at each scheduled visit. Descriptive statistics for continuous variables consists of mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, numbers and percentages will be summarized.

Additional analysis may be performed as appropriate for the following exploratory efficacy endpoints.

Clinical Cure

Clinical cure is the proportion of subjects who exhibit clinical cure at Day 28.

Clinical cure is defined as having all signs and symptoms completely resolved, including inflammatory/non-inflammatory lesions and pruritus.

A Cochran-Mantel-Haenszel general association test adjusted by study site (small sites pooled) stratification will be performed to compare the complete cure rates between the two treatment groups.

This analysis will be performed on the I-ITT population.

Microscopic Cure

Microscopic cure is defined as microscopic or dermatoscopic demonstration of the absence of mites, eggs, and/or scybala, and negative for burrows.

The number and percent of subjects who exhibit microscopic cure (Yes or No) at Day 28 will be presented by treatment group.

Additional analyses can be performed on the I-ITT population by applying a logistic regression model adjusted for baseline factors.

Number of New Lesions

The number of new lesions at Day 28 will be analyzed using a negative binomial regression model to compare the treatment difference. The model will include treatment group and study site (small sites pooled) as fixed factors, and baseline total lesion count as a covariate.

This analysis will be performed on the I-ITT population.

Total Lesion Counts

Total lesion counts will be calculated as the sum of pre-existing lesions and new lesions. The baseline captures the total lesions on the day of first study drug administration.

The change from baseline to Day 28 will be analyzed using an analysis of covariance (ANCOVA) model with treatment and study site (small sites pooled) as factors and baseline total lesion counts as a covariate.

This analysis will be performed on the I-ITT population.

Complete Cure in ITT subjects who were infested at baseline

A subset of subjects in ITT population who were infested at baseline will be summarized to display the proportion of the completely cured subjects.

More analysis can be performed to further examine the treatment differences for this subset of ITT subjects. Details will be provided in the SAP.

8.5.3.3 Pooling of Study Sites

This is a study conducted at multiple study sites. Every effort will be made to have each site enroll at least 8 subjects per arm. In case there are "small" sites with fewer-than-8 "index" subjects, these sites will be pooled together as a single, combined site for efficacy analyses if the combined site has at least 8 "index" subjects per arm. In the situation when the combined site still has less than 8 "index" subjects per arm, the smallest site with at least 8 "index" subjects per arm will be pooled to this combined site for efficacy analyses. The complete cure rates at Day 28 will be summarized descriptively by treatment groups and by sites before and after pooling the sites. Assessment of site-to-site variability will be conducted on the original sites prior to pooling. In addition, the above demographics and baseline characteristics will be presented by site before and after pooling sites.

8.5.4 Safety Analyses

Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by System Organ Class (SOC) and Preferred Term (PT) for each treatment group. All AEs will be captured throughout the study period from the enrollment to the final visit (Visit 3) or the ET visit. Any AEs reported before treatment will be captured as medical history. AEs that occur after the first dose of study treatment will be considered as treatment-emergent adverse events (TEAE). Within each SOC or PT, subjects will be counted only once if they had one or more than one event reported during the treatment period (the subject is counted for the event with the greatest severity).

Adverse events will be summarized by presenting:

- the number and percentage of subjects experiencing any TEAE
- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT
- the number and percentage of subjects experiencing any SAE
- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT and maximum severity

- the number and percentage of subjects experiencing any TEAE grouped by SOC and PT and maximum relationship to IP
- the number and percentage of subjects experiencing any TEAE leading to study medication discontinuation.
- The number and percentages of subjects experiencing any unexpected life-threatening adverse reaction

A listing will be produced for all subjects who reported SAEs or who discontinued study medication due to TEAEs.

All AEs (ie, pretreatment AEs and TEAEs) will be listed by subject. However, only TEAEs will be included in the summary tables.

General Skin and Eye Irritation Assessments

Skin and eye irritation will be captured as adverse events, as defined in Section 9.1. Eye irritation assessment ratings will be summarized descriptively for each treatment group by visit.

Vital Signs

Vital signs will be summarized descriptively for each treatment group by visit for the observed value as well as for the change from baseline value.

Prior and Concomitant Medications

The number and percent of subjects who took prior medications will be summarized descriptively by the ATC class and Preferred Term as coded in the WHO-Drug dictionary (WHO-DD) for each treatment group. Concomitant medications will be summarized similarly.

9 ADVERSE EVENT MONITORING

9.1 Definition

An AE is defined as any untoward medical occurrence in a subject or clinical investigation (vital signs, physical change, etc.) following the subject's first dose of IP that does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable or unintended sign (including an abnormal finding on vital signs, physical change, etc.), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

This includes any adverse occurrence that is new in onset or aggravated in severity, duration or frequency from the baseline condition (including the physical examination), or abnormal results of diagnostic procedures (including vital sign abnormalities).

Examples of untoward medical events that should be considered AEs are those that:

- resulted in discontinuation from the study,
- required treatment or any other therapeutic intervention,
- required further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality),
- are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

Examples of what an AE is not:

- A surgical procedure
- A situation where an untoward event did not occur, (e.g. a social hospitalization)
- The disease being studied, unless progression is more severe than anticipated
- Lack of efficacy
- Baseline conditions that have not worsened in severity or frequency
- Abnormal findings or test results (unless considered clinically significant in the opinion of the investigator or specifically defined elsewhere in the protocol) related to the disease being studied (unless more severe than expected).

9.2 Procedures

Subjects will be queried at every visit through the last visit regarding the occurrence and nature of any AEs. All AEs will be reported, whether or not they are deemed to be related to IP.

A description of the event or diagnosis including dates, severity, relationship to the IP, action taken and outcome, and whether or not the event was also serious, must be reported on the AE Case Report Form (CRF) for each adverse event recorded in the subject's chart.

9.3 Severity

Adverse events are graded according to seriousness and severity. The seriousness of an event is determined by the regulatory criteria in Section 9.7.

The Investigator will evaluate the severity of each AE. Adverse event severity will be graded as follows:

Mild: Awareness of symptoms but easily tolerated

Moderate: Discomfort enough to interfere with but not prevent daily activity

Severe: Unable to perform usual activity

9.4 Relationship

The Investigator will judge the likelihood that the AE was related to the IP according to the following criteria:

- Not related: There is no possible temporal and/or causal relationship to the IP.
- Related: There is a possible temporal and/or causal relationship to the IP.

9.5 Action Taken and Outcome

The Action Taken with IP for every AE will be reported as Dose Not Changed or Dose Withdrawn. The Outcome of each AE will be entered as either: Recovered/Resolved, Recovered/Resolved with Sequelae, Not Recovered/Not Resolved, Fatal, or Unknown.

9.6 Adverse Event Follow-up

Investigators will follow unrelated AEs until the final study visit (Day 14 or Day 28). All SAEs, and AEs deemed by the Investigator to be related to IP or treatment, will be followed until the event has resolved.

9.7 Serious Adverse Events

An AE that results in any of the following outcomes is serious:

- Death (note that death is the outcome of an SAE and the cause of death should be listed as the AE)
- Life-threatening event. An event, in the view of either the investigator or sponsor, which places the patient 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)

- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity, permanent damage or disability or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Other important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization for elective surgery for a prior condition that did not worsen or for social reasons will not be treated as serious.

9.7.1 Serious Adverse Event Reporting

Any SAE which occurs after the first dose is administered until the last visit must be reported to Concentrics Research whether or not it is judged related to the IP. Concentrics Research must be notified within 24 hours after the site/investigator becomes aware of the SAE. Concentrics Research has the responsibility to notify ParaPRO LLC of the event.

If the Principal Investigator determines that the event is serious, the following procedures are to be implemented:

- The Investigator will report the SAE directly to Concentrics Research via the SAE fax number (**317-672-1271)**, and/or by emailing to gio.events.reporting@concentricsresearch.com .

  Concentrics Research's Medical Monitor contact is:

  Medical Monitor

  William Miller, MD
  Medical Director
  Concentrics Research
  9335 Delegates Row
  Indianapolis, IN 46240
  Cell: 800-210-5734
  Email: bill.miller@concentricsresearch.com

- Investigator will provide, at a minimum, the protocol number, subject's initials, subject

number, date of the SAE, SAE term and relationship to IP. The SAE report form should be submitted with any supporting data available or copies of CRF pages.

Schulman IRB will be notified of the SAE by the site within the timeframes described below:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 10 business days of the investigator becoming aware of the event
2. Any other unanticipated problem should be reported to the IRB within 10 business days of the investigator becoming aware of the problem.

An initial report followed promptly by a complete report will be forwarded Schulman IRB.

9.7.2 Serious Adverse Event Follow-up

Investigators will follow all SAEs until the SAE has resolved.

The Investigator and Medical Monitor will determine if additional follow-up is required. Follow-up information relating to an SAE must be submitted to Concentrics Research as soon as additional data related to the event are available. All efforts must be taken to obtain follow-up information promptly.

Follow-up information may consist of:

- A hospital discharge summary for subjects who are hospitalized or hospitalized over a prolonged period due to the SAE. If possible, the discharge summary should be obtained when it becomes available.
- A copy of the autopsy report, if a death occurs and an autopsy is performed, should be obtained if possible when it becomes available.

Any SAE that is ongoing at Visit 3 or ET should be followed as described above. Data after Visit 3 should be recorded on the source documents and submitted to Concentrics Research on a SAE report form. For ongoing SAEs, the Principal Investigator must submit follow-up reports to Concentrics Research regarding the subject's subsequent course until the case is closed.

9.8 Unexpected Adverse Event

As defined by 21 CFR 312.32 (a), an unexpected adverse drug experience is:

"An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation."

The study sponsor will expedite reporting all serious unexpected suspected adverse reactions (SUSARs): initial reporting by the sponsor for nonfatal or non-life-threatening SUSARs must be submitted as soon as possible but no later than within 15 calendar days following the sponsor's initial receipt of the information, and for fatal or life-threatening SUSARs, initial reports must be submitted no later than 7 calendar days following the sponsor's initial receipt of the information. Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report without delay as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

Such expedited reports will comply with the applicable regulatory requirements and with the FDA's Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (21 CFR 312.32).

9.9 Pregnancy

If a subject becomes pregnant during the study, the investigator must notify the Medical Monitor immediately upon learning of the pregnancy. The outcome of any pregnancies occurring on the study must be followed up to term. The investigator will be provided with a Pregnancy Outcome Form by the Medical Monitor. This form must be completed fully and returned to the Medical Monitor. Any spontaneous miscarriage or congenital anomaly or birth defect must be recorded as a Serious Adverse Event and full details will be requested. Any complications during pregnancy should be recorded as an AE and may constitute an SAE if they fulfill any of the specified criteria for an SAE.

10 INVESTIGATOR OBLIGATIONS

10.1 Ethical and Regulatory Considerations

This study will be conducted in accordance with Good Clinical Practice (GCP) Guidelines, 21 CFR Parts 11, 50 Subparts A and B, 54, 56, and 314, and the Consolidated Guidance for Industry, GCP E6, April 1999; and 1996 ICH GCP E6.

10.2 Institutional Review Board

The Concentrics Research will ensure that an appropriately constituted Institutional Review Board (IRB), in compliance with the requirements of 21 CFR 56, reviews and approves the clinical study before the study is initiated. IRB approval must refer to the study by exact protocol title, number, and amendment number (if applicable), identify the documents reviewed, and state the date of review.

Concentrics Research will ensure that ParaPRO LLC approves any changes to the IC template prior to submission to the IRB.

Should changes to the IC form become necessary during the study, Concentrics Research will ensure that the changes are approved by ParaPRO LLC prior to submission to the IRB. Should changes to the study protocol become necessary, Concentrics Research will ensure that the protocol amendment is approved by the IRB prior to implementation. Concentrics Research will ensure that protocol administrative changes have been reviewed by the IRB.

Concentrics Research must be copied on any correspondence initiated by the site to the IRB during the course of the study.

10.3 Informed Consent

A properly executed, written IC, in compliance with 21 CFR Part 50 and HIPAA authorization, will be obtained from each subject prior to enrollment and the initiation of screening evaluations required by this protocol. A copy of the IC form planned for use will be reviewed by ParaPRO LLC for acceptability and submitted by or on behalf of the Investigator, together with the protocol, to the IRB for review and approval prior to the start of the study. Consent forms will be written in language fully comprehensible to the prospective subject.

All revisions of the protocol must be reflected in the IC form, if applicable, and reviewed and approved by the IRB. Subjects must be made aware of those applicable changes in the protocol and must consent to participate in the revised protocol.

Household members will sign a properly executed written Informed Consent form approved by the IRB as described above.

10.4 Subject Confidentiality

All communications, reports, and subject samples will be identified only by a coded number and/or initials to maintain subject confidentiality. All records will be kept confidential to the extent permitted by law. If a waiver or authorization separate from the statement in the IC is required for permitting access to a subject's medical records (e.g. HIPAA), the investigator will obtain such authorization prior to enrolling a subject in the study. The Principal Investigator should keep a separate log of subjects, codes, names, and addresses. Documents which identify the subject by name (for example, the IC form) should be kept in strict confidence.

ParaPRO LLC and its business associates agree to keep all subject information confidential. Only coded, blinded data will be released. Data resulting from analyses will be entered into a database that is not accessible to the public. Subject data will be identified only by the subject screen number, randomization number and initials, and not by any other annotation or identifying information.

ParaPRO LLC and its business associates will take every possible step to reduce the risk of releasing information to the public that would enable subjects to be personally identified.

11 STUDY MONITORING

11.1 Clinical Monitoring

An initiation meeting will be conducted by Concentrics Research or an approved representative. At this meeting the protocol, the procedure for completing the eCRFs, and pertinent aspects of the eCRFs will be reviewed with the Principal Investigator and all study staff.

Monitoring visits will be conducted during the study. The Principal Investigator will make a reasonable amount of time available to the CRA on reasonable notice to assist with monitoring.

At each visit, the CRA will review the eCRFs and source documents to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol.

11.2 Auditing Procedures

In addition to the monitoring visits outlined above, an investigational site may undergo a quality assurance audit. Concentrics Research or ParaPRO LLC representatives or a regulatory agency such as the FDA may conduct the audit. If a regulatory agency requests an audit of the study site, the Investigator is required to inform Concentrics Research (or ParaPRO LLC) immediately.

12 CHANGES TO THE PROTOCOL AND STUDY TERMINATION

12.1 Protocol Amendment and Administrative Change

All changes to the protocol must be documented by amendments, or administrative changes where applicable, and the amended protocol must be signed by ParaPRO LLC and the Investigators. The amended protocol and a revised IC form, if necessary, will be submitted to the IRB for approval. If the protocol modifications affect the eCRFs, they will also be revised and provided to the site.

12.2 Termination of the Study

ParaPRO LLC and the Principal Investigator reserve the right to terminate the study at any time. In terminating the study, ParaPRO LLC and the Principal Investigator will ensure that adequate consideration is given to the protection of each subject's interest.

13 SOURCE DOCUMENTS, CASE REPORT FORMS AND RECORD RETENTION

13.1 Source Documents

The Investigator will complete and maintain source documents for each subject participating in the study. The source documents should contain all demographic and medical information, including vital sign data. The subject's source documents file should also indicate that he/she is participating in the clinical study, referencing the study number and the IP. All information required by the protocol should be documented in the source records. An explanation must be given for any omissions. Each evaluation recorded will be performed at the time specified in the protocol.

13.2 Electronic Case Report Forms

Electronic Case Report Forms (eCRFs) will be used in this study. The Investigator is responsible for the quality of the data recorded in the eCRF. The data recorded should be a complete and accurate account of the subject's record collected during the study.

The Investigator and other staff who have been delegated responsibility for entering data into the eCRF at each visit will be trained in the use of the eCRFs before the first subject at that site is enrolled. The Investigator must review all entries for completeness and correctness. The electronic data capture system will keep an audit trail of all changes made after the eCRF pages are initially completed and submitted. The study monitor will review the eCRFs for completeness and adherence to the protocol

13.3 Record Retention

The Principal Investigator will maintain adequate records so that the conduct of the study can be fully documented and monitored. Copies of protocols, test result originals, all IP accountability records, correspondence, subject Informed Consent forms, and any other documents relevant to the conduct of the study will be kept on file by the Principal Investigator. Study documents will not be destroyed. For regulatory inspections, it will be necessary to have access to complete study subject records, provided that subject confidentiality is maintained.

Per the Clinical Development Agreement between ParaPRO LLC and Concentrics Research, investigators must retain subjects' records for a period of 2 years after FDA approval or until written approval to destroy the documentation is provided by ParaPRO LLC. The documentation must be retained longer if so required by local law. Investigators must notify Concentrics Research and ParaPRO LLC, in writing, of changes in address, sales of practices or site closures in order to make arrangements for the maintenance of study files.

14 FINAL REPORT/PUBLICATION STATEMENT

Any formal presentation or publication of data collected as a direct or indirect result of this trial will be considered as a joint publication by the investigator(s) and ParaPRO LLC.

Individual investigators may publish data arising from their own subjects with permission from ParaPRO. The Principal Investigator will provide ParaPRO LLC with copies of written publications (including abstracts and posters) at least 60 days in advance of submission. This review is to permit ParaPRO LLC to review the communication for accuracy (thus avoiding potential discrepancies with submissions to regulatory authorities), to verify that confidential information is not inadvertently divulged (including patent protection), to allow adequate input or supplementary information that may not have been available to the Principal Investigator, and to allow establishment of co-authorship.

Data will be reviewed by all participating investigators prior to publication. ParaPRO LLC will have 60 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 30 days to review all abstracts.

15 REFERENCES

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16 APPENDIX [1]: EXAMPLE OPEN-LABEL PRODUCT LABEL