CLINICAL STUDY PROTOCOL

PROTOCOL NUMBER: MAP-8184

A MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP STUDY COMPARING PERMETHRIN CREAM, 5% (MAYNE PHARMA, INC.) WITH ELIMITE™ IN PATIENTS WITH ACTIVE SCABIES

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SIGNATURE PAGE

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STUDY TITLE : **A Multi-Center, Double-Blind, Randomized, Parallel-Group Study Comparing Permethrin Cream, 5% (Mayne Pharma, Inc.) with Elimite™ in patients with active scabies**

Signatures of the noted individuals ensure that all designated persons have agreed this version is final:

17 OCT 2016
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INVESTIGATOR SIGNATURE PAGE

The signature below constitutes approval of this protocol and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements of confidentiality and in accordance with ICH GCP and local regulatory requirements.

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

Section	Description of change
Principal Contacts	**Biorasi Project Manager changed**
Glossary of Abbreviations	Updated the Glossary, adding missing entries. Acronyms were updated thorough the text
Section 1.2 Rationale of the Study	Updated a reference to CDC treatment guidance for scabies.
Section 3.1 Study Design	Phrase "application of standard of care" for the household members was changed to "Household members will receive one 60 g tube of the standard of care generic Permethrin Cream, 5% at the Baseline visit, sufficient for two applications…".
3.2 Number of Subjects and Sites	Changed to 3.2 Number of Subjects. Removed Number of sites from the protocol. Changed number of subjects to 140. Added provision that the number of subjects may be increased based on the reference product availability
Section 4.1 Study Population	Changed number of subjects to 140 (per protocol population = 112) as per the new Sample Size Determination (see Section 8.2).
Section 4.2.1 Inclusion Criteria #5	Added that household members will be provided with standard of care treatment "if deemed necessary by the Investigator" to match protocol design.
Section 4.2.1 Inclusion Criteria #7	Added new inclusion criterion: 6.7. Subject must be able to apply study product to self. If the subject is a child, then parent/guardian will apply study product to him/her.
Section 4.2.2 Exclusion Criteria #3	Updated the exclusion criteria by replacing the reference to the Section 5.11 with the actual list of prohibited medication.
Section 4.2.2 Exclusion Criteria #4	Updated the exclusion criteria by adding history of seizures.
Section 4.2.2 Exclusion Criteria #8	Updated an exclusion criterion by adding "…synthetic pyrethroids, pyrethrin, chrysanthemums or ragweed".
Section 5.5 Reserve Sample Retention	Clarified language. Added a reference to the Pharmacy Manual.
Section 5.6 Treatment Assignment (Randomization)	Updated language as per the vendor specifications. Added details on how the randomization code will be supplied with each block of the investigational product and moved this paragraph to the next section (5.7 Blinding). Added Section **5.6.1 Assignment of Retreatment**, capturing the process for dispensing the investigational product for the retreatment.
Section 5.7 Blinding	Deleted that the dispensed investigational product may be opened in front of the study pharmacist, or designated study personnel.
Section 5.8 Treatment Administration	The following phrase has been removed: "Subjects will apply investigational product once a week for two weeks, preferably in the evening whether or not the area(s) appear clinically healed."
Section 5.11 Prior,	Replaced "Oral corticosteroids" with "Systemic corticosteroids" in the prohibited

Concomitant and Prohibited Therapy	medication list.
Section 6.3 Schedule of Activities	Visit 4: added bullet point on reapplication of the standard of care by the household members of the participating study subject requiring retreatment Visit 5: added "Vital signs"
Section 8.2 Sample Size Determination	Probability of study success for the sample size being reevaluated, which lead to the change in the sample size
12.2 Appendix B. Schedule of Events	Footnote 5 stating "Vital signs are to be performed if Inclusion/Exclusion Criteria are satisfied at Screening" deleted as redundant
12.3 Appendix C. Declaration of Helsinki	Removed
12.3 Appendix C. Subject Diary	Added
12.4 Appendix D. Patient Self-Assessment	Added

Additional formatting and stylistic adjustments have been made and typographical errors corrected to facilitate reading process.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference On Harmonization
ID	Identification
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified Intent-To-Treat
OTC	Over-the-Counter
PD	Protocol Deviation
PDRR	Protocol Deviation Review Request
PMH	Past Medical History
PP	Per-Protocol
PRN	Pro Re Nata (as needed)
PSA	Patient Self-Assessment
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event

SOC	Standard of Care
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
WHO	World Health Organization

PROTOCOL SYNOPSIS

Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Mayne Pharma, Inc.	Permethrin Cream	Permethrin, 5%

Study Title

A Multi-Center, Double-Blind, Randomized, Parallel-Group Study Comparing Permethrin Cream, 5% (Mayne Pharma, Inc.) with Elimite™ in patients with active scabies.

Type of Study

Bioequivalence with Clinical Endpoints.

Objectives

Primary: To demonstrate bioequivalence between Permethrin Cream, 5% (Mayne Pharma, Inc.) and Elimite™ in patients with active scabies.

Secondary: To demonstrate comparative safety of Permethrin Cream, 5% (Mayne Pharma, Inc.) vs Elimite™ and tolerability of Permethrin Cream, 5%.

Methodology

This is a multi-center, double-blind, randomized, two arm parallel design study. This study is comprised of two phases: screening and treatment. The screening period will be up to 5 days, followed by the treatment phase of 28±4 days. During the treatment phase subjects will be randomized to receive either test or reference treatments in a double-blind manner in an outpatient setting. Randomization of subjects will be in a 1:1 ratio for the test and reference drug arms and will be stratified by site.

Screening will begin at visit 1, during which eligibility will be determined and prohibited treatments will be discontinued. Randomization will occur following the confirmation of the eligibility criteria at visit 2 (baseline, Day 1) i.e. initiation of treatment phase. The treatment phase will be 28±4 days in duration wherein subject will receive treatment with investigational product (either test or reference) on Day 1 or Baseline (visit 2). Safety and tolerability assessments will be performed on Day 7 (visit 3). Efficacy, safety and tolerability will be assessed on Day 14 (visit 4) followed by the End of study visit on Day 28 (visit 5). If positive identification of scabies is confirmed at Day 14 (visit 4), the subject will be retreated with the second application of the investigational product.

Planned Number of Subjects

Number of subjects to be allocated to treatments according to a 1:1 randomization will depend on the limited availability of Reference product. Currently, enough drug is available for a total of N=140 (enrolled subjects) to achieve N=112 per protocol population. Should additional Reference product become available prior to completion of the clinical phase of the study, enrollment will be increased

Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Mayne Pharma, Inc.	Permethrin Cream	Permethrin, 5%

to a total of up to N = 228 (enrolled subjects) to achieve N = 182 (per protocol) population.

Eligibility Criteria

Subjects who satisfy ALL of the following inclusion and have NONE of the following exclusion criteria may be enrolled in the study:

Inclusion Criteria

1. Male or non-pregnant, non-lactating female subject at least 12 years of age or older.
2. Subject must have a positive identification for mites, eggs, or mite fecal matter by microscopic examination of a skin scraping.
3. Subjects must have at least two of the three following: a) excoriations and inflammatory papules with a typical distribution pattern and localization (webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, skin surface of external genitalia, or areolae); b) presence of burrows; c) family or contacts with moderate to severe itching which increases during the night.
4. Subjects must be willing to make every effort to immediately disinfect clothes, towels, and linens and all potentially infected household items upon diagnosis of infestation to prevent re-infestation.
5. All household members with prolonged physical contact with the subject must be willing to attend Baseline visit and receive treatment with standard of care if deemed necessary by the Investigator in order to prevent re-infestation of the subject enrolled.
6. Subject or representative must read and sign an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved Informed Consent Form (ICF); for minor subjects (18 years or younger in most states) the parent or legal guardian should sign the ICF and the child will be required to sign the Assent Form that will written in such a way as to be understandable to a child.
7. Subject must be able to apply study product to self. If the subject is a child, then parent/guardian will apply study product to him/her.

Exclusion Criteria

1. Females who are pregnant as shown in a urine pregnancy test at the Baseline visit, prior to randomization, or lactating, or of childbearing potential (for purpose of this study a female of childbearing potential is considered to be not surgically sterile or postmenopausal for at least 1 year) who are not using or do not agree to use an acceptable form of contraception (oral /implant /injectable /transdermal contraceptives, intrauterine device (IUD), condom,

Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Mayne Pharma, Inc.	Permethrin Cream	Permethrin, 5%

diaphragm, or abstinence) during the study, or who intends to become pregnant during the study; contraceptive method must also be consistent throughout the study.

2. Treatment for scabies <4 weeks prior to enrollment, including permethrin, benzyl alcohol, lindane, crotamiton, malathion, and ivermectin.
3. Use of prohibited medications:
   - Topical or oral scabicidal/antiparasitic treatment including: permethrin, benzyl alcohol, benzyl benzoate, lindane, crotamiton, malathion, ivermectin, precipitated sulfur, albendazole, keratolytic cream, tea tree oil, or oil of the leaves of Lippia multiflora Moldenke within 28 days of visit 2.
   - Systemic corticosteroids (including inhaled steroids) taken within 14 days of visit 2.
   - Topical corticosteroids including hydrocortisone taken within 24 hours of visit 2.
   - Topical antipruritics, including antihistamines within 24 hours of any study visits.
   - Oral antihistamine including diphenhydramine (Benadryl) taken within 24 hours of any study visits.
   - Topical antibiotics including mupirocin taken within 24 hours of any study visits.
4. Patients with immunosuppressive disorders requiring therapy, severe systemic disease, history of HIV infection and/or seizures.
5. Patients with crusted/Norwegian scabies.
6. Presence of underlying skin disease that would obscure evaluation of the papules and burrows associated with scabies infection as determined by the Investigator.
7. Presence of severe cutaneous bacterial or fungal infections requiring therapy (including systemic and topical antibiotics) as determined by the Investigator.
8. Sensitivity or allergy to Permethrin Cream or any of its components, synthetic pyrethroids, pyrethrin, chrysanthemums or ragweed.
9. A recent (less than 1 year) history of alcoholism, drug abuse, or other problems which would likely make the subject unreliable for the study.
10. Participation in another investigational study or using any investigational product within the 30 days prior to the Baseline visit.
11. Participation of family member, or another member of the household (including regular bedmates) in the current study.
12. Total number of bedmates and family members with prolonged physical contact is greater than 6 (including study subject).

Sponsor: Mayne Pharma, Inc.	**Name of Finished Product:** Permethrin Cream	**Name of Active Ingredient(s):** Permethrin, 5%

13. Any employees of the clinic, investigators, or family members of the study staff.
14. Patients who in the opinion of the Investigator would be non-compliant with the requirements of the study protocol.

Investigational Products, Dose and Mode of Administration:

Test Drug: Permethrin Cream, 5%, 60g, topical, manufactured by Mayne Pharma International Pty Ltd.

Reference Product: Elimite™ 60g, topical, marketed by Prestium Pharma, Inc. ("Prestium"), the branded subsidiary of Renaissance Pharma.

Standard of Care (SOC): Generic Permethrin Cream, 5% 60g available in the market will be used for treatment of the household members with active scabies or at a "high risk" of the disease.

Dose During the Active Treatment Period: Subjects will receive a maximum of two doses of the investigational product during the study. The first dose will be applied on Day 1 in an outpatient setting, after the visit to the clinical site (preferably in the evening). The second dose will be applied on Day 14±2 only if retreatment is necessary. Household members will receive one 60 g tube of the standard of care generic Permethrin Cream, 5% at the Baseline visit, sufficient for two applications: at the time of the Baseline visit of the participating study subject, and in two weeks - if the re-treatment will be necessary of the standard of care at Baseline visit.

Route: Topical application, covering the entire area of the skin from the neck down to the feet.

Study Duration: 28 Days

Primary Endpoint: The primary endpoint will be the proportion of patients that are identified as cured at Study Day 28. Cure is defined as the absence of new lesions and the healing of all old lesions. Residual, dry, non-inflammatory papules are not counted as active.

Secondary Endpoint: The secondary endpoint will be the proportion of patients that are identified as cured at Study Day 14.

Safety: Analysis of safety variables will be based on all adverse event (AE) capture measuring severity and duration utilizing MedDRA terminology for consistency. Vital signs will also be reviewed and analyzed at the Baseline and at visit 5 (End of Study visit).

Tolerability: Analysis of tolerability will be based on scores of Stinging/Burning and Itching sensations collected during Patient Self-Assessments at visits 2-5 between the test and reference treatment groups.

Statistical Methods: To establish bioequivalence, the continuity-corrected 90% confidence interval

Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Mayne Pharma, Inc.	Permethrin Cream	Permethrin, 5%

of the difference in the proportion of subjects with treatment success (defined as the absence of new lesions and the healing of all old lesions) between the test and reference products treatment groups at Study Day 28 must be within [-0.20, +0.20].

Results in the (Per-Protocol) PP population will be considered definitive and those in the mITT population as supportive.

To assess treatment differences in the secondary endpoint, the proportion of subjects that are identified as cured in the test and reference treatment groups at Study Day 14 will be analyzed following the same approach as described for Day 28.

Populations for Analysis

Safety Population: The safety population is any randomized individual who was enrolled into the study, and (b) received at least one dose of study treatment.

Modified Intent-to-Treat (mITT) Population: A modified intent-to-treat individual is any randomized individual who (a) met inclusion/exclusion criteria, (b) was enrolled into the study, (c) received at least one dose of the assigned study treatment, and (c) had at least one post-baseline visit.

Per Protocol (PP) Population: A per-protocol subject is any randomized individual who (a) met inclusion/exclusion criteria, (b) was enrolled into the study, (c) received the assigned study treatment, (d) had not taken any concomitant medications prohibited by the protocol or experienced any major deviations that interfered with or may have interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy, and (e) completed the primary endpoint evaluation within the designated visit window (±4 days).

Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of scabies during the study will be discontinued, included in both the mITT and PP population analyses as treatment failures. Subjects who discontinue early for reasons other than treatment failure will be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

Efficacy analyses will be performed using the per-protocol population as definitive and the mITT population as supportive. Safety analyses will be performed using the Safety population.

Efficacy

Primary Endpoint: The proportion of subjects considered to be cured (defined as the absence of new lesions and the healing of all old lesions) on Study Day 28. To establish bioequivalence, the continuity-corrected, 90% confidence interval for the test-to-reference difference in proportions of subjects cured must be within the equivalence limits -0.20 to 0.20. Results in the PP population will be considered definitive and those in the mITT population as supportive.

Sponsor:	**Name of Finished Product:**	**Name of Active Ingredient(s):**
Mayne Pharma, Inc.	Permethrin Cream	Permethrin, 5%

Secondary Endpoint: The proportion of subjects that are identified as cured at Study Day 14. Bioequivalence will be assessed using the same approach as in the primary endpoint.

Tolerability: Tolerability, including itching and burning, will be assessed by the Patient Self-Assessment (PSA) for Stinging/Burning and Itching, depicted in Section 6.2.3 of the protocol. Descriptive statistics using categorical methods will be used to compare tolerability measures between the test and reference treatment groups.

Safety

Medical Data Coding of the Verbatim terms provided by the Investigators for AEs and Concomitant Medications will be performed using relevant MedDRA and WHO Drug dictionaries respectively.

Safety Data Analysis will include subjects' disposition, numbers of completed and discontinued subjects, and causalities for early discontinuation. AEs/SAEs data will be summarized and all AEs will be listed for individual subjects showing both verbatim and preferred terms. The number and percent of subjects taking concomitant medications will be summarized using WHO Drug dictionary classifications.

AEs and SAEs Assessment. All AEs/SAEs will be captured in electronic Case Report Form (eCRF) and study logs. Serious Adverse Events will be reported by the Investigators using SAE Report Form during the 24-hour interval to Biorasi Safety for future analysis and processing. The occurrence of treatment-emergent AEs (TEAEs) will be summarized by treatment group using MedDRA Preferred Terms (PTs), System Organ Classifications (SOCs), severity, outcome and causality. Separate summaries of treatment-emergent SAEs and AEs related to treatment will be generated.

Prohibited Medication

List of prohibited medication is supplied in Section 5.11 of the protocol.

PRINCIPAL CONTACTS

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1. BACKGROUND AND RATIONALE

1.1 Background to the Disease

Scabies is a contagious skin disease caused by an infestation of the human scabies mite, *Sarcoptes scabiei* variety *hominis.* The scabies mite burrows and lives in the superficial layers of the skin and the females lay their eggs in tiny burrows, which can be identified as tiny raised and crooked (serpiginous) grayish-white or skin-colored lines on the skin surface [1]. Mites can only live for 48-72 hours without a human host, however they can survive as long as 1-2 months on a human host. The most common symptoms of a scabies infestation are a pimple-like (papular) skin rash and intense itching that often increases at night. The symptoms are cause by a hypersensitivity of the skin to the mite and mite fecal matter and the rash is most commonly seen in areas such as the wrist, elbow, armpit, and webbing between the fingers, breast areola, and cutaneous area of external genitalia, waist, belt- line, and buttocks. Generally, the head, face, neck, palms, and soles of feet are unaffected areas in older children and adults [2].

Scabies is found worldwide, affecting people of all races and social classes. It spreads rapidly among people in crowded living conditions, such as extended care facilities and nursing homes, as it is most commonly transmitted through direct skin-to-skin contact with another infected person. The common symptoms often arise within 2-6 weeks after exposure for a person who has never been affected and as soon as 1-4 days after exposure for a person who has previously had scabies. In most cases, between 10 and 15 mites are present on an affected individual, though severe cases, known as crusted (Norwegian) scabies, could involve more than hundreds of mites and generally occurs in individuals with weak immune systems such as the elderly, disabled, or debilitated.

Diagnosis of a scabies infestation is made based on the appearance and distribution of the papular skin rash and identification of burrows. It is also common to confirm diagnosis with examination of a skin scraping under a microscope to identify the mite, mite eggs, or mite fecal matter (scybala). Treatment for scabies includes the use of scabicides, such as permethrin cream, lindane, ivermectin, and crotamiton lotion, which act as insect-selective neurotoxins that result in paralysis and eventual death of the itch mites. The standard of care is to treat not only the infected individual, but also sexual partners and other household members who have had prolonged skin-to-skin contact with the infected individuals (including bedmates) at the same time to prevent re-infestation.

Scabicides should be applied to the entire body from the neck down to the feet and toes (the area of application may be extended to the scalp and face if these areas are affected, which was observed in infants and immunocompromised individuals). The scabicide should be applied to clean skin and left on for the recommended time of application before washing it off. Elimite™ (permethrin) 5% Cream is recommended as a single application, which is usually sufficient to eradicate typical scabies, whether a symptomatic case or asymptomatic carrier. The usual adult dose is 30 grams. Demonstrable living mites after 14 days indicate that retreatment is necessary.

In addition, the standard of care dictates that all bedding, clothing, and towels that the infected individual

may have come in contact with should be decontaminated by washing in hot water and drying in a hot dryer, by dry-cleaning, or by sealing in a plastic bag for at least 72 hours.

1.2 Rationale of the Study

Systemic absorption of permethrin cream is limited to 0.5% during the first 48 hours following dermal application [3]. In these settings, a conventional pharmacokinetic human study to demonstrate that Mayne Permethrin cream (5% w/w) is bioequivalent to the Reference Listed Drug [RLD] Elimite™ is not appropriate.

Mayne Pharma, Inc. proposes to initiate a clinical endpoint bioequivalence (BE) study for a Permethrin Cream, 5% formulation for the treatment of active scabies in comparison to Elimite™ Permethrin cream (5% w/w).

- **Test Product:** Permethrin Cream, 5% manufactured for Mayne Pharma, Inc. by Mayne Pharma International Pty Ltd., 1538 Main North Road, Salisbury South SA 5016 Australia
- **Reference Product:** Elimite™ marketed by Prestium Pharma, Inc. ("Prestium"), the branded subsidiary of Renaissance Pharma.

As per Center of Disease Control (CDC) Suggested General Guidelines on Scabies treatment, infested person, as well as household members and sexual contacts, particularly those who have had prolonged direct skin-to-skin contact with the infested person should receive an antiparasitic treatment [4]. All persons should be treated at the same time to prevent re-infestation. In consideration of this recommendation, the household members of the enrolled subject will be examined and treated at the same time as the enrolled subject with an FDA-approved generic Permethrin Cream, 5%. The treatment received by the household members of the enrolled subject will be referred to as "Standard of Care" throughout the study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To demonstrate bioequivalence between Permethrin Cream, 5% (Mayne Pharma, Inc.) and Elimite™ in patients with active scabies.

2.1.2 Secondary Objective

To demonstrate comparative safety of Permethrin Cream, 5% (Mayne Pharma, Inc.) vs Elimite™ and tolerability of Permethrin Cream, 5%.

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary endpoint will be the proportion of patients that are identified as cured at Study Day 28. Cure is defined as the absence of new lesions and the healing of all old lesions. Residual, dry, non-inflammatory papules are not counted as active.

2.2.2 Secondary Endpoint

The secondary endpoint will be the proportion of patients that are identified as cured at Study Day 14.

2.3 Safety Variables

Analysis of safety variables will be based on all adverse event (AE) capture measuring severity and duration utilizing MedDRA terminology for consistency. Vital signs will also be reviewed and analyzed at the Baseline and at visit 5 (End of Study visit).

2.4 Tolerability Assessments

Analysis of tolerability will be based on scores of Stinging/Burning and Itching sensations collected during Patient Self-Assessments at visits 2-5 between the test and reference treatment groups.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a multi-center, double-blind, randomized, two-arm parallel design study to compare the treatment success of the test product, Permethrin Cream, 5% (Mayne Pharma, Inc.), and the Reference product, Elimite™ in patients with active scabies. The diagnosis of scabies is made based on the evaluation of burrows, inflammatory papules and excoriations and with a typical distribution pattern and localization (webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, skin surface of external genitalia, or areolae), presence of family or contacts with moderate to severe itching which increases during the night, and positive identification of mites, mite eggs, or mite fecal matter (scybala) via microscopic evaluation of skin lesion scrapings [1,2]. Treatment success in this study is based on previously published studies of scabies infestations and defined as the absence of new lesions and the healing of all old lesions due to scabies mites and eggs within the treatment area [5-7]. The assigned investigational product will be applied topically (after washing) preferably in the evening on the day of the Baseline visit (Day 1).

Eligibility criteria requires that all regular bedmates and family members with prolonged physical contact with the subject will agree to be assessed by the Investigator for clinical signs of scabies infestation and receive treatment with standard of care scabicidal drug, if necessary. This requirement is detailed in Section 5.8.2.

If signs of active scabies infestation are present at visit 4 (Day 14±2), the study subject will be retreated with a second application of their assigned IP. Household members of the participating study subject will be asked to reapply the standard of care generic Permethrin Cream, 5% at the same visit.

This study is comprised of two phases: screening and treatment. The screening phase will be up to 5 days in duration and treatment phase will be 28±4 days in duration. Approximately 140 subjects (or as many as 228 subjects), at least 12 years of age, male or female, of any race, who meet the inclusion and exclusion criteria, will be enrolled to achieve the desired per protocol subject number. The double-blind randomization of subjects will be in a 1:1 ratio for Test and Reference, and will be stratified by site.

Screening will begin at visit 1 during which informed consent will be obtained from the subject prior to any study-related procedures, and eligibility will be determined by the Investigator. Following receipt of informed consent, the subject's medical history will be recorded along with concomitant medications and, at this point, prohibited treatments must be assessed as they should be discontinued according to the timeframes outlined in section 5.11. A physical examination will be performed for all subjects and a urine pregnancy test will be performed for women of childbearing potential. The subject's scabies infestation will be evaluated for papules and burrows during the visual examination. Presence of acarids, feces, or ova will be assessed via microscopic exam of skin lesion scraping. Subjects who meet all inclusion/exclusion criteria will return to the office for visit 2 within 5 days.

At visit 2 (baseline) the subject's concomitant medications will be updated and any changes to medical history will be recorded. Randomization will occur at this visit and subjects will be instructed on investigational product application and completion of subject diaries. Visits 1 and 2 can be combined, if requirements detailed in Section 6.3.2 are met. All regular bedmates of the subject and individuals with prolonged physical contact with the subject will undergo an assessment by the Investigator and receive one 60 g tube with standard of care generic Permethrin Cream, 5% during the Baseline visit to prevent cross-infestation within the household.

Subject will return at visit 3 (Day 7±1) with the used investigational product tube and subject diaries. Compliance with investigational product applications will be assessed. Safety and tolerability assessments will be conducted.

At visit 4 (Day 14±2), subjects will return for efficacy, safety and tolerability assessments. If signs of active scabies infection are present at this visit, the subject will be treated with a 2nd application of their assigned investigational product as defined in Section 5.6.

Final efficacy, safety and tolerability assessments will occur at visit 5 (Day 28±4). If the subject was retreated, the used tube of the investigational product will be returned at this visit. The duration of each subject's participation in the study will be a maximum of 37 days.

The primary endpoint is the proportion of subjects considered to be cured (defined as the absence of new lesions and the healing of all old lesions) on Study Day 28. To establish bioequivalence, the continuity-corrected, 90% confidence interval for the test-to-reference difference in proportions of subjects cured must be within the equivalence limits -0.20 to 0.20. The evaluation in the PP population will be definitive while that in the mITT population will be considered as supportive.

The secondary endpoint is the proportion of subjects considered to be cured on Study Day 14. Bioequivalence will be assessed using the same approach as in the primary endpoint.

3.2 Number of Subjects

Based on the limited availability of Reference product, a total of approximately 140 subjects, at least 12 years of age, male or female, of any race, who meet the inclusion and exclusion criteria, will be enrolled to achieve a per protocol population of approximately 112 across the United States. Should additional Reference product become available prior to completion of the clinical phase of the study, enrollment will be increased, up to 228, to achieve a per protocol population of up to approximately 182.

4. SELECTION AND WITHDRAWAL OF STUDY POPULATION

4.1 Study Population

Approximately one hundred and forty (140) subjects, and as many as two hundred and twenty-eight subjects, of age 12 years and older with clinical and parasitological confirmation of active scabies will be enrolled in this multi-center study.

4.2 Eligibility Criteria

Subjects who satisfy ALL of the following inclusion and have NONE of the following exclusion criteria may be enrolled in the study:

4.2.1 Inclusion Criteria

1. Male or non-pregnant, non-lactating female subject at least 12 years of age or older.
2. Subject must have a positive identification for mites, eggs, or mite fecal matter by microscopic examination of a skin scraping.
3. Subjects must have at least two of the three following: a) excoriations and inflammatory papules with a typical distribution pattern and localization (webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, skin surface of external genitalia, or areolae); b) presence of burrows; c) family or contacts with moderate to severe itching which increases during the night.
4. Subjects must be willing to make every effort to immediately disinfect clothes, towels, and linens and all potentially infected household items upon diagnosis of infestation to prevent re-infestation.
5. All household members with prolonged physical contact with the subject must be willing to attend Baseline visit and receive treatment with standard of care if deemed necessary by the Investigator in order to prevent re-infestation of the subject enrolled.
6. Subject or representative must read and sign an IRB/IEC-approved Informed Consent Form (ICF); for minor subjects (18 years or younger in most states) the parent or legal guardian should sign the ICF and the child will be required to sign the Assent Form that will written in such a way as to be understandable to a child.
7. Subject must be able to apply study product to self. If the subject is a child, then parent/guardian will apply study product to him/her.

4.2.2 Exclusion Criteria

1. Females who are pregnant as shown in a urine pregnancy test at the Baseline visit, prior to randomization, or lactating, or of childbearing potential (for purpose of this study a female of

childbearing potential is considered to be not surgically sterile or postmenopausal for at least 1 year) who are not using or do not agree to use an acceptable form of contraception (oral /implant /injectable /transdermal contraceptives, IUD, condom, diaphragm, or abstinence) during the study, or who intends to become pregnant during the study; contraceptive method must also be consistent throughout the study.

2. Treatment for scabies <4 weeks prior to enrollment, including permethrin, benzyl alcohol, lindane, crotamiton, malathion, and ivermectin.

3. Use of prohibited medications:
   - Topical or oral scabicidal/antiparasitic treatment including: permethrin, benzyl alcohol, benzyl benzoate, lindane, crotamiton, malathion, ivermectin, precipitated sulfur, albendazole, keratolytic cream, tea tree oil, or oil of the leaves of Lippia multiflora Moldenke within 28 days of visit 2.
   - Systemic corticosteroids (including inhaled steroids) taken within 14 days of visit 2.
   - Topical corticosteroids including hydrocortisone taken within 24 hours of visit 2.
   - Topical antipruritics, including antihistamines within 24 hours of any study visits.
   - Oral antihistamine including diphenhydramine (Benadryl) taken within 24 hours of any study visits.
   - Topical antibiotics including mupirocin taken within 24 hours of any study visits.

4. Patients with immunosuppressive disorders requiring therapy, severe systemic disease, history of HIV infection and/or seizures.

5. Patients with crusted/Norwegian scabies.

6. Presence of underlying skin disease that would obscure evaluation of the papules and burrows associated with scabies infection as determined by the Investigator.

7. Presence of severe cutaneous bacterial or fungal infections requiring therapy (including systemic and topical antibiotics) as determined by the Investigator.

8. Sensitivity or allergy to Permethrin Cream or any of its components, synthetic pyrethroids, pyrethrin, chrysanthemums or ragweed.

9. A recent (less than 1 year) history of alcoholism, drug abuse, or other problems which would likely make the subject unreliable for the study.

10. Participation in another investigational study or using any investigational product within the 30 days prior to the Baseline visit.

11. Participation of family member, or another member of the household (including regular bedmates) in the current study.

12. Total number of bedmates and family members with prolonged physical contact is greater than 6 (including study subject).

13. Any employees of the clinic, investigators, or family members of the study staff.
14. Patients who in the opinion of the Investigator would be non-compliant with the requirements of the study protocol.

4.2.3 Criteria for Inclusion of Minor Subjects

Subjects under the age of 18 must sign the Assent Form that will be written in such a way as to be understandable to a child and to obtain parental or legal guardian consent prior to enrollment in this study. Subjects aged less than 12 years will not be enrolled.

4.3 Withdrawal and Early Discontinuation

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care. The Investigator, Sponsor, or Medical Monitor may also withdraw the subject at any time if it is medically necessary or in the interest of subject safety.

A subject will be discontinued from this study if any of the following criteria are met:

- Withdrawal of consent by the subject is received
- In the opinion of the Investigator, it is not in the subject's best interests to continue in the study.
- Occurrence of an AE/SAE, which, in the opinion of the Investigator, warrants discontinuation of the subject from the study.
- Pregnancy
- Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study. This includes known cases of non-compliance of household members with the standard of care treatment.
- If subject is deemed to be a treatment failure, which is defined as any subject whose condition worsens and who requires alternate or supplemental therapy for the treatment of scabies during the study.

Subjects discontinuing, or withdrawing from, the study sooner than their Day 28 visit will undergo the End of Study assessments (as detailed in Section 6.3.5). In addition, if the subject is discontinuing the study and has not returned the dispensed Investigational Product, then the site will remind the subject to return the dispensed investigational product during the End of study visit. In such cases, the Investigational Product dispensed to the subject will be collected and Investigational Product accountability will be performed as per Section 5.10 during the End of Study visit (see Schedule of Activities in Appendix B).

After the End of Study visit, the subject may resume dosing with any medication prescribed by the subject's physician, including Prohibited Medications listed in section 5.11.

If a subject does not return for a scheduled visit, every effort will be made to contact the subject and

document the End of Study visit assessments. The Investigator must document the primary reason for discontinuation of a study subject on the appropriate electronic Case Report Form (CRF).

Randomized subjects who discontinue due to an adverse event will have all events documented and followed to satisfactory resolution, as detailed in Section 7.4.

5. INVESTIGATIONAL PRODUCT AND TREATMENT OF SUBJECTS

5.1 Investigational Products [IP]

5.1.1 Test Product

The test product is Permethrin Cream 5% w/w manufactured by Mayne Pharma International Pty Ltd., supplied in 60 g tubes. The formulation composition of the test product consists of the following ingredients:

Active Ingredient **-** Each gram contains permethrin 50 mg (5%).

Inactive Ingredients **-** Fractionated coconut oil (MCT-NF) [7.5%], Isopropyl myristate NF [0.8%], Glyceryl monostearate NF [2.0%], Lanolin alcohols NF [0.2%], Mineral oil NF [0.01%], Butylated hydroxytoluene NF (BHT) [2.4%], Polyoxyethylene 2 cetyl ether (ceteth 2) [2.4%], Polyoxyethylene 10 cetyl ether (ceteth 10) [2.4%], Glycerol NF [0.5%], Water USP [74.96%], Polyoxyethylene 20 cetyl ether (ceteth 20), [2.0%], Carbomer 974P NF [0.26%], 5% NaOH Aqueous solution [1.6%], Formaldehyde solution NF [0.27%].

5.1.2 Reference Product/Comparator

The reference product or comparator is Elimite™ marketed by Prestium Pharma, Inc. (“Prestium”), the branded subsidiary of Renaissance Pharma. Elimite™ is supplied in 60 g tubes. The formulation composition of the reference product, Permethrin 5% w/w (Elimite™) consists of the following ingredients according to the FDA-approved labelling:

Active Ingredient - Each gram contains permethrin 50 mg (5%).

Inactive Ingredients **-** Butylated hydroxytoluene, carbomer homopolymer type B, fractionated coconut oil, glycerin, glyceryl monostearate, isopropyl myristate, lanolin alcohols, mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.

5.2 Standard of Care [SOC]

Generic Permethrin Cream, 5% available in the market will be supplied by the Sponsor in an open-label fashion as a Standard of Care (SOC) to each site and will be used for treatment of the household members. To avoid any possible unblinding issues, the SOC supplied by the Sponsor will not be the reference product of this study, Elimite™.

5.3 Packaging and Labeling

The investigational product tubes to be dispensed to the subject will be packaged in diaper-label to ensure

blinding. Labeling will be in accordance with Good Manufacturing Practice. The labels on each investigational product tube will not provide any information in regards to treatment arm.

The SOC, Permethrin Cream, 5% available in the market will be supplied in an open-label fashion.

5.4 Storage of investigational product and SOC

Study Medication supplies (include investigational product and SOC) will be stored at 20° to 25°C (68° to 77°F) and protected from moisture. All study medication supplies must be kept in a secure cabinet or room. Only the study pharmacist, or designated study personnel will have access to study medication supplies.

5.5 Reserve Sample Retention

Each shipment of investigational product received by the site will contain investigational product tubes to be reserved for retention. When the site receives a shipment of investigational product, study pharmacist, or designated study personnel will randomly select one block of the investigational product for retention and store them separately. For all subsequent shipments, the same procedure is to be followed. Detailed guidance is provided in the study ***Pharmacy Manual***.

As per the Code of Federal Regulations Part 21, Section 320.38(e), "Each reserve sample shall be stored under conditions consistent with the product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the clinical study in which the sample from which the reserve sample was obtained was used."

The Investigator will store the retention sample investigational product until such time or until notification is received from the Sponsor that the samples are no longer required and proper instruction of what to do with the sample is given by the Sponsor.

5.6 Treatment Assignment (Randomization)

The block randomization code will be generated and held by an independent third party throughout the conduct of the study in order to minimize bias. Blocks of two (2) tubes will be supplied to the sites. Site's dispensing pharmacist will randomly select a tube with an investigational product from the block for the study subject. Next enrolled subject will receive the remaining investigational product from the same block until the block is entirely used.

5.6.1 Assignment of Retreatment

Based on the clinical judgement and requirements described in the protocol, the Investigator may provide

a retreatment to the study subject. Only one retreatment is allowed per subject. The retreatment assignment must belong to the same treatment arm. In order to dispense the correct treatment, the following process is to be followed:

1. Study pharmacist will contact the Drug Depot, specifying subject's identifying information.
2. Drug Depot will specify which kit number shall be dispensed for retreatment.

Please refer to the study ***Pharmacy Manual*** for details.

5.7 Blinding

This is a double-blind study, thus all clinic staff, study monitors, and subjects will be blinded to the randomization scheme. The packaging of the test and the reference products will be similar in appearance to make difference in treatment less obvious to the subjects. To maintain adequate blinding of Investigators and subject evaluators, it is recommended that the investigational product dispensation and accountability be performed by the study pharmacist, or designated study personnel who will not be involved in any other activities of this study. Neither the Investigator nor the patient should be able to identify the received treatment. The dispensed investigational product will NOT be opened by the subject at the study center. The randomization scheme will not be available to the physician, the study pharmacist or designated study personnel for investigational product dispensation and accountability and nursing staff or study coordinators involved in the collection, monitoring, revision, or evaluation of adverse events or to clinical staff who could have an impact on the outcome of the study.

A sealed copy of the randomization code will be supplied with each block of the investigational product and will be retained at each clinical site. Randomization codes must be available to the FDA or other regulatory agency investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

The randomization code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Qualified Investigator to complete a serious adverse event report or the clinical report. In such situations, the randomization information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded. Biorasi Project Manager should be contacted by telephone prior to unblinding but no later than 24 hours after unblinding. As the study is blinded, the Investigator should promptly document and explain to the Sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

5.8 Treatment Administration

5.8.1 Investigational Product Dispensation and Application

At visit 2 (Baseline or Day 1), subjects will receive the randomized treatment along with a Subject Diary (Appendix C. Subject Diary). Subjects will be instructed to bring the dispensed study medication (used tube of investigational product) along with the subject diary for visit 3 (day 7) for investigational product

accountability.

Each subject will be instructed (verbally and in form of written instructions) on proper application method, clothing and bedding disinfection requirements, subject diary completion, and general instructions regarding the study. Subjects will apply investigational product on Day 1 after leaving the study site.

Subjects will be instructed to cleanse with warm water (but NOT the hot bath due to risk of increased adsorption and increased risk of systemic adverse events) and a non-medicated soap and dry thoroughly. Nails should be clipped back and any debris must be removed prior to the application. Subjects will apply a thin layer of investigational product to the entire surface from the neck down to the soles and bottom of the feet (NOT including face and head). Subjects should pay special attention when applying cream to the areas between fingers and toes, under nails, wrists, armpits, skin surface of external genitalia, breasts and buttocks. The investigational product should be applied at bedtime and kept overnight for a minimum of 8 hours and a maximum of 14 hours before washing it off.

Subjects will be informed that residual itching may persist for several weeks after the successful treatment, which does not necessarily indicate treatment failure. Oral or topical antipruritics may me prescribed based on the Investigator's clinical judgement in order to reduce itching, taking into account prohibited medication and washout periods detailed in the Section 5.11.

In general, one application of the Permethrin is curative for scabies. However, in the event that signs of active scabies infestation are present at visit 4 (Day 14±2), the subject will be retreated with second application of their assigned investigational product. In this case, the subject will follow the same application recommendations and will complete the diary, returning the used investigational product tube and subject diary to the visit 5 (Day 28±4).

5.8.2 Administration of Standard of Care

In the current study, all household members with prolonged physical contact with the subject must agree to be assessed by the Investigator. Affected (or "high risk") household members, as determined by the Investigator, must be willing to receive a treatment with an open-label standard of care, which will be provided to them on the day of visit 2 (baseline). Providing an antiparasitic treatment to the household members of the affected individual is dictated by the clinical and epidemiological necessity due to high risk of cross-contamination within the family members. Individuals receiving standard of care will not be considered as a part of study population.

All affected (or "high risk") household members must receive treatment with the standard of care on the same day as the enrolled subject and will follow the same recommendations for disinfection of personal clothing and bedding items. Please see Appendix A. Study Flowchart.

5.9 Treatment Compliance

Subjects will apply the investigational product after the visit 2 (Day 1), preferably in the evening.

Subjects will be advised to bring back used investigational product tube during visit 3. The study pharmacist, or designated study personnel will perform investigational product accountability to ensure that the subject took application of the investigational product. Compliance with the application and disinfection requirements will be determined from the Subject Diary, which the subject will be instructed to use to record date and time of the application and application removal, as well as confirmation of disinfection of clothing and compliance of family members with SOC treatment.

Missed applications and deviations from the application instructions (e.g.: if cream was washed with soap and water within 8 hours of treatment, cream was not applied to the whole body during each application, was not performed prior to application of the investigational product, etc.) will be considered as a deviation from the protocol.

5.10 Accountability, Destruction and Return of Study Supplies

The Sponsor will supply sufficient quantities of the investigational product for the following:

(1) completion of this study

(2) retention, as per applicable regulations

The study pharmacist or designated study personnel will maintain a Site Investigational Product Accountability Log and a Subject Investigational Product Accountability Log itemizing all investigational product dispensed to and returned from each subject during the study and the amount of SOC dispensed to the household members of each subject. Investigational product compliance check will be performed at visit 3 (Day 7) and at visit 5 (Day 28) - for subjects receiving second application of the Investigational product. All investigational products must be accounted for, and any discrepancies explained.

The study pharmacist or designated study personnel is responsible for keeping accurate records of the clinical supplies received from the Sponsor, all supplies retained in inventory at the site, and investigational product dispensed to or returned from each subject and should accurately reflect the drug accountability of the investigational product at all times.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

Prior to site closure and at appropriate intervals during the study, a representative from Biorasi or Sponsor will perform Investigational Product accountability and reconciliation. At the end of the study, the Investigator will retain all the original documentation regarding Investigational Product accountability, return, and/or destruction, and copies will be sent to the Sponsor.

With the exception of retention samples, all unused and used investigational product tubes will be retained at the investigative site and must be returned to the Sponsor or its designee for destruction at the end of the study.

5.11 Prior, Concomitant and Prohibited Therapy

Current medications and any medications taken within the 30 days prior to the start of the study will be recorded as prior/concomitant medications (using their generic name, if known) with the corresponding indication. The medications to be recorded include prescription and all over-the-counter (OTC) medications and all dietary supplements. All medications taken on a regular basis, including aspirin and acetaminophen, should be recorded prior to commencing the use of the investigational product. Any medications started during the study (including "as needed" medications) will be recorded in the concomitant medication list as soon as the Investigational Site will become aware of the medication being added.

If the Investigator becomes aware of a subject having taken a prohibited medication, they will report the incident to the Medical Monitor and Biorasi within 24 hours, and the Medical Monitor and/or Sponsor will provide written approval of the subject's continuation or discontinuation in the study.

Prohibited medications include:

1. Topical or oral scabicidal/antiparasitic treatment including: permethrin, benzyl alcohol, benzyl benzoate, lindane, crotamiton, malathion, ivermectin, precipitated sulfur, albendazole, keratolytic cream, tea tree oil, or oil of the leaves of Lippia multiflora Moldenke within 28 days of visit 2.
2. Systemic corticosteroids (including inhaled steroids) taken within 14 days of visit 2.
3. Topical corticosteroids including hydrocortisone taken within 24 hours of visit 2.
4. Topical antipruritics, including antihistamines within 24 hours of any study visits.
5. Oral antihistamine including diphenhydramine (Benadryl) taken within 24 hours of any study visits.
6. Topical antibiotics including mupirocin taken within 24 hours of any study visits.

6. STUDY PROCEDURES AND SCHEDULE OF ACTIVITIES

The following sections describe the procedures to be completed during the study. Subjects are to be assessed by the same Investigator or site personnel whenever possible.

6.1 Administrative Procedures

6.1.1 Subject Informed Consent

A signed and dated, study-specific, Institutional Review Board (IRB) approved Informed Consent Form must be obtained from each subject prior to performing any study related procedures. No study related procedures or activities may be performed until each subject is fully informed and the consent form is signed and dated. Any subject under the age of 18 must have the signature parent or legal guardian on informed consent form. All subjects will be given a copy of the signed and dated consent form.
Subjects between the age of 12 and 18 must sign the Assent Form that will be written in such a way as to be understandable to a child. Parental or legal guardian consent will be obtained prior to enrollment in this study.

6.1.2 Documentation of Screen Failures

Investigators will maintain documentation of pre-screening activities, to include information on potential study candidates evaluated and reasons that patients considered for the study did not qualify.
Investigators must account for all subjects who sign informed consent and will maintain a log of subjects screened and indicate who was enrolled or excluded and the reason why. If the subject is found not to be eligible prior to enrollment, the reason(s) for ineligibility must be documented by the Investigator.
Subject Numbers assigned to subjects who fail Screening will not be re-used.

6.1.3 Contraception and Pregnancy Avoidance Measures

The study will require that all subjects must agree to use adequate contraception throughout the study.

Adequate contraception is defined as follows:

- Female subjects must be surgically sterile, postmenopausal (for at least one year).
- Female subjects not surgically sterile or postmenopausal (for at least one year), and nonvasectomized male subjects, must practice at least one of the following methods of birth control:
    - total abstinence from sexual intercourse (minimum one complete menstrual cycle prior to Screening visit, throughout the study)
    - a vasectomized partner
    - hormonal contraceptives (oral, parenteral, or transdermal) for at least three months prior

to study drug administration or intrauterine contraception/device double-barrier method (such as male condom, female condom, diaphragm, sponge, or cervical cap *together with* spermicidal foam/gel/film/suppository).

6.2 Study Procedures and Evaluations

6.2.1 Clinical Evaluations

The following clinical evaluations will be conducted during the course of the study:

6.2.1.1 Subject Demographics

Basic demographic information, including date of birth, sex, ethnicity, and race will be recorded at the Screening visit.

6.2.1.2 Medical history

Medical history will be collected at the Screening visit and updated at the visit 2. Relevant medical history (with particular emphasis on previous scabies infestations, related skin disorders and other medical conditions that may lead to exclusion) and significant ongoing medical conditions or diseases will be documented.

6.2.1.3 Physical examination

Physical examination, including height, weight, and evaluation of organs and systems (General Appearance, Heart/Cardiovascular, Lungs, Gastrointestinal, Ears / Nose / Throat, Extremities, and Skin) will be assessed.

6.2.1.4 Vital Signs

Vital signs will be collected at the Screening visit; on the Baseline, and at visit 5 (or upon subject discontinuation). Vital signs will include body temperature (oral), heart rate and blood pressure (systolic and diastolic). Blood pressure and pulse rate will be measured after the subject has been sitting restfully for at least 5 minutes. Any abnormal characteristics will be evaluated by the Investigator from based on their significance. Abnormal vital signs will be considered AEs if they require therapeutic medical intervention, and/or if the Investigator considers them to be AEs due to the clinical judgement.

6.2.1.5 Visual Examination of Lesions

At the Screening (visit 1) and Baseline (visit 2) visits, visual examination of skin lesions will be performed by the Investigational Site. Active lesions, defined as inflammatory papules, excoriations and burrows will be assessed and mapped to the body areas (webbed spaces of the fingers, flexor surfaces of the wrists, elbows, axillae, belt line, feet, skin surface of external genitalia, areolae and other areas). Residual, dry, non-inflammatory papules will not be counted as active. At visits 3, 4 and 5 the examination will be repeated, identifying the course of healing of old lesions and identification of new elements. The examination results will be captured in the eCRF and in the source documentation.

6.2.1.6 Adverse Event Assessments

Beginning with the first dose/application of the investigational product and through visit 5 (End of Study), the Investigator and study personnel will review each subject's clinical evaluation findings and query the subject directly regarding AEs (see Section 7, Safety Data Collection, Recording and Reporting). Subjects must be followed for AEs until the final required protocol visit or until all drug-related toxicities and SAEs have resolved (or are considered chronic/stable), whichever is later.

6.2.1.7 Concomitant Medication Recording

All medications (both prescription and nonprescription, and including vitamins, herbals, topicals, inhaled, and intranasal) taken within 30 days prior to the start of the investigational product and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand name, if known) with the corresponding indication. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed) medication use.

6.2.2 Laboratory Evaluations

The following laboratory evaluations will be conducted during the course of the study:

6.2.2.1 Microscopic Examination of Skin Scraping

During the Screening visit (Visit 1), the Investigator or designee will perform a scraping of skin lesions in order to verify the presence of the mites, eggs, or mite fecal matter (scybala) under the light microscopy. This can be done by carefully removing the mite from the end of its burrow using the tip of a needle or by obtaining multiple wide superficial scrapings of crusted, papular, or lesioned areas of the skin to examine under a microscope for mites, eggs, or mite's fecal matter.

New lesions identified at visits 3, 4 or 5 will be confirmed by microscopic evaluation of skin scraping.

6.2.2.2 Pregnancy test

A urine pregnancy test will be performed at Screening and at the End of Study (EOS) visit for females of childbearing potential (refer to Section 6.1.3 Contraception and Pregnancy Avoidance Measures for definitions). The Screening results must be available and must be negative before the subject takes the first dose/first application of Investigational Product.

6.2.3 Patient Self-Assessment

Subjects will perform a self-assessments of itching and stinging/burning sensations (Appendix D. Patient Self-Assessment) at visits 2, 3, 4 and 5, as detailed in Tables 1 and 2. During each visit, subject will be provided with a Patient Self-Assessment Worksheets to record the grading of itching and stinging/burning sensations. The Patient Self-Assessment Worksheets will be filed along with the source documentation and the self-assessments data provided by the subject will be captured by the Investigational Site in the eCRF. Information captured on the Patient Self-Assessment will not be documented as an Adverse Event.

Table 1: Itching

Itching – Intense, distracting irritation or tickling sensation in the last 24 hours

Score	Grade	Definition
0	None	No Itching
1	Mild	Barely perceptible, slightly present itch
2	Moderate	Distinct presence of itch
3	Severe	Marked, intense, yet tolerable itch
4	Very Severe	Unbearable, intense itch

Table 2: Stinging/Burning

Stinging/Burning – Sensation of the skin is painfully hot or noticeable tingling sensation in the last 24 hours

Score	Grade	Definition
0	None	Absent
1	Mild	Slight, barely present
2	Moderate	Distinct presence
3	Severe	Marked, intense

6.2.4 Subject Diary Compliance Review

Subjects will fill out their diaries upon each treatment application noting the following:

- Time and date of application
- Time and date of removal (washing off of the study drug)
- Confirmation that subject disinfected personal clothes, towels, linens and all potentially infected household items
- Confirmation that the complete skin surface from the neck down to the soles and bottom of the feet has been covered by the application

Subjects will return their diaries to the clinical site at visit 3 (Day 7±1 Day) for compliance review. The Investigator will verify that the subject complied with the application requirements and disinfection regimen. Both the subject and the study staff will sign off on completed diary. If the subject has missed a treatment application notation, this is considered a protocol deviation and must be reported. Refer to Section 5.9 for additional information regarding the treatment compliance.

6.3 Schedule of Activities

6.3.1 Visit 1: Screening Visit (Days -5 to 1)

Subjects will undergo Screening procedures within 1-5 days prior to investigational product administration. All Screening procedures will be completed prior to randomization but only after obtaining voluntary written informed consent. Subjects satisfying all inclusion and none of the exclusion criteria may be enrolled in the study. Screening Procedures include:

- Review and signing the Informed Consent.
- Inclusion/Exclusion Criteria review.
- Demographics.
- Medical history.
- Physical examination.
- Vital signs.
- Visual examination of skin lesions.
- Microscopic examination of skin scraping to identify scabies mites, eggs, or fecal matter (see Section 6.2.2.1).
- Assessment of concomitant and prohibited medications.
- Pregnancy test and evaluation of contraception use (for females of child bearing potential).
- Identifying bedmates and family members with prolonged physical contact with the subject. These members will be invited to attend Baseline visit and must be willing to undergo clinical assessment for scabies infestation followed by antiparasitic treatment with standard of care.
- Baseline visit scheduling.

6.3.2 Visit 2: Baseline (Day 1)

The Baseline visit can be performed at the same visit as Screening, or up to 5 days later. However, if visit 2 is completed on a different day than visit 1, then all visit 2 procedures must be performed regardless of any duplicate procedures completed at visit 1.

If subject's eligibility can be confirmed at the Screening visit, procedures for visits 1 and 2 can be combined and conducted on the same day, which then is Day 1. Following requirements must be met at the day of the Screening visit:

a) all screening procedures are completed and results, such as microscopy of skin scrapings are obtained by the Investigational Site;

b) washout requirements for prohibited medications are fulfilled, as outlined in section 5.11;

c) regular bedmates of subject and individuals with prolonged physical contact with the subject (family members), if identified, are present, and were assessed by the Investigator. Affected (or "high risk") family members / bedmates are willing to receive a treatment with a standard of care and the treatment with standard of care is initiated on the same day as the Baseline visit of the

subject. Study subjects and their bedmates must be on the same schedule of treatment applications in order to reduce risk of re-infestation. Otherwise, subjects cannot be enrolled.

The following procedures will be performed:

- Evaluation of bedmates and family members with prolonged physical contact for clinical signs of scabies infestation.
- Changes in medical history.
- Assess concomitant and prohibited medications.
- Visual examination of skin lesions.
- Vital signs.
- Patient Self-Assessment (see Section 6.2.3).
- Confirmation subject still meets all Inclusion/Exclusion Criteria prior to Randomization.
- Randomization of eligible subjects.
- Dispensation of investigational product.
- Dispensation of standard of care antiparasitic treatment to bedmates and family members, identified as affected with scabies and at "high risk".
- Complete the Site Investigational Product Accountability Log and a Subject Investigational Product Accountability Log
- Education on application, storage, diary completion, and dispensing of subject diary.
- Visit 3 scheduling.

6.3.3 Visit 3: Interim Evaluation (Day 7±1 Day)

The following procedures will be performed:

- Assess adverse events.
- Assess concomitant and prohibited medications.
- Visual examination of skin lesions.
- Patient Self-Assessment (see Section 6.2.3).
- Assess subject compliance by reviewing the subject diary. Subject diary will be returned and filed with the subject's source documents (see Section 6.2.4). Both the subject and the study staff will sign off on completed diary.
- Collect the dispensed investigational product and complete the Site Investigational Product Accountability Log and a Subject Investigational Product Accountability Log.
- Visit 4 scheduling.

6.3.4 Visit 4: Interim Evaluation (Day 14±2 Day)

The following procedures will be performed:

- Assess adverse events.
- Assess concomitant and prohibited medications.

- Visual examination of skin lesions.
- Patient Self-Assessment (see Section 6.2.3).
- For subjects showing active signs of scabies:
    - Assess subject for signs of active scabies and dispense the investigational product for second application. Complete the Site Investigational Product Accountability Log and a Subject Investigational Product Accountability Log.
    - Education on application, storage, diary completion, and re-dispensing of subject diary.
    - Household members of the participating study subject will be asked to reapply the standard of care generic Permethrin Cream, 5%.
- Visit 5 scheduling.

6.3.5 Visit 5: End of Study / Early Termination, and Final Safety Check (Day 28±4)

The following procedures will be performed:

- Assess adverse events.
- Assess concomitant and prohibited medications.
- Visual examination of skin lesions.
- Vital signs
- Patient Self-Assessment (see Section 6.2.3).
- Pregnancy Test (for females of childbearing potential).
- For subjects receiving second application of the investigational product:
    - Assess subject compliance by reviewing the subject diary. Subject diary will be returned and filed with the subject's source documents (see Section 6.2.4). Both the subject and the study staff will sign off on completed diary.
    - Collect the dispensed investigational product and complete the Site Investigational Product Accountability Log and a Subject Investigational Product Accountability Log.

If the Investigator assesses the subject's condition at any time and determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as treatment failure. Visit 5 Early Termination procedures will be performed, and a standard of care treatment may be advised at the Investigator's discretion.

Subjects discontinuing from the study sooner than the Day 28 visit will undergo the Early Termination (ET) visit at the earliest possible date. If the Investigator decides to discontinue a subject at any time during the study, a standard care of treatment may be advised at the Investigator's discretion, and an EOS/ET visit preferably prior to receiving any standard of care treatment.

6.3.6 Unscheduled Visit

Subjects will be encouraged to report any complications or adverse effects during their participation. Investigator may evaluate the subject at an unscheduled visit, if subject's condition will be considered as worsening.

7. SAFETY DATA COLLECTION, RECORDING AND REPORTING

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for events not considered "related" or "probably related" to study drug, final diagnosis, if known, and any action(s) taken. For AEs to be considered intermittent, the events must be of similar nature and severity and each intermittent AE will be reported separately. AEs and SAEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded, monitored and followed-up until the resolution (or until the Investigator deems the event to be stable/chronic).

7.1 Definitions

7.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to Baseline, or become explainable). Laboratory abnormalities and changes in vital signs are considered to be AEs only if they necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

7.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to the Biorasi Safety and Pharmacovigilance as a serious adverse event (SAE) using SAE report form within 24 hours of occurrence or notification to the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an out-patient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly/birth defect	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Other Important Medical Event	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE and SAE:

Mild	The event is transient and easily tolerated by the subject.
Moderate	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.3 Causality of Adverse Events

The Investigator will use the following definitions to assess the relationship of the AE/SAE to the use of

investigational product:

Definitely Related	The event occurred within a reasonable time after drug administration or drug concentration and body fluids demonstrated that the study drug was present: the event could not be reasonably explained by known characteristics including concomitant therapies; the adverse event abated after discontinuing the study drug.
Probably Related	The event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.
Possibly Related	The event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	The event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	The event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to study drug or has a much more likely alternative etiology).

If an Investigator's opinion of possibly, probably not, or not related to study drug is given, an alternate etiology must be provided by the Investigator for the AE.

7.4 Adverse Event Collection Period

Any AE/SAE prior to the Baseline visit will be considered past medical history (PMH). The AE reporting period for this study begins upon receiving the first application of investigational product and ends at the final protocol required visit. SAE(s) that are observed or spontaneously reported during the subject's participation in the trial will be captured and monitored until the Investigator deems the event to be chronic or not clinically significant or the subject to be stable.

7.5 Adverse Event Reporting

In the event of a SAE, whether related to study drug or not, the Investigator or representative must make an accurate and adequate report consisting of at least the minimum criteria (Site and Subject ID, Date site became aware of the event, SAE Term, Seriousness criteria, Study Drug information, Investigator/Reporter and site address) within 24 hours by email, fax, or telephone to Biorasi Safety and Pharmacovigilance team. Biorasi Safety and Pharmacovigilance team will complete the SAE report onto a MedWatch 3500A form for evaluation and convey for review by the Medical Monitor and Sponsor contact. Accurate Completion of the MedWatch 3500A form will consist of all data supplied such as Subject's demography, SAE narrative, concomitant medication, laboratory parameters and relevant medical history.

In addition, if required by the applicable IRB/IEC, the Investigator will submit the SAE reports to the IRB/IEC within 15 calendar days of discovering the SAE, or alternatively, within accordance of applicable

regulations or IRB/IEC requirements.

Copies of each report with the associated documentation (i.e., queries, medical records, lab records, IRB/IEC communications and all source documents) will be kept in the site's study file.

A subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the Investigator or may be referred to another appropriate physician for treatment and follow-up. The Investigational Site will be responsible for collection and forwarding follow-up SAE information to the Biorasi Safety and Pharmacovigilance.

MEDICAL MONITOR
Sergey Yagoda, MD, PhD
Biorasi Safety and Pharmacovigilance
E-mail : syagoda@biorasi.com
Address: 19495 Biscayne Blvd., Suite #900, Aventura, FL 33180
Fax : +1 (786) 221-3531

7.6 Unblinding due to SAE

Treatment assignment for an individual subject should be unblinded only in an emergency by the Investigator, when knowledge of the treatment assignment is urgently needed for the clinical management or welfare of the subject. Treatment should be provided in accordance with the medical condition and with regard to the information provided in the Investigator's Brochure.

The Investigator must document the breaking of the code, and the reasons for doing so on the eCRF, in the site file, and in the medical notes.

The Investigator must notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break. Subject always to clinical need and where possible, all other members of the research team should remain blinded.

8. DATA ANALYSIS

The sections below summarize the intended statistical methods and analyses of data for the study. A more detailed statistical analysis plan will be written prior to finalization of the clinical trial database. Any changes to the planned methods and analyses will be described and justified in the protocol and/or in the final clinical study report, as appropriate.

Descriptive statistical methods will be used to summarize the data from this study, with confidence intervals calculated for the primary and secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and proportions for categorical data. The term "treatment group" refers to randomized treatment assignment: active-test and active-reference. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment assignment, subject number, and then by date within each subject number.
Unless specified otherwise, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.
All statistical analyses will be conducted with the SAS® System, version 9.1.3 or higher.

8.1 Subject Population/Data Sets to Be Evaluated

The subject populations are defined as follows:

1. **Safety Population:** The safety population is any randomized individual who (a) was enrolled into the study, and (b) received at least one dose of study treatment.
2. **Modified Intent-to-Treat (mITT) Population:** A modified intent-to-treat subject is any randomized individual who (a) met inclusion/exclusion criteria, (b) was enrolled into the study, (c) received at least one dose of the assigned study treatment, and (c) had at least one post-baseline visit.
3. **Per Protocol (PP) Population:** A per-protocol subject is any randomized individual who (a) met inclusion/exclusion criteria, (b) was enrolled into the study, (c) received the assigned study treatment, (d) had not taken any concomitant medications prohibited by the protocol or experienced any major deviations that interfered with or may have interfered with the therapeutic administration of the treatment or the precise evaluation of treatment efficacy, and (e) completed the primary endpoint evaluation within the designated visit window (±4 days).

Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of scabies during the study will be discontinued, included in both the mITT and PP population analyses as treatment failures. Subjects who discontinue early for reasons other than treatment failure will be excluded from the PP population, but included in the mITT population, using Last Observation Carried Forward (LOCF).

Efficacy analyses will be performed using the per-protocol population as definitive and the mITT population as supportive. Safety analyses will be performed using the Safety population.

8.2 Sample Size Determination

Under the assumption that the Reference product has a cure rate of at least 88%, sample size evaluations were conducted, via computer simulation, to determine the probability (power) of the calculated 90% continuity-corrected confidence interval on the Test-to-Reference difference in cure proportions to be contained in the bioequivalence interval [-0.20, +0.20]. When the Test product was assumed to have the same 88% cure rate, the required number of PP subjects in each treatment group was determined to be 56 (112 total) for a power ≥0.80. Allowing for up to 20% of the subjects to not qualify for the PP population, 70 subjects in each treatment group (140 total) would be needed.

If it is assumed that the Test product cure rate might deviate from that of the Reference by as much as 2% (e.g. 86% instead of 88%) and if a higher power, ≥0.95, was desired, then 91 PP subjects in each treatment group (182 total) would be needed. To allow for up to 20% of the subjects to not qualify for the PP population, 114 subjects in each treatment group (228 total) would need to be enrolled.

8.3 Statistical Analyses

8.3.1 Subject Disposition and Demography

Descriptive statistics will be generated by treatment group for selected continuous variables. The number and percentage of subjects in each class of categorical demographic and Baseline variables (e.g., gender, ethnicity, and race) will be tabulated by treatment group. Individual subject demographic and Baseline characteristic data will be listed.

8.3.2 Assessment of Bioequivalence as Primary and Secondary Endpoints

Bioequivalence assessment will be evaluated by comparing proportions of patients cured in the test and the reference treatment groups. Bioequivalence between the test and the reference product will be established if the 90% confidence interval for the difference in proportions cured between test and reference treatment is contained within the equivalence limits [-0.20, +0.20].

In this case, the compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$ (meaning test product is not bioequivalent to the reference);

H_A: $-0.20 \leq p_T - p_R \leq 0.20$ (supporting bioequivalence);

where p_T = cure rate of test treatment, p_R = cure rate of reference treatment.

Let n_T = sample size of test treatment group, n_R = sample size of reference treatment group and

se = $(\widehat{p_T}(1-\widehat{p_T})/n_T + \widehat{p_R}(1-\widehat{p_R})/n_R)^{\frac{1}{2}}$.

The 90% confidence interval will be estimated as follows, using Yates correction:

$L = (\hat{p}_T - \hat{p}_R) - 1.645 \times se - (\frac{1}{n_T} + \frac{1}{n_R})/2$

$U = (\hat{p}_T - \hat{p}_R) + 1.645 \times se + (\frac{1}{n_T} + \frac{1}{n_R})/2$

H_0 is rejected if L ≥ -0.20 and U ≤ 0.20 resulting in accepting H_A and concluding bioequivalence of the two products.

The primary endpoint is the evaluation at Day 28. The results in the PP population will be considered definitive, with those in the mITT population as supportive.

As a secondary endpoint evaluation, patients' clinical progress at visit 4 (Day 14) will be assessed and proportion of cured patients in each of the treatment arms will be compared using the procedure above.

8.3.3 Assessment of retreatment

Proportion of subjects requiring retreatment in each of the treatment groups will be compared descriptively.

8.3.4 Assessment of Tolerability

Descriptive statistics using categorical methods will be used to compare tolerability measures (scores of Stinging/Burning and Itching sensations collected during Patient Self-Assessments) between the test and reference treatment groups.

8.3.5 Assessment of Safety

The reporting of safety data is descriptive, and will include all subjects who receive at least one dose of investigational product. The variables for safety endpoints are AEs and vital signs measurements. AEs will be summarized based on the frequency of AEs and their severity for all treated subjects. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

If a subject experiences multiple events that map to a single preferred term, the greatest severity and strongest Investigator assessment of relation to study drug will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study drug.

Summaries of treatment-emergent AEs will include any AEs reported beginning with the first dose of study drug on Day 1. The occurrence of treatment-emergent adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study drug will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.

These data will be summarized by treatment group. Previous and concomitant medications will be presented in a data listing.

9. REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

9.1 Ethical Conduct of the Study

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World

Medical Association (2013) (See Appendix C). In addition, the study will be conducted in accordance with the protocol, the ICH guideline on

GCP, and applicable local regulatory requirements and laws.

9.2 Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (e.g., recruitment advertisements, if applicable) from the IRB/IEC. All correspondence with the IRB/IEC will be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to the Sponsor or its designee.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In case of such an event, the Investigator must notify the IRB/IEC and the Sponsor in writing immediately after the implementation.

9.3 Other Required Approvals

In addition to IRB/IEC approval, all other required approvals (e.g. approval from local Research and Development Board or Scientific Committee) required by the individual site for participating in this study will be obtained by the Investigator prior to recruitment of subjects into the study and shipment of the investigational product(s). It is the responsibility of the Investigator to notify the Sponsor and the CRO of the requirement of such approvals prior to participating tin the study.

9.4 Informed Consent

It is the responsibility of the Investigator to give each subject (or the subject's acceptable representative), prior to inclusion in the trial, full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. The subjects must be informed about their right to withdraw from the trial at any time.

Furthermore, it is the responsibility of the Investigator, or a person designated by the Investigator, to obtain signed informed consent from each subject or the subject's legally acceptable representative prior to inclusion in the trial. The Investigator will retain the original of each subject's signed consent form.

The informed consent form will be in compliance with ICH GCP, local regulatory requirements, and legal

requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use.

9.5 Subject Confidentiality

All parties will ensure protection of subject personal data and will not include subject names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's CRF).

9.6 Publication

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

10. ADMINISTRATIVE OBLIGATIONS

10.1 Source Documentation Forms

The Investigator/institution will permit study-related monitoring, audits/inspections, IRB/IEC review and regulatory inspection providing direct access to source documents, including all medical records or pertinent data relevant to the audit/inspection. Source documents will represent a record of the raw data. Source document templates may be provided by either the clinical site or the Sponsor. If provided by the clinical site, the source document template must be provided to the Sponsor prior to subject recruitment. The source documents will become part of the subject's permanent medical record maintained by the clinical site. If computerized systems are used to create, modify, maintain, archive, retrieve or transmit source data, they must comply with the applicable regulatory regulations and/or guidances (ex. 21 CFR Part 11 and 312).

Electronic CRFs (eCRFs) will be used in this study. eCRFs are required and should be completed for each subject participating in the study. eCRFs will contain data captured from subject source documents and results of laboratory tests. In most cases, the source documents are contained in the subject's chart at the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts. Data must be transcribed from the source documents (e.g. physical exam report, associated medical records, date and version of informed consent form) onto the eCRF by clinical site personnel prior to data monitoring.

Any corrections to entries made in the source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms.

Investigator will sign eCRFs electronically after completion of data entry, to attest that the data contained on the CRFs is complete and accurate. Completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

10.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs, SAE forms, source documents, detailed records of drug disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records will be retained by the Investigator according to the International Conference on Harmonization (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor will be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain Sponsor's written permission before disposing of any records, even if retention requirements have been met.

10.3 Quality Control (QC) and Quality Assurance (QA)

10.3.1 Study Site Monitoring Visits

During study conduct, the Sponsor or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The Investigator/institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may also be subject to quality assurance audits performed by the Sponsor or companies working with or on behalf of the Sponsor, and/or review by the IRB/IEC, and/or to inspection by appropriate regulatory authorities

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

10.3.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. The site should document all protocol deviations (PDs) in the subject's source documents. In the event of a significant deviation, the site will notify the Sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessments. Deviations from the inclusion/exclusion criteria will not be permitted unless written approval by the Mayne Pharma, Inc. has been obtained. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator will contact Biorasi Safety and Pharmacovigilance at the below mentioned address in order to determine the appropriate course of action.

BIORASI SAFETY AND PHARMACOVIGILANCE
E-mail: safety@biorasi.com
19495 Biscayne Blvd., Suite #900
Aventura, FL 33180
Fax: +1 (786) 221-3531

Site will be responsible for proper maintaining and filing of all PD related documentation in the site files.

10.4 Trial Discontinuation/Investigative Site Termination

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the trial.

10.4.1 Criteria for Premature Termination or Suspension of the Study

The following criteria may result in either temporary suspension or early termination of the study:

- New information regarding the safety or efficacy of the investigational product that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The Sponsor reserves the right to discontinue the trial for other valid administrative reasons.

10.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

10.4.3 Procedures for Premature Termination or Suspension of the Study or Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

11. REFERENCES

1. Chosidow, O. (2000). Scabies and pediculosis. The Lancet, 355(9206), 819-26.
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4. CDC - Scabies – Treatment. http://www.cdc.gov/parasites/scabies/treatment.html. September 6, 2016.
5. Goldust, M., Rezaee, E., Raghifar, R., Hemayat, S. (2013). Treatment of scabies: the topical ivermectin vs permethrin 2.5%. Annals of Parasitology, 59(2), 79-84.
6. Ranjkesh, M.R., Naghili, B., Goldust, M., Rezaee, E. (2013). The efficacy of permethrin 5% vs. oral ivermectin for the treatment of scabies. Annals of Parasitology, 59(4), 189- 194.
7. Bachewar, N.P., Thawani, V.R., Mali, S.N., Gharpure, K.J., Shingade, V.P., Dakhale, G.N. (2009). Comparison of safety, efficacy, and cost effectiveness of benzyl benzoate, permethrin, and ivermectin in patients of scabies. Indian J Pharmacol, 41(1), 9-14.

12. APPENDICES

12.1 Appendix A. Study Flowchart

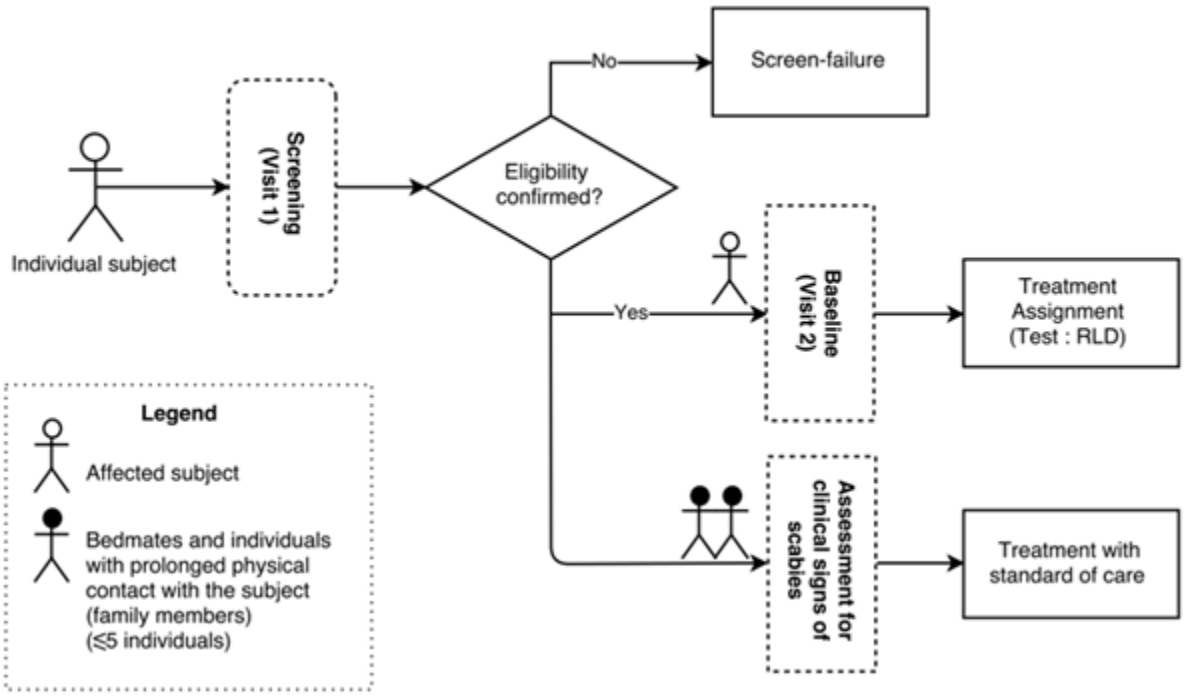


Figure 1. Enrolling Subjects with Affected or High-Risk bedmates/Family Members

12.2 Appendix B. Schedule of Events

Visit Number	Visit 1 Screening	Visit 2 Baseline[1]	Visit 3 Interim	Visit 4 Interim	Visit 5 EOS/ET[2]
Visit Day	Day -5 to 1	Day 1	Day 7 (±1)	Day 14 (±2)	Day 28 (±4)
Informed Consent	X				
Eligibility Criteria	X				
Subject Demographics	X				
Medical History	X				
Physical Examination	X[3]				
Randomization		X[4]			
Vital Signs	X	X			X
Urine Pregnancy Test[5]	X				X
Visual Examination of Lesions	X	X	X	X	X
Microscopic Examination of Skin Scraping[6]	X				
Patient Self-Assessment		X	X	X	X
Investigational Product Dispensation		X		X[7]	
Treatment with Investigational Product		X		X[8]	
Investigational Product Accountability			X		X[8]
Subject Diary Compliance Review			X		X[8]
Concomitant and Prohibited Medication Review	X	X	X	X	X
Adverse Events Assessment			X[8]	X	X

[1] Visit 2 (Baseline) may be completed on the same day as visit 1 (Screening). If Screening and Baseline are completed on the same day, assessments performed on both Screening and Baseline need only be performed once. Refer to Section 6.3.2 for details and restrictions.
[2] End of Study/Early Termination.
[3] Physical examinations are to be performed if Inclusion/Exclusion Criteria are satisfied at Screening
[4] Prior to Randomization, the Investigator must confirm the subject still meets all Inclusion/Exclusion Criteria.
[5] For females of child-bearing potential.
[6] Any new lesions identified at visits 3, 4 or 5 will be confirmed by microscopic evaluation of skin scraping.
[7] Applicable for subjects requiring second application of the investigational product.
[8] AE reporting period for this study begins upon receiving the first application of investigational product and ends at the final protocol required visit.

12.3 Appendix C. Subject Diary

SUBJECT DIARY

Protocol Number :	**MAP-8184**
Study Title :	**A Multi-Center, Double-Blind, Randomized, Parallel-Group Study Comparing Permethrin Cream, 5% (Mayne Pharma, Inc.) with Elimite™ in patients with active scabies**

To be completed by the study team member

SUBJECT NUMBER :								SUBJECT INITIALS:	

SUBJECT TREATMENT INFORMATION		
Study Visit	**Baseline**	**Day 14**
Dose Application	**1st Application**	**2nd Application**
Status	☒ Required	☐ Required ☐ Not Required

HOUSEHOLD MEMBERS TREATMENT INFORMATION	
No of Household Members with Active scabies	
Number of Standard of Care tubes provided	

VISIT 2: BASELINE (DAY 1)

VISIT DATE AT CLINIC: | | | | | | | | | |

D D M M M Y Y Y Y

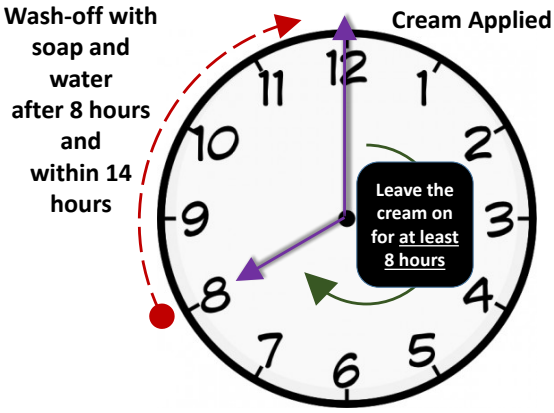
PRIOR TO APPLICATION OF THE STUDY DRUG

Please follow the instructions given below and check the box for confirmation of the same. Provide supervision to children and those who require assistance.

Activity	Instructions	Status check (Tick)
LAUNDRY DISINFECTION	▪ Machine-wash personal clothes, towels, linens and other items of all household members with scabies that have everyday physical contact for the last week with in a hot water (at least 50 °C or 120 °F) ▪ Dry these items using a high heat cycle. ▪ Non-washable items can be put into the dryer for at least 20 minutes on a high heat. Alternatively, they can be sealed in a plastic bags for a week.	☐ Yes ☐ No
NAILS HYGIENE	▪ Clip fingernail and toenails with your scissors or clipper ▪ Wash and scrub under-the-nails areas in hot soapy water	☐ Yes ☐ No
BODY HYGIENE	▪ Take a warm shower (NOT a hot bath) using a non-medicated soap ▪ Dry thoroughly and cool-down before the next step	☐ Yes ☐ No

APPLICATION OF THE STUDY DRUG

Activity	Instructions for Application of study drug	Status check (Tick)
Application of Cream	▪ Apply thin layer of the Study Drug to the entire body from the neck down to the bottom of the feet. ▪ Pay special attention to the areas between fingers and toes, under nails, wrists, armpits, skin surface of around genitalia (but NOT internally), breasts and buttocks. ▪ The cream rubs completely into the skin so you do not need to keep applying more cream until you can see it on the skin. ▪ Avoid contact with eyes. Flush with water immediately if the cream gets into your eyes ▪ Record the date and time of Application. ▪ Leave the cream on your body for **8-14 hours** before washing it out (for example, you can leave it overnight). Re-apply the Study Drug to hands if	☐ Yes ☐ No **Date of Application** D D M M M Y Y Y Y **Time of Application** H H M M

APPLICATION OF THE STUDY DRUG		
Activity	**Instructions for Application of study drug**	**Status check (Tick)**
	they are washed with soap and water within 8 hours of treatment.	
AFTER Application of Cream	 ▪ Record the date and time when the cream was washed off. ▪ Wear clean clothes after treatment is completed. Do not wear the same clothes that were worn while treating; likewise, change bedding and towels etc.	☐ Yes ☐ No **Date of Wash-off** D D M M M Y Y Y Y **Time of Wash-off** H H M M

TREATMENT CHECK FOR AFFECTED HOUSEHOLD MEMBERS	
Household members are to follow the same instruction as detailed above for you (subject of the study). Please ensure you and your affected household members take treatment on the same day.	
Activity	**Status check (Tick)**
LAUNDRY DISINFECTION : Machine-wash personal clothes, towels, linens and other items	☐ Yes ☐ No
NAILS HYGIENE : Finger nails clipped and wash hands in hot soapy water	☐ Yes ☐ No
BODY HYGIENE : Warm shower using a non-medicated soup	☐ Yes ☐ No
CREAM APPLICATION: Apply cream and leave on for 8 hours	☐ Yes ☐ No
CREAM WASH-OFF: Wash-off cream after 8 hours and within 14 hours	☐ Yes ☐ No

Please answer the following questions by ticking the correct box:

1. Have you had any health problems since your last visit to clinic?

Yes☐ No☐

2. Have you had any local skin reactions since your last visit to clinic?

Yes☐ No☐

3. Have you taken any new medications since your last visit to clinic?

Yes☐ No☐

In case of medical emergency call 911 immediately.

Remember the next study visit date is Day 7 i.e. 6 days from Visit 2 (Day 1): _____

Subject's Initials: ___-___ -___

Date: ___ ___ -___ ___ ___ -___ ___ ___ ___

Initials of Site Staff verifying the completeness of the Subject Diary: ___-___ -___

Date of Verification: ___ ___ -___ ___ ___ -___ ___ ___ ___

VISIT 4: INTERIM (DAY 14)

VISIT DATE AT CLINIC:

D	D	M	M	M	Y	Y	Y	Y

Does the subject require second Application of the Study Drug? ☐ **Yes** ☐ **No**

Note for Site Staff:

If **YES**: Dispense the study drug and provide this Subject Diary

If **NO**: File this Subject Diary along with the Source Document Worksheet.

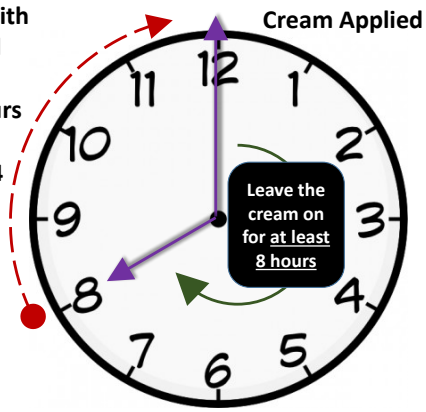
PRIOR TO APPLICATION OF THE STUDY DRUG

Please follow the instructions given below and check the box for confirmation of the same. Provide supervision to children and those who require assistance.

Activity	Instructions	Status check (Tick)
LAUNDRY DISINFECTION	▪ Machine-wash personal clothes, towels, linens and other items of all household members with scabies that have everyday physical contact for the last week with in a hot water (at least 50 °C or 120 °F) ▪ Dry these items using a high heat cycle. ▪ Non-washable items can be put into the dryer for at least 20 minutes on a high heat. Alternatively, they can be sealed in a plastic bags for a week.	☐ Yes ☐ No
NAILS HYGIENE	▪ Clip fingernail and toenails with your scissors or clipper ▪ Wash and scrub under-the-nails areas in hot soapy water	☐ Yes ☐ No
BODY HYGIENE	▪ Take a warm shower (NOT a hot bath) using a non-medicated soap ▪ Dry thoroughly and cool-down before the next step	☐ Yes ☐ No

APPLICATION OF THE STUDY DRUG

Activity	Instructions for Application of study drug	Status check (Tick)
Application of Cream	▪ Apply thin layer of the Study Drug to the entire body from the neck down to the bottom of the feet. ▪ Pay special attention to the areas between fingers and toes, under nails, wrists, armpits, skin surface of around genitalia, breasts and buttocks. ▪ The cream rubs completely into the skin so you do not need to keep applying more cream until you can see it on the skin. ▪ Avoid contact with eyes. Flush with water immediately if the cream gets into your eyes ▪ Record the date and time of Application ▪ Leave the cream on your body for 8-14 hours before washing it out (for example, you can leave it	☐ Yes ☐ No **Date of Application** D D M M M Y Y Y Y **Time of Application** H H M M

APPLICATION OF THE STUDY DRUG		
Activity	**Instructions for Application of study drug**	**Status check (Tick)**
	overnight). Re-apply the Study Drug to hands if they are washed with soap and water within 8 hours of treatment.	
AFTER Application of Cream	**Wash-off with soap and water after 8 hours and within 14 hours**  ▪ Record the date and time of the cream was washed off. ▪ Wear clean clothes after treatment is completed. Do not wear the same clothes that were worn while treating; likewise, change bedding and towels etc.	☐ Yes ☐ No **Date of Wash-off** D D M M M Y Y Y Y **Time of Wash-off** H H M M

TREATMENT CHECK FOR AFFECTED HOUSEHOLD MEMBERS	
Household members are to follow the same instruction as detailed above for you (subject of the study). Please ensure you and your affected household members take treatment on the same day.	
Activity	**Status check (Tick)**
LAUNDRY DISINFECTION : Machine-wash personal clothes, towels, linens and other items	☐ Yes ☐ No
NAILS HYGIENE : Finger nails clipped and wash hands in hot soapy water	☐ Yes ☐ No
BODY HYGIENE : Warm shower using a non-medicated soup	☐ Yes ☐ No
CREAM APPLICATION: Apply cream and leave on for 8 hours	☐ Yes ☐ No
CREAM WASH-OFF: Wash-off cream after 8 hours and within 14 hours	☐ Yes ☐ No

Please answer the following questions by ticking the correct box:

1. Have you had any health problems since your last visit to clinic?

Yes☐ No☐

2. Have you had any local skin reactions since your last visit to clinic?

Yes☐ No☐

3. Have you taken any new medications since your last visit to clinic?

Yes☐ No☐

In case of medical emergency call 911 immediately.

Remember the next study visit date is Day 28 i.e. 14 days from Visit 4 (Day 14): _____

Subject's Initials: ___-___ -___

Date: ___ ___ -___ ___ ___ -___ ___ ___ ___

Initials of Site Staff verifying the completeness of the Subject Diary: ___-___ -___

Date of Verification: ___ ___ -___ ___ ___ -___ ___ ___ ___

12.4 Appendix D. Patient Self-Assessment

PATIENT SELF-ASSESSMENT

PROTOCOL NO: MAP-8184	SUBJECT NUMBER :								Subject Initials:	

Visit Number	*Visit 2 [Baseline]*	*Visit 3 [Interim]*	*Visit 4 [Interim]*	Visit 5 [EOS/ET]
Visit Day	Day 1	Day 7	Day 14	Day 28
Check one	☐	☐	☐	☐

VISIT DATE :									
	D	D	M	M	M	Y	Y	Y	Y

This self-assessment is aimed to see how bad are the itching and stinging/burning sensations that you may experience during the last 24 hours. Please rate these feelings by marking one most suitable option from each table below.

ITCHING

(Intense, distracting irritation or tickling sensation in the last 24 hours)

Score	Grade	Definition	**Check one**
0	None	No Itching	☐
1	Mild	Barely perceptible, slightly present itch	☐
2	Moderate	Distinct presence of itch	☐
3	Severe	Marked, intense, yet tolerable itch	☐
4	Very Severe	Unbearable, intense itch	☐

STINGING/BURNING

(Sensation of the skin is painfully hot or noticeable tingling sensation in the last 24 hours)

Score	Grade	Definition	**Check one**
0	None	Absent	☐
1	Mild	Slight, barely present	☐
2	Moderate	Distinct presence	☐
3	Severe	Marked, intense	☐

Subject Initials: _____ Date: _____