CLINICAL STUDY PROTOCOL

A Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® Ivermectin 0.5% Lotion in the Treatment of Head Lice

Protocol Identifying Number: MAP-7189

Sponsor: Mayne Pharma, LLC

1240 Sugg Parkway,

Greenville, NC 27834 USA

Phone: +1 (252) 717-1382

Fax: +1 (252) 758-8522

Funded by: Mayne Pharma, LLC

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

Chandra Vattikonda — 03-Jan-2018

Chandra Vattikonda, M.Pharm., Ph.D.
Senior Director, Clinical Pharmacology
Mayne Pharma Inc.

Date

03 JAN 2018

Phoevos Hughes, J.D.
Project Director
Biorasi LLC

Date

04 Jan 2018

Sergey Pavlenko, MD
Medical Monitor
Biorasi Safety and Pharmacovigilance

Date

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Protocol Amendment 2 Summary of Changes

Section	Description of Change
Synopsis, Inclusion Criteria #1	The index subject must be the youngest family member, under the age of 18, changed to index subject must be the youngest family member, through 18 years of age.
Synopsis, Inclusion Criteria #4	Index subject 6 months of age and a maximum 18 years of age changed to Index subject is at least 6 months through 18 years of age.
Synopsis, Inclusion Criteria #6	Assent form administration age for children changed from 6-18 years to 6-17 years.
Section 4.1, Description of Study Design	Subject population changed from 6 months to 18 years changed to 6 months through 18 years.
Section 5.1, Inclusion Criteria #1	The index subject must be the youngest family member, under the age of 18, changed to index subject must be the youngest family member, through 18 years of age.
Section 5.1, Inclusion Criteria #4	Index subject 6 months of age and a maximum 18 years of age changed to Index subject is at least 6 months through 18 years of age.
Section 5.1, Inclusion Criteria #6	Assent form administration age for children changed from 6-18 years to 6-17 years.
Section 5.3, Criteria for Inclusion of Minor Subjects	Subjects under the age of 18 must sign assent form changed to subjects aged 6 years through 17 years of age must sign assent form.

Change made to Sponsor representative when transfer of oversight took place at Mayne Pharma, LLC

Protocol Amendment 1 Summary of Changes

Affected Section(s)	Summary of Revisions Made	Rationale
Protocol Synopsis, Inclusion Criteria # 6	Assent form administration age for children changed from 12-18 years to 6-18 years.	Assent Age Range approved by IRB directly contradicts Assent Age Range listed in Protocol Inclusion Criteria # 6 (12-18 years).
Section 5.1, Inclusion Criteria # 6	Assent form administration age for children changed from 12-18 years to 6-18 years.	Assent Age Range approved by IRB directly contradicts Assent Age Range listed in Protocol Inclusion Criteria # 6 (12-18 years).
Section 6.1.7, Blinding	Replaced the word 'IWRS' with 'Unblinded Treatment List' to unblind the treatment for the individual subject, if situation arises.	A decision was made to perform Randomization and Unblinding the treatment of an individual subject manually instead of using IWRS.

List of Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Forms
EOS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMV	Interim Monitoring Visit
IRB	Investigational Review Board
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
Mayne	Mayne Pharma, LLC/ Mayne Pharma International Pty Ltd
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRT	Mean Residence Time
OTC	Over the Counter
PI	Principal Investigator
PMH	Past Medical History
PP	Per-Protocol
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
US	United States
WHO	World Health Organization

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 International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and local regulatory requirements.

Print Name	
Title	
Address of Institution / Site	
Telephone Number:	

INVESTIGATOR SIGNATURE: _____ DATE: _____

Synopsis

Study Title	A Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® 0.5% Lotion in the Treatment of Head Lice
Protocol Number	MAP-7189
Development Phase	3
Type of Study	Clinical Endpoint Bioequivalence
Test Product	Ivermectin 0.5% Lotion Sklice® 0.5% Lotion Placebo Lotion
Name of Active Ingredient	Ivermectin
Route, Dose and Dosage Regimen	Route: Topical application Dose: Apply full tube amount (4 oz.) to dry hair to completely cover scalp and hair. Apply closest to the scalp first, and then apply outwards towards the ends of the hair. Regimen: One 10-minute application then thoroughly rinse with warm water
Sponsor	Mayne Pharma, LLC Greenville, NC, USA
Study Objectives	The primary objective of the study is to establish the efficacy of a single application of Ivermectin 0.5% lotion in the treatment of head lice (*Pediculus humanus capitis)* under at-home conditions compared with Sklice® 0.5% lotion, and to demonstrate that both active lotions have superior efficacy compared to Placebo. The secondary objective of the study is to demonstrate the safety and local tolerability of Ivermectin 0.5% lotion compared with Sklice® 0.5% lotion.

Study Endpoints	The primary efficacy endpoint is the proportion of index subjects who are lice free (defined as no live lice, adults or nymphs) 14 days (Day 15) after treatment. The secondary efficacy endpoint is the number and percentage of all index subjects who are lice-free at Day 2.
Number of Subjects and Sites	The planned overall sample size for this clinical trial is approximately 280 index subjects, who will be randomized at approximately 6 geographically diverse clinical research centers in the United States
Eligibility Criteria	Subjects who satisfy ALL the following **inclusion** and have NONE of the following **exclusion** criteria may be enrolled in the study: **INCLUSION CRITERIA:** 1. Subjects must have an active head lice infestation defined as: At least 3 live lice (adults and/or nymphs) present on the scalp and/or hair, as determined by a trained evaluator. The index subject must be the youngest family member, through the age of 18, presenting with an active head lice infestation. 2. Household members that have an active head lice infestation defined as: At least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator (with the exception of the male head of household who may self-assess as being lice free) will receive the Standard of Care with an over-the-counter head lice treatment product. Up to 3 infested household members may receive treatment, if more than 3 household members are infested, the entire household will be excluded from the study. 3. Subject is male or female. 4. Index subject is at least 6 months through 18 years of age at time of enrollment. 5. Subject is in good general health based on medical history. 6. Each subject must have an appropriately signed Informed Consent agreement. A caregiver must sign an Informed Consent agreement for children not old enough to do so. Children ages 6-17 years of age will be administered a child's Assent Form. 7. The caregiver of a subject must be willing to allow all household members to be screened for head lice. If other household members are found to have an active head lice infestation, they must be willing and able to

participate in receiving the Standard of Care. No more than one working male per household may be excluded from evaluation if he is assessed as being lice free by himself or the caregiver and cannot come in due to his work schedule. If this individual may have lice, he must come to the test facility; otherwise the entire household will be excluded from study participation.

8. Subject and/or their caregiver must be physically able and willing to apply the test product according to established treatment methods.
9. Subject agrees not to use any other form of lice treatments (commercial, community-anecdotal, or mechanical/manual) while participating in the study.
10. Following application and rinsing of the test product, subject agrees not to shampoo, wash, or rinse their hair or scalp until the 24-hour post-treatment evaluation has been completed.
11. Subject agrees to not cut or chemically treat their hair while participating in the study.
12. Subject agrees to follow all study instructions, including attending all follow-up appointments.
13. Female index subjects of childbearing potential must be willing to have a urine pregnancy test prior to inclusion in this study.
14. In the event of a subject judged to be incapable of self-treating, the household must have a caregiver willing to apply the treatment at home.

EXCLUSION CRITERIA:

1. Index subjects with greater than 3 household members with at least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator will be automatically excluded from the trial.
2. Youngest household member is over 18 years of age.
3. History of irritation or sensitivity to ivermectin or the lotion components, pediculicides or hair care products.
4. Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation, such as an erythema score that is >2, blisters, vesicles which, in the opinion of the investigative

personnel or medical monitor, will interfere with safety and/or efficacy evaluations.

5. Presentation at the treatment site with eczema or atopic dermatitis.
6. Treatment for head lice (Over the counter [OTC], home remedy and/or Prescription) in the last 15 days.
7. Any condition or illness that, in the opinion of the investigator, may compromise the objective of the protocol.
8. Is receiving any other treatment which, in the opinion of the investigator or medical monitor, may interfere with the study results.
9. Females (including caregivers who come in contact with the investigational product) who are pregnant, nursing or planning a pregnancy which could include index subjects. If a household has a pregnant female who has an active case of lice, the entire household is excluded from participation. If this pregnant household member does not have an active infestation, this individual must NOT be the caregiver (one who provides treatment to other household members).
10. Index subject of child-bearing potential, and unwilling to use an adequate method of contraception for the duration of the study. Adequate methods of contraception include: abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, Intra uterine devices, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly, surgical sterilization. Index subjects and/or their caregivers will be considered non-child-bearing if the following has occurred: full hysterectomy or bilateral oophorectomy is considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization.
11. Participation in a previous investigational drug study within the past 30 days.
12. Does not understand the requirements for study participation and/or may likely exhibit poor compliance, in the opinion of the investigator.
13. Does not have a known household affiliation with their household members (i.e., do not stay in one household consistently, sleeping at one place several nights and then at another place or location). Household is defined as living in a shared area or space (for example the same house or apartment unit).

Withdrawal and Early Discontinuation	*A subject will be discontinued from this study if <u>any</u> of the following criteria are met:* • Withdrawal of consent by the subject is received. • In the opinion of the Investigator or Medical Monitor it is not in the subject's best interests to continue in the study. • Occurrence of an Adverse Event (AE) or Serious Adverse Event (SAE), which, in the opinion of the Investigator, warrants discontinuation of the subject from the study. • Pregnancy as informed by the subject or as determined by a positive urine pregnancy test. If found to be positive, subject will be discontinued from the study. • Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study, as determined by the Investigator. • Subject is deemed to be a treatment failure if upon revisit it is determined that they are still infested. They will be terminated from the study and provided the standard of care at that point in the study. • Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant • The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

Prohibited Concomitant Medication/Products and Treatments	• Head lice treatment product (over the counter [OTC], home remedy and/or Prescription) may include:
	  • Nix
	  • Rid
	  • Kwell
	  • LiceMD
	• No medications are contraindicated for use with topical ivermectin lotion

Study Agents	• Ivermectin 0.5% Lotion • Sklice® 0.5% Lotion • Placebo Lotion
Study Duration	15 Days +/- 3 Day window
Statistical Analysis	**ANALYSIS POPULATIONS** **Safety Population** includes all subjects who were randomized and dispensed treatment. This is the population that will be used for the safety assessments. **Modified Intent-to-Treat (mITT) population** includes all Index subjects who met all inclusion/exclusion criteria, were randomized, dispensed treatment, and had at least

one post-treatment efficacy evaluation. This is the primary population for determination of the superiority of the active treatments over placebo.

Per-Protocol (PP) population includes all mITT subjects who applied their dispensed treatment, had no protocol deviations which could have interfered with the accurate assessment of treatment efficacy, and returned for the Day 15 visit within the allowed window. This is the primary population for the efficacy comparisons between the two active treatment groups.

EFFICACY ANALYSIS

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of index subjects who are lice free (defined as no live lice, adults or nymphs) 14 days (Day 15) after treatment. The superiority of Test and Reference treatment's cure proportions over that of the placebo will be evaluated using continuity-corrected Z-tests ($\alpha = 0.05$, 2-sided). The comparability of the Test and Reference treatments will be evaluated using a 90% continuity-corrected confidence interval on the difference between their cure proportions and a bioequivalence margin = 0.20 (20%).

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the number and percentage of all index subjects who are lice free at Day 2.

SAFETY ANALYSIS

Descriptive statistics on the severity and duration of adverse events (AEs) from all subjects will be determined for each treatment group for any AE that occurs in at least 5% of the subjects.

Analysis of tolerability will be based on scores of Stinging/Burning and Itching sensations collected during Subject Self-Assessment and Site Assessment at all follow-up visits between the test and reference treatment groups.

1 Key Roles

PRINCIPAL CONTACTS

CLINICAL PROTOCOL AND CONDUCT INQUIRIES	**Chandra Vattikonda, M.Pharm., Ph.D.** Senior Director, Clinical Pharmacology Mayne Pharma Inc. email: Chandra.Vattikonda@maynepharma.com 1240 Sugg Parkway, Greenville, NC 27834 USA Phone: +1 (252) 707-6266 Fax: +1 (252) 758-8522 **Phoevos Hughes, J.D.** Project Director Biorasi LLC email: phughes@biorasi.com 19495 Biscayne Blvd., Suite #900 Aventura, FL 33180 Phone: +1 (786) 888-2245
CLINICAL SAFETY INQUIRIES	**Sergey Pavlenko, MD** Medical Monitor Biorasi Safety and Pharmacovigilance email: spavlenko@biorasi.com 19495 Biscayne Blvd., Suite #900 Aventura, FL 33180 Fax: +1 (786) 221-3531
REPORTING OF SERIOUS ADVERSE EVENTS (SAES), PROTOCOL DEVIATIONS	**Biorasi Safety and Pharmacovigilance** email: MAP7189_safety@biorasi.com 19495 Biscayne Blvd., Suite #900 Aventura, FL 33180 Fax: +1 (786) 221-3531

2 Study Introduction

2.1 Background Information

The head louse, or *Pediculus humanus capitis*, is a wingless, parasitic insect that can be found on the head, eyebrows, and eyelashes of people. Head lice feed on human blood several times a day and live close to the human scalp.

Head lice are found worldwide. In the United States, infestation with head lice is most common among pre-school children attending child care, elementary schoolchildren, and the household members of infested children. Although reliable data on how many people in the United States get head lice each year are not available, an estimated 6 million to 12 million infestations occur each year in the United States among children 3 to 11 years of age. [1]

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class cause death primarily through binding selectively and with high affinity to glutamate-gated chloride channels, which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). The selective activity of compounds of this class is attributable to the fact that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans. [2]

Safety of Ivermectin was evaluated in two pivotal trials. Supportive safety data is also available from five other sponsor-conducted Phase 1 and 2 trials. Adverse events which occurred in less than 1% of subjects included conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation. Evaluation of cutaneous safety, scalp irritation (Phases 1, 2, 3) and ocular irritation (Phase 3), did not reveal clinically notable signals. [3]

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Ivermectin, yet it was found not to be genotoxic in vitro in the Ames test, the mouse lymphoma assay, or the unscheduled DNA synthesis assay in human fibroblasts. [4]

2.2 Rationale

There are many FDA-approved drugs (including prescription and nonprescription drugs) for the treatment of head lice infestation, but genetic resistance of lice to lindane and to the most commonly used treatments, pyrethroids, is not uncommon in the United States, thus development of additional drugs for this indication is encouraged. [5]

Because the infestation is communicable, children diagnosed with head lice infestation may be precluded from attending school until they have received effective treatment, indicating the need for a safe and bioequivalent alternative. [7] There is a public health need for products for the treatment of head lice with a favorable side effect profile and approval for use in children less than 4 years of age. [3]

The proposed study is aimed to evaluate the safety and efficacy of Ivermectin 0.5% lotion. A randomized, multi-center, double-blind, placebo controlled, parallel group trial has been selected in order to evaluate the efficacy and safety of Mayne Pharma's Ivermectin 0.5% lotion compared to Sklice® 0.5% lotion in the treatment of head lice. [3]

The index subjects will be selected according to predefined inclusion and exclusion criteria. The study treatment duration of 15 days is expected to be sufficient to show a treatment effect.

2.3 Potential Risks and Benefits

2.3.1 Known Potential Risks

Safety and efficacy has been established for pediatric patients 6 months of age or older. Ivermectin 0.5% lotion is not recommended for patients under 6 months of age due to the increased risk of systemic absorption, given a high ratio of skin surface area to body mass.

The following reactions, reported in less than 1% of subjects treated with Ivermectin 0.5% lotion include:

- Conjunctivitis
- Ocular hyperemia
- Eye irritation
- Dandruff
- Dry skin
- Skin burning sensation

In the case of accidental or significant exposure, the following adverse effects have been reported most frequently:

- Rash
- Edema
- Headache
- Dizziness
- Asthenia
- Nausea
- Vomiting
- Diarrhea

Other adverse effects that have been reported include:

- Seizure
- Ataxia
- Dyspnea
- Abdominal pain
- Paresthesia
- Urticaria
- Contact dermatitis

A theoretical concern exists about medication errors that might result in the ingestion of the ivermectin product (particularly in young children), therefore it should only be administered under the direct supervision of an adult.

2.3.2 Known Potential Benefits

The adverse event profile observed reveals a product safe for use in children as young as 6 months. The demonstration of efficacy with a single 10-minute treatment is unique amongst anti-lice products and will likely improve compliance. Ivermectin 0.5% lotion represents a significant addition to the current armamentarium for the treatment of head lice.

This medication is widely used and prescribed because the benefits associated with the use of it is greater than the risk of the side effects. Ivermectin 0.5% lotion has demonstrated robust efficacy in comparison to placebo with a single 10-minute treatment for head lice in subjects 6 months of age and older.

3 Objectives and Purpose

The primary objective of the study is to establish the efficacy of a single application of Ivermectin 0.5% lotion in the treatment of head lice under at-home use conditions compared with Sklice® 0.5% lotion, and to demonstrate that both active lotions have superior efficacy compared to Placebo.

The secondary objective of the study is to demonstrate the safety and local tolerability of Ivermectin 0.5% lotion compared with Sklice® 0.5% lotion.

4 Study Design and Endpoints

4.1 Description of the Study Design

This is a Phase 3 Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® 0.5% Lotion in the Treatment of Head Lice. The subject population includes healthy male and female subjects aged 6 months through 18 years who are infested with *Pediculus humanus capitis*. The youngest infested household member will be considered the index subject. Household members, up to a maximum of 3 members, infested with an active head lice infestation defined as at least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator will receive treatment with an over-the-counter head lice treatment product at baseline.

The planned overall sample size for this clinical trial is approximately 280 index subjects, who will be randomized at different geographical clinical research centers in the United States.

Potential subjects will be screened and the index subject will be eligible for enrollment into the study. During the baseline visit (Day 1), which can occur on the same day as screening (Day 0), the Investigator will record subject's demographics, medical history, review concomitant medication, identifying any prohibited therapies the subject may receive, perform physical examination, collect vital signs and perform urine pregnancy test. Eligible subjects will be randomized in a ratio of 3:3:1 to receive either the Mayne Pharma's Ivermectin 0.5% lotion, Sklice® 0.5% lotion, or placebo lotion treatment and will be trained on the application of the study drug and subject's diary completion. Infested household members, up to 3 members per household, will be treated with an over-the-counter head lice treatment product on-site.

The study drug will be applied as a single, at-home dose. Subjects will be instructed to apply a full tube amount (4 oz.) of Ivermectin 0.5% lotion to fully coat dry hair and scalp, avoiding the eyes and mucus membranes. The lotion will be left on the hair and scalp for 10 minutes, then rinsed off with warm water. The tube is intended for a single use; all used tubes should be returned at the second visit (first follow-up visit) to the clinical site for product accountability. In addition to receiving the study drug, the index subjects and household members will be instructed on an overall lice management program, which includes:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash (in hot water) personal care items such as combs, brushes and hair clips.
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits after treatment.

Index subjects will return for post-baseline visits assessments at Days 2, 8, and 15, returning used tubes of the study drug at Day 2, which will be accounted for along with diary cards, which will be reviewed by the site personnel for completeness. The Investigator will perform a visual assessment for the presence or absence of head lice, record local application site reactions, and perform an ocular irritation assessment. The site will provide a Subject Self-Assessment worksheet to record tolerability of treatment. Urine pregnancy testing will be performed at the Screening Visit and the Final Study Visit, with interim visits confirming pregnancy has not occurred through questioning of the index subject.

4.2 Study Endpoint

4.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of index subjects who are lice free (defined as no live lice, adults or nymphs) 14 days (Day 15) after treatment.

4.2.2. Secondary Endpoint

The secondary efficacy endpoint is the number and percentage of all index subjects who are lice-free at Day 2.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet ALL of the following criteria:

1. Subjects must have an active head lice infestation defined as: At least 3 live lice (adults and/or nymphs) present on the scalp and/or hair, as determined by a trained evaluator. The index subject must be the youngest family member, through the age of 18, presenting with an active head lice infestation.
2. Household members that have an active head lice infestation defined as: At least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator (with the exception of the male head of household who may self-assess as being lice free) will receive the Standard of Care with an over-the-counter head lice treatment product. Up to 3 infested household members may receive treatment, if more than 3 household members are infested, the entire household will be excluded from the study.
3. Subject is male or female.
4. Index subject is at least 6 months through 18 years of age at time of enrollment.
5. Subject is in good general health based on medical history.
6. Each subject must have an appropriately signed Informed Consent agreement. A caregiver must sign an Informed Consent agreement for children not old enough to do so. Children 6-17 years of age will be administered a child's Assent Form.
7. The caregiver of a subject must be willing to allow all household members to be screened for head lice. If other household members are found to have an active head lice infestation, they must be willing and able to participate in receiving the Standard of Care. No more than one working male per household may be excluded from evaluation if he is assessed as being lice free by himself or the caregiver and cannot come in due to his work schedule. If this individual may have lice, he must come to the test facility; otherwise the entire household will be excluded from study participation.
8. Subject and/or their caregiver must be physically able and willing to apply the test product according to established treatment methods.
9. Subject agrees not to use any other form of lice treatments (commercial, community-anecdotal, or mechanical/manual) while participating in the study.

10. Following application and rinsing of the test product, subject agrees not to shampoo, wash, or rinse their hair or scalp until the 24-hour post-treatment evaluation has been completed.
11. Subject agrees to not cut or chemically treat their hair while participating in the study.
12. Subject agrees to follow all study instructions, including attending all follow-up appointments.
13. Female index subjects of childbearing potential must be willing to have a urine pregnancy test prior to inclusion in this study.
14. In the event of a subject judged to be incapable of self-treating, the household must have a caregiver willing to apply the treatment at home.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Index subjects with greater than 3 household members with at least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator will be automatically excluded from the trial.
2. Youngest household member is over 18 years of age.
3. History of irritation or sensitivity to ivermectin or the lotion components, pediculicides or hair care products.
4. Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation, such as an erythema score that is >2, blisters, vesicles which, in the opinion of the investigative personnel or medical monitor, will interfere with safety and/or efficacy evaluations.
5. Presentation at the treatment site with eczema or atopic dermatitis.
6. Treatment for head lice (Over the counter [OTC], home remedy and/or Prescription) in the last 15 days.
7. Any condition or illness that, in the opinion of the investigator, may compromise the objective of the protocol.
8. Is receiving any other treatment which, in the opinion of the investigator or medical monitor, may interfere with the study results.
9. Females (including caregivers who come in contact with the investigational product) who are pregnant, nursing or planning a pregnancy which could include index subjects. If a household has a pregnant female who has an active case of lice, the entire household is excluded from participation. If this pregnant household member does not have an active infestation, this individual must NOT be the caregiver (one who provides treatment to other household members).
10. Is of child-bearing potential, including index subjects, and unwilling to use an adequate method of contraception for the duration of the study. Adequate methods of contraception include: abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, Intra uterine devices, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly, surgical sterilization. Index subjects and/or caregivers will be considered non-child-bearing if the following has occurred: full hysterectomy or

bilateral oophorectomy is considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization.

11. Participation in a previous investigational drug study within the past 30 days.
12. Does not understand the requirements for study participation and/or may likely exhibit poor compliance, in the opinion of the investigator.
13. Does not have a known household affiliation with their household members (i.e., do not stay in one household consistently, sleeping at one place several nights and then at another place or location). Household is defined as living in a shared area or space (for example the same house or apartment unit). [6]

5.3 Criteria for Inclusion of Minor Subjects

Subjects aged 6 years through 17 years of age 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.

5.4 Strategies for Recruitment and Retention

- Expected total number of screened subjects will be 311.
- Given a 10% screen failure rate, an anticipated number of enrolled subjects will be 280.
- Assumed dropout rate is 10%, therefore an expected number of 252 subjects will complete the study.
- Source of subjects will be primarily from area schools, along with referrals by local pediatricians to these participating, dedicated clinical lice centers.
- Retention of subjects will be supported by thorough visit reminders and proper education on the study itself, including study duration, activities and responsibilities.
- Approximately 6 geographically diverse clinical research centers in the US will be participating.

5.5 Subject Withdrawal and Termination

5.5.1 Potential Reasons for Withdrawal

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 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 or Medical Monitor it is not in the subject's best interests to continue in the study.
- Occurrence of an Adverse Event (AE) or Serious Adverse Event (SAE), which, in the opinion of the Investigator, warrants discontinuation of the subject from the study.
- Pregnancy as informed by the subject or as determined by a positive urine pregnancy test.

- Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study, as determined by the Investigator.
- Subject is deemed to be a treatment failure if upon revisit it is determined that they are still infested. They will be terminated from the study and provided the standard of care at that point in the study.
- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 Handling of Subject Withdrawals or Termination

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects. 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.

5.6 Premature Suspension or Termination of 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.

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.

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.
- Appropriate therapy and follow-up should be ensured for any study subject by the sponsor.
- Ensure where required by applicable regulatory requirements that the regulatory authority is properly informed.
- If the sponsor terminates the study or the subject withdraws, the end of treatment visit and/or discontinuation visit should be conducted.

6 Study Drug

6.1 Study Agent (s) and Control Description

6.1.1 Acquisition

The drug depot will receive study agents and perform IP accountability and monitoring, including assurance of adequate contents and quantities, based upon the IP packing list. For acquisition of study agents at the clinical sites, study agents will be shipped to each individual clinical site through the designated drug depot. The drug depot will provide initial study agents for study initiation and resupply thereafter, as needed.

6.1.2 Formulation, Appearance, Packaging and Labeling

6.1.2.1. Reference Product

The reference product Sklice®, marketed by Arbor Pharmaceuticals, is supplied in 4 oz. tubes. It is an off-white/tan lotion. The formulation composition Sklice® consists of the following ingredients according to the FDA-approved labelling:

Study agent lotion: 0.5%; each gram of lotion contains 5 mg of ivermectin active ingredient.

Inactive ingredients: water, olive oil, oleyl alcohol, Crodalan AWS, lanolin alcohol, cyclomethicone, shea butter, sodium citrate, sorbitan tristearate, methylparaben, propylparaben, and citric acid.

6.1.2.2. Test

The test product is Ivermectin Lotion 0.5% manufactured by Mayne Pharma International Pty Ltd., supplied in 4 oz. tubes. It is a white to off-white lotion. The formulation composition of the test product consists of the following ingredients:

Study agent Lotion: 0.5%; each gram of lotion contains 5 mg of ivermectin active ingredient.

Inactive ingredients: Medium Chain Triglycerides, Carbomer Homopolymer, Polyoxyl 50 Stearate, Glyceryl Monostearate, Propylene Glycol, Paraffin Liquid, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Citric Acid Anhydrous, Sodium Citrate, Triethanolamine, Sodium hydroxide, Purified water.

6.1.3 Product Storage and Stability

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15° to 30°C (59°F to 86°F). Do not freeze. All study drug supplies will be kept in a secure cabinet or room with controlled access. Only the designated study personnel will have access to study drug supplies.

The Investigator will maintain temperature monitoring of the study drug with daily temperature readings. All temperature excursions must be reported to the Sponsor using the Temperature Excursion Form. If the study drug was exposed to the temperature excursion outside the range 15-30^{o}C, or within this range, but for the period greater than 24 hours, the study drug must be quarantined until the Medical Monitor / Sponsor's approval on future use. Please refer to the Pharmacy Manual for additional detail on the Temperature Excursions and temperature monitoring during the shipment and storage at the site pharmacy.

6.1.4 Preparation

Ivermectin 0.5% lotion requires no preparation prior to use.

6.1.5 Dosing and Administration

Apply full tube amount (4 oz.) to dry hair to completely cover the scalp and hair for index subjects ages 5 and older. For babies, please apply 1 oz. of product, equivalent to ¼ of the study tube amount. For toddlers, please apply 2 oz., equivalent to ½ of the study tube amount. Apply closest to the scalp first, and then apply outwards towards the ends of the hair.

Leave on the hair and scalp for 10 minutes, and then rinse off with water.

The tube is intended for single use, do not retreat.

Keep out of reach of children. Use on children should be under the direct supervision of an adult.

Avoid contact with eyes. Do not swallow. Thoroughly wash hands after applying lotion.

Ivermectin lotion should be used in the context of an overall lice management program:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash (in hot water) personal care items such as combs, brushes and hair clips.
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits, as recommended per the FDA Guidance on the treatment of Head Lice.

6.1.6 Route of Administration

Ivermectin 0.5% lotion, is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

6.1.7 Blinding

This is a double-blind study, thus Sponsor, CRO, assessor site staff, study monitors, and subjects will be blinded to the randomization scheme. The packaging of the study drug products will be similar in appearance to make difference in treatment less obvious to the subjects. Blank, opaque diaper labels will be applied to each study tube for maintenance of study blinding. Each tube will be packaged in individualized cartons. Neither the Investigator nor the subject should be able to identify the received treatment. The dispensed investigational product will NOT be opened by the index subject and their family members at the study center.

The blinding code must not be broken except in emergency situations for which the identification of the study treatment of a subject is required by the Investigator to complete a serious adverse event report. In such situations, the Medical Monitor or the Investigator will use the Unblinded Treatment List in order to unblind the treatment for the individual subject. Unblinded information will be held by designated individual(s), and the date and reason for breaking the blind must be recorded.

The Medical Monitor must 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).

6.1.8 Duration of Therapy

The study is comprised of three phases: Screening, Treatment, and Follow-Up. The duration of this study is 15 days (+/- 3). The Screening Phase is Day -1-0. The Treatment Phase is Day 1. Preferably, screening and treatment will occur on the same day. The Final Study Visit is on day 15 (+/- 3 days) following administration of the study product.

6.1.9 Tracking of Dose and Treatment Compliance

Subject diaries will be distributed and accounted for, along with return of used test tubes. Subjects will fill out their diaries upon treatment application noting the following:

- Time and date of application
- Time and date of removal (washing off the study drug)
- Confirmation that subject disinfected personal clothes, towels, linens and all potentially infected household items
- Confirmation that the entire scalp and hair has been covered by the application

Subjects will return their diaries to the clinical site for compliance review at Follow-up Day 2. 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 the treatment application notation, this is considered a protocol deviation and must be reported.

6.2 Study Drug Accountability

The Sponsor will supply sufficient quantities of the study drug for the completion of this study.

The study pharmacist or designated study personnel will maintain a Drug Receipt Log and a Subject Study Drug Accountability Log itemizing all study drug received, dispensed to and returned from each subject during the study. All dispensed tubes must be accounted for, and any discrepancies explained. Study site should contact site Clinical Research Associate (CRA) in case of any dispensing errors or if discrepancies are discovered.

Prior to site closure and at appropriate intervals during the study, site CRA will perform study drug accountability and reconciliation. At the end of the study, the Investigator will retain all the original documentation regarding study drug accountability, return, and copies will be sent to the Sponsor.

All unused and used Study Drug tubes will be returned to the Sponsor or its designee for destruction at the end of the study.

7 Study Procedures and Schedule of Events

7.1 Study Procedures/Evaluations

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

Medical history will be collected at the Screening and Baseline Visits. Relevant medical history, alcohol and tobacco history, and past history of head lice will be documented.

All medications (both prescription and nonprescription, including vitamins, herbals, topical, inhaled, and intranasal) taken within 30 days prior to the start of the Study Drug and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand names, if known) with the corresponding indication, start and stop dates. 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.

Vital signs will be collected at Baseline Visit 1 and Final Study Visit 5. Vital signs will include body temperature, 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 of vital signs will be evaluated by the Investigator based on

their significance. Any abnormal vital signs will be considered AEs if they require therapeutic medical intervention, and/or if the Investigator considers them to be AEs based on his/her clinical judgement.

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 at the Screening Visit.

7.1.1 Study Specific Procedures

In addition to the regular standard of clinical care, the following study specific procedures will be included as part of the study.

Past medical history of and previous treatment of head lice must be recorded irrespective of the term it was given. Corresponding condition shall be captured in the subject's Medical History.

Visual Assessment of Head Lice:
Subjects and their household members will be thoroughly assessed for a minimum of 15 minutes for the presence or absence of live head lice, including adult lice, nymphs, and nits. Results will be recorded on the Site Assessment form.

Skin/Scalp Irritation Assessment:
Subjects will be assessed for skin and scalp pruritus, erythema, excoriation, and pyoderma. Results will be recorded on the Site Assessment form.

Ocular Irritation:
Subjects will be assessed for eye irritation, conjunctivitis, and ocular hyperemia. Results will be recorded on the Site Assessment form.

Subject Diary:
Administration of a checklist for laundry disinfection measures, application and removal of the study drug for index subject.
Subject Assessments:
Administration of questionnaires for subject-reported outcomes. The site will provide a Subject Self-Assessment Worksheet to record the grading of Itching and Stinging/Burning sensations. Analysis of tolerability will be based on scoring scales of Stinging/Burning and Itching sensations collected during Subject Self-Assessment at all follow-up visits between the test and reference treatment groups.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

A urine pregnancy test will be performed for females of childbearing potential, this includes index subjects. The baseline result must be available and must be negative before the index subject can apply the study drug. A positive pregnancy test will disqualify the entire household from participation in the study.

7.3 Study Schedule

7.3.1 Screening

Screening Visit Day -1 to 0 (Visit 1)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Record demographic information, obtain medical history, alcohol and tobacco use, and history of head lice.

- Review medications history and concomitant/prohibited medications to determine eligibility based on inclusion/exclusion criteria.
- Verify inclusion/exclusion criteria.

- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect urine sample for pregnancy testing for all index subjects of child bearing potential.
- Perform assessment for living head lice on index subjects and household members for a minimum of 15 minutes. The index subject must be the youngest family member presenting with at least 3 live lice. After the index subject has been identified, additional infested household members will also be assessed for infestation (up to 3 per household).
- Household members must have an active head lice infestation defined as: At least 1 live louse (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator (with the exception of the male head of household who may self-assess as being lice free).
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit Day 1 (Visit 1/ Visit 2)

- Review concomitant and prohibited medications.
- Record vital signs, results of examinations, other assessments.
- Perform assessment for living head lice on index subject and household members (up to 3 per household) for visual confirmation of infestation for a minimum of 15 minutes.
- Provide Standard of Care treatment on-site to infested household members (up to 3 per household).
- Randomize the index subject.
- Provide the study treatment for index subject.
- Provide index subject with subject diary and homecare instructions.
- Record Subject Self-Assessment for index subjects.
- Inform index subject when to come back for their first follow-up visit.

7.3.3 Follow-up

Follow-up Visit Day 2 (Visit 3) (+/- 1 Day)

- Record adverse events as reported by participant or observed by investigator.
- Collect used test tube product from index subject.
- Concomitant and prohibited medication review.
- Perform assessment for living head lice on index subject for visual confirmation of infestation for a minimum of 15 minutes.
- If active lice are present on index subject, provide Standard of Care and withdraw the subject from the study.
- Record Subject Self-Assessment for index subjects.
- Perform skin/scalp irritation and ocular irritation for index subjects and record results on Site Assessment form.
- Record index subject's adherence to treatment program through collection of subject diary.
- Inform index subject when to come back for their follow-up visit.

Follow-up Visit Day 8 (Visit 4) (+/- 2 day)

- Record adverse events as reported by participant or observed by investigator.
- Concomitant and prohibited medication review.
- Perform assessment for living head lice on index subject for visual confirmation of infestation for a minimum of 15 minutes.
- If active lice are present, provide Standard of Care and withdraw the subject from the study.
- Record Subject Self-Assessment for index subjects.
- Perform skin/scalp irritation and ocular irritation for index subjects and record results on Site Assessment form.
- Inform index subject when to come back for their final study visit.

7.3.4 Final Study Visit

Final Study Visit Day 15 (Visit 5) (+/- 3 days)

- Record adverse events as reported by participant or observed by investigator.
- Perform vital signs, results of examinations, and other assessments.
- Concomitant and prohibited medication review.
- Collect urine sample for pregnancy testing for any index subject of child bearing potential.
- Perform assessment for living head lice on index subject for visual confirmation of infestation for a minimum of 15 minutes.
- Record Subject Self-Assessment for index subjects.
- Perform skin/scalp irritation and ocular irritation for index subjects and record results on Site Assessment form.
- Provide rescue standard of care treatment for any index subjects requiring additional treatment.

7.3.5 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 is considered to be worsening.

7.3.6 Rescreening

If for some reason a subject is approved to participate in the study, but cannot return to the clinical site within 24 hours of their screening visit, they may be rescreened within 1 week. This rescreening may also occur if all household members cannot be assessed at the clinical site within 24 hours of the index subject's approval to participate in the study. Rescreening will be considered on an individual subject basis and must first be approved by the Investigator or Medical Monitor.

7.4 Concomitant Medications, Treatments, and Procedures

All medications (both prescription and nonprescription, and including vitamins, herbals, topical, inhaled, and intranasal) taken within 30 days prior to the start of the Study Drug and through the final study visit will be recorded on the appropriate eCRF (using their generic and brand names, if known) with the corresponding indication, start and stop dates. 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.

Previous treatment of head lice must be recorded irrespective of the term it was given. Corresponding condition shall be captured in the subject's Medical History.

7.4.1 Precautionary Medications, Treatments, and Procedures

In previous studies for topical Ivermectin, no exploration of drug-drug interactions was performed.

7.5 Prohibited Medications, Treatments, and Procedures

Head lice treatment products (over the counter [OTC], home remedy and/or Prescription) are prohibited 15 days prior to and during the study. These include, but are not limited to:

- Nix
- Rid
- Kwell
- LiceMD

7.6 Rescue Medications, Treatments, and Procedures

If live lice are present on Day 2, Day 8 or Day 15, the subject will receive an over-the-counter (OTC) rescue treatment for head lice and their study participation will be considered complete and will be considered a treatment failure, with subjects to be considered in both the mITT and PP population.

7.7 Participant Access to Study Drug at Study Center

Participants will receive the study medication at their Enrollment/Baseline Visit.

8 Assessment of Safety

8.1 Specification of Study Parameters

The Investigator will monitor each subject for clinical 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).

8.1.1 Definition of Adverse Events (AE)

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. Treatment-emergent AEs (TEAE) will include any AEs reported beginning with the first application of study drug on Day 1.

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. I.e., if a new signs or symptom or worsening of a sign or symptom was believed by the investigator to be related to the study drug and not the disease, then it was recorded as an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to baseline, or become explainable). 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.

8.1.2 Definition of Serious Adverse Events (SAE)

If an AE meets any of the following criteria, it is to be reported to the Sponsor's Safety department 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.

8.1.3 Definition of Unanticipated Problems

An Unexpected Adverse Event is any AE that is not identified in nature, severity, or frequency in the current Investigator's Brochure or product information.

A Serious and Unexpected Suspected Adverse Reaction (SUSAR) is any suspected adverse reaction to the study product that is both serious and unexpected.

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

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.

8.2.2 Relationship to Study Drug

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 not related to study drug is given, an alternate etiology must be provided by the Investigator for the AE.

8.2.3 Expectedness

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The Investigator will monitor each subject for clinical evidence of adverse events on a routine basis throughout the study. 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.

8.4 Reporting Procedures

8.4.1 Adverse Event Reporting

8.4.2 Serious 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 Pavlenko, MD
Biorasi Safety and Pharmacovigilance
E-mail: spavlenko@biorasi.com
19495 Biscayne Blvd., Suite #900, Aventura, FL 33180
Fax: +1 (786) 221-3531

8.4.3 Unanticipated Problem Reporting

All Serious and Unexpected Suspected Adverse Reactions (SUSAR) will be submitted as expedited reports to the applicable regulatory authorities/federal agencies.

8.4.4 Reporting of Pregnancy

If a subject, or female partner of male subject becomes pregnant during the participation in the study, the Investigator will immediately discontinue the subject from the study and contact the Medical Monitor and the Sponsor. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Sponsor's Safety Team using the Pregnancy Data Collection Form. Generally,

follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Detailed guidance on the reporting of Pregnancies will be provided in SAE and Pregnancy Reporting Guidance.

8.5 Safety Oversight

Safety oversight will be under the direction of a medical monitor, working with the Biorasi Safety team. The medical monitor is an expert that advises the study investigators and monitors participant safety. The role of the medical monitor is to:

- Review all adverse events on a regular basis throughout the trial
- Be available to advise the investigators on trial-related medical questions or problems
- Evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study

The medical monitor remains blinded throughout the conduct of the clinical trial unless unblinding is warranted to optimize management of an adverse event or for other safety reasons.

9 Clinical Monitoring

Conducting Interim Monitoring Visits (IMV) helps verify that the rights, safety and well-being of Study participants are being protected, the Study data is accurate, complete, and verifiable from Source Documents and the Study is being conducted in compliance with the currently approved Protocol/amendment(s), Good Clinical Practice (GCP), Biorasi SOPs and site SOPs (if any) and other Regulatory requirement(s).

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

A separate Clinical Monitoring Plan (CMP) will be used in this study. The CMP will outline in detail the parameters for clinical site monitoring, including who will conduct the monitoring, the frequency of monitoring, at what level of detail monitoring will be performed, and the distribution of reports.

10 Statistical Considerations

The sections below summarize the intended statistical methods and analyses of data for the study.

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, active-reference, and placebo. 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 9.4. or higher.

10.1 Statistical and Analytical Plans

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.

10.2 Data Sets to Be Evaluated

The subject populations are defined as follows:

Safety Population includes all subjects who were randomized and dispensed treatment. This is the population that will be used for the safety assessments.

Modified Intent-to-Treat (mITT) population includes all Index subjects who met all inclusion/exclusion criteria, were randomized, dispensed treatment, and had at least one post-treatment efficacy evaluation. This is the primary population for determination of the superiority of the active treatments over placebo.

Per-Protocol (PP) population includes all mITT subjects who applied their dispensed treatment, had no protocol deviations which could have interfered with the accurate assessment of treatment efficacy, and returned for the Day 15 visit within the allowed window. This is the primary population for the efficacy comparisons between the two active treatment groups.

Subjects whose condition worsens and require alternate or supplemental therapy for the treatment of head lice 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 on both the per-protocol population and the mITT population. Safety analyses will be performed using the Safety population as defined.

10.3 Statistical Hypotheses

Primary Efficacy Endpoint:

The primary efficacy endpoint is the proportion of index subjects who are lice free (defined as no live lice, adults or nymphs) 14 days (Day 15) after treatment.

Secondary Efficacy Endpoint:

The secondary efficacy endpoint is the number and percentage of all index subjects who are lice-free at Day 2.

10.4 Description of Statistical Methods

10.4.1 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.

10.4.2 Assessment of Bioequivalence and Superiority for Primary and Secondary Endpoints

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

The 90% confidence interval criteria are the same as rejecting the null hypotheses for the following two, one-sided t-tests, each at the $\alpha = 0.05$ significance level:

Ho: $\pi_T - \pi_R < -0.20$ Ho: $\pi_T - \pi_R > 0.20$

Ha: $\pi_T - \pi_R \geq -0.20$ Ha: $\pi_T - \pi_R \leq 0.20$

Combined Ha: $-0.20 \leq \pi_T - \pi_R \leq 0.20$

where,

π_T and π_R = the true cure proportions for Test and Reference treatments, respectively.

The Bioequivalence results in the PP population will be considered definitive, with those in the mITT population considered supportive.

The superiority assessments for each active treatment vs. the Placebo will be conducted using two-sided, continuity corrected Z-tests based on the following hypotheses:

Ho: $\pi_T = \pi_P$ Ho: $\pi_R = \pi_P$

Ha: $\pi_T \neq \pi_P$ Ha: $\pi_R \neq \pi_P$

where,

π_T, π_R, and π_P = the true cure proportions for Test, Reference, and Placebo treatments, respectively.

If both null hypotheses are rejected ($p<0.05$) and the observed cure proportions for the Test and Reference treatments are greater than that for the Placebo, then Superiority will be considered to have been demonstrated.

The Superiority results in the mITT population will be considered definitive, with those in the PP population considered supportive.

10.4.3 Safety Analyses

The reporting of safety data is descriptive, and will include all subjects in the Safety population. The variables for safety endpoints are AEs. AEs will be summarized based on their frequency and their severity. 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.

10.5 Sample Size

Under the assumption that the Test and Reference treatments are equally efficacious with a true cure rate of at least 67%, and that the placebo has a true cure rate no greater than 27%, computer simulations were performed to determine the probability (power) of study success for different sample sizes. Study success in a simulated trial was defined as having the 90% continuity-corrected confidence interval in the PP population for the Test-to-Reference difference in cure proportions be contained in the bioequivalence interval [-0.20, +0.20] at the same time that both active treatments were demonstrated in the mITT population to have cure rates that were greater than, and statistically different ($p<0.05$) from, that of the placebo. It was assumed that approximately 90% of the mITT subjects would qualify as PP ones.

It was determined that for at least an 80% probability of study success, 280 mITT index subjects would be needed (120:120:40; Test: Reference: Placebo) to obtain 252 PP ones (108:108:36; Test: Reference: Placebo).

11 Source Documents and Access to Source Data/Documents

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, Sponsor representative, 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 guidance (ex. 21 CFR Part 11 and 312).

12 Ethics/Subject Protection

12.1 Ethical Standard

The study will be conducted according to the protocol, GCP, as outlined in the ICH Guidelines and Code of Federal Regulations. Written informed consent for the study must be obtained from all subjects before protocol specific procedures are performed. Subjects must be informed of their right to withdraw from the study at any time and for any reason.

12.2 Institutional Review Board

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, subject's diaries, 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.

12.3 Informed Consent Process

12.3.1 Other Informational Documents Provided to Participants

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.

12.3.2 Consent Procedures and Documentation

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 forms 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, 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, and shared with the subject and/or their representative for continued inclusion in the study.

12.4 Participant and Data 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).

13 Data Handling and Record Keeping

13.1 Study Records 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.

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.

13.2 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 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 Sponsor has been obtained. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator will contact the Sponsor or designee at the below mentioned address in order to determine the appropriate course of action.

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

Protocol Compliance review:

- Verify that the Investigator and Investigational Site personnel are adhering to the IRB/IEC approved Protocol and all amendments. In addition to the Protocol, the Monitoring Plan may include (or reference) verification strategies which define a percentage of data points to be reviewed or other methodologies for verification of Investigational Site compliance. The Monitoring Plan should be followed regarding verification and study specific problem escalation, however the below are items that are often reviewed to verify Protocol compliance:
    - Checking that the correct randomization and Protocol-defined procedures, assessments and sampling requirements (if applicable) are being followed.
    - If unblinding has occurred (accidental or intentional), determine if the unblinding was done by authorized personnel, after consultation with the relevant Study team member(s) (e.g. Medical Monitor or Sponsor) and that the occurrence and reporting was appropriately documented in Source Documents, the regulatory binder and CRF, as required.
- Verify that the Investigator is enrolling only eligible Study participants and all entry criteria are satisfied for each Study participant verified, as per the current approved Protocol. Documentation and verification of participant status in the study.
- Verify that no prohibited medications or changes in dose for indication-related medications are being used without prior approval from Medical Monitor or Sponsor Designee.

- Address any protocol deviations with site personnel during the IMV and identify ways to prevent the recurrence of similar issues e.g. training the site team on that particular issue.

13.3 Publication and Data Sharing Policy

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.

14 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

15 Literature References

1. Frequently Asked Questions. Parasites, Lice, Head Lice. Centers for Disease Control. C2015 [cited 2017 May 17]. Available from: https://www.cdc.gov/parasites/lice/head/gen_info/faqs.html

2. Center for Drug Evaluation and Research, Application number 202736Orig1s000, Medical Review(s). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202736Orig1s000MedR.pdf

3. Ivermectin Clinical Review. Food and Drug Administration. c 2009. [cited 2017 May 17]. Available from: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM331169.pdf

4. Sklice® Lotion Prescribing Information, Center for Drug Evaluation and Research, February 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202736Orig1s000LBL.pdf

5. Head Lice Infestation: Developing Drugs for Topical Treatment Guidance for Industry, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), October 2016. Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

6. Study Comparing the Safety and Efficacy of 0.5% Ivermectin Cream to Placebo in Lice Infested Subjects. ClinicalTrials.gov Identifier NCT00994422. c2017 [cited 2017 May 17]. Available from: https://clinicaltrials.gov/ct2/show/NCT00994422?term=NCT00994422&rank=1

7. Center for Drug Evaluation and Research, Application number 202736Orig1s000, Summary Review(s). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202736Orig1s000SumR.pdf

16 Appendices

16.1 Schedule of Events

Visit Number	Visit 1 Screening[1]	Visit 2 Baseline[2]	Visit 3 Follow-up	Visit 4 Follow-up	Visit 5 EOS/ET[3]
Visit Day	**Day -1 to 0**	**Day 1**	**Day 2[4]**	**Day 8 (±2)**	**Day 15 (±3)**
Informed Consent	X				
Eligibility Criteria	X				
Subject Demographics	X				
Medical History	X				
Physical Examination	X[5]				
Investigational Product Dispensation/Randomization		X[6]			
Vital Signs[7]		X			X
Urine Pregnancy Test[8]	X				X
Head Lice Visual Assessment	X[9]	X[9]	X	X	X
Household Members Standard of Care Treatment		X			
Local Skin/Scalp Irritation Assessment			X	X	X
Ocular Irritation Assessment			X	X	X
Subject Self-Assessment		X	X	X	X
Investigational Product Accountability			X		
Subject Diary Dispensation		X			
Subject Diary Collection and Compliance Review			X		
Concomitant and Prohibited Medication Review	X	X	X	X	X
Adverse Events Assessment			X[10]	X	X

[1] Rescreening will be permitted for out of window index subjects and those subjects whose household members cannot accompany them at their initial screening visit.
[2] 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 7. Study Procedures and Schedule of Events for details and restrictions.
[3] Index subjects identified as treatment failures will be terminate early from the study and be provided the standard of care rescue treatment.
[4] Must be within 24 hours of treatment.
[5] Physical examinations are to be performed if Inclusion/Exclusion Criteria are satisfied at Screening.
[6] Prior to Randomization, the Investigator must confirm the subject still meets all Inclusion/Exclusion Criteria.
[7] Vital signs will include body temperature, heart rate and blood pressure (systolic and diastolic). Blood pressure and heart rate will be measured after the subject has been sitting restfully for at least 5 minutes.
[8] For female index subjects of child-bearing potential.
[9] For both index subjects and infested household members.
[10] AE reporting period for this study begins upon receiving the first application of investigational product and ends at the final protocol required visit.

16.2 Subject Diary

Subject Diary

Protocol Number: MAP-7189

Study Title: **A Randomized, Multi-Center, Double-blind, Placebo Controlled, Parallel Group Trial to Evaluate Efficacy and Safety of Mayne Pharma's Ivermectin 0.5% Lotion Compared to Sklice® Ivermectin 0.5% Lotion in the Treatment of Head Lice**

SUBJECT NUMBER:							***SUBJECT INITIALS:***			
BASELINE VISIT DATE:										
	D	***D***	***M***	***M***	***M***	***Y***	***Y***	***Y***	***Y***	

To be completed by the study team member & cover page to remain at the site

SUBJECT TREATMENT INFORMATION	
Study Visit	**Visit 2** ☐
HOUSEHOLD MEMBERS TREATMENT INFORMATION	
Number of Infested Household Members	
Number of Non-Infested Household Members	
Total Number of Household Members	
Infested Household Member # 1 Standard of Care Treatment ☐ **Yes** ☐ **No**	
Infested Household Member # 2 Standard of Care Treatment ☐ **Yes** ☐ **No**	
Infested Household Member # 3 Standard of Care Treatment ☐ **Yes** ☐ **No**	

SUBJECT NUMBER:							SUBJECT INITIALS:			
VISIT DATE:										
	D	D	M	M	M	Y	Y	Y	Y	

APPLICATION OF THE STUDY DRUG		
Activity	Instructions for Application of study drug	Status check (Tick)
Application of Lotion	• Apply full tube amount (4 oz.) to fully coat dry hair and scalp for children ages 5 and older • For babies, apply 1 oz. (1/4 of a tube) and for toddlers apply 2 oz. (1/2 of a tube). • Avoid contact with eyes and mucus membranes • Record the date and time the lotion was applied • Leave on for 10 minutes	☐ Yes ☐ No **Date of Application** D D M M M Y Y Y Y **Time of Application** H H M M
AFTER	• After 10 minutes fully rinse lotion off with warm water • Record the date and time the lotion was washed off • Caregivers to properly wash hands after treatment.	☐ Yes ☐ No **Date of Removal** D D M M M Y Y Y Y **Time of Removal** H H M M
AFTER (cont.)	• **Do not shampoo, wash, or rinse hair or scalp until the 24-hour post-treatment evaluation has been completed.**	☐ Yes ☐ No **Date to Shampoo Hair** D D M M M Y Y Y Y **Time to Shampoo Hair** H H M M

ASSOCIATED STEPS WITH STUDY TREATMENT	
Activity	**Status check (Tick)**
LAUNDRY DISINFECTION: • Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding & towels.	☐ Yes ☐ No

• Wash (in hot water) personal care items such as combs, brushes, & hair clips	

SUBJECT NUMBER:							***SUBJECT INITIALS:***			
VISIT DATE:										
	D	***D***	***M***	***M***	***M***	***Y***	***Y***	***Y***	***Y***	

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 ☐ If yes, please discuss with Principal Investigator at your next visit.:

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

Yes ☐ No ☐ If yes, please discuss with Principal Investigator at your next visit:

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

Yes ☐ No ☐ If yes, please discuss with Principal Investigator at your next visit

In case of medical emergency call 911 immediately.

Remember the next study visit date is on (Next Day): _____

Subject's Signature: _____

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

AND/OR

Caregiver's Signature: _____

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

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

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

16.3 Subject Self-Assessment

SUBJECT SELF ASSESSMENT

SITE PERSONELL TO COMPLETE:

SUBJECT NUMBER:							**SUBJECT INITIALS:**			
VISIT DATE:										
	D	**D**	**M**	**M**	**M**	**Y**	**Y**	**Y**	**Y**	

Visit Number	*Visit 2 [Baseline]*	*Visit 3 [Follow Up]*	*Visit 4 [Follow Up]*	*Visit 5 [Final Study Visit]*
Visit Day	*Day 1* ☐	*Day 2* ☐	*Day 8* ☐	*Day 15* ☐

TO BE COMPLETED BY SUBJECT AND/OR CAREGIVER:

This assessment is aimed to rate the itching and stinging/burning sensations you may have experienced after the application of the lotion. Please rate the experience in the tables below.

ITCHING

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

Score	Grade	Definition	**Check one**
0	None	The scalp does not itch.	☐
1	Mild	Occasional episodes of itching, not bothersome.	☐
2	Moderate	Frequent, several times a day, bothersome.	☐
3	Severe	Nearly constant, frequent, very bothersome.	☐

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 and/or Caregiver (Initials): _____ Date_____

Completed & Reviewed By (Initials): _____ Date_____

16.4 Site Assessment

SITE ASSESSMENT

SUBJECT NUMBER:							**SUBJECT INITIALS:**			
VISIT DATE:										
	D	**D**	**M**	**M**	**M**	**Y**	**Y**	**Y**	**Y**	

SITE PERSONNEL TO COMPLETE:

1. Head Lice Evaluation minimum of 15 minutes:

Live Adult Lice Present: ☐ **Yes** ☐ **No** **Number of:** _____

Live Nymphs Present: ☐ **Yes** ☐ **No** **Number of:** _____

2. Skin/Scalp Irritation Assessment (include forehead, neck and ears):

		Type of Irritation		
Rating	Pruritus= Itching	Erythema= Redness of the scalp	Excoriation= Breaking of the skin, usually caused by scratching	Pyoderma= Sores filled with clear fluid, pus or crusting
None = 0	The scalp does not itch.	No redness of the scalp.	No broken skin on the scalp.	No lesions visible on the scalp.
Mild = 1	Occasional episodes of itching, not bothersome.	Faint, barely perceptible erythema with limited distribution.	One or two areas on the scalp on which skin is broken.	One or two lesions visible with crusting or other evidence of infection.
Moderate = 2	Frequent, several times a day, bothersome.	Diffuse pink areas of scalp are readily visible.	More than two separate areas of the scalp with broken skin but not generalized across the scalp.	Presence of more than two lesions with crusting or other evidence of infection, but not generalized across the scalp.
Severe = 3	Nearly constant, frequent scratching, very bothersome.	Large areas of the scalp are red.	Widespread breaking of the skin involving most of the scalp.	Lesions with crusting or other evidence of infection, involving most of the scalp.

Pruritus Score= _____

Erythema Score= _____

Excoriation Score=_____

Pyoderma Score= _____

3. Ocular Irritation Assessment:

Eye irritation present: ☐ **Yes** ☐ **No**

Conjunctivitis present: ☐ **Yes** ☐ **No**

Ocular Hyperemia present: ☐ **Yes** ☐ **No**

Completed By (Initials): _____ Date_____