Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence and Safety of Ivermectin Lotion 0.5% (Actavis Laboratories UT, Inc.) to SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) in the Treatment of Human Head Lice Infestation

Study Number 71691702

NCT03301649

Protocol Approval Date: 1 February 2018

1.0 TITLE PAGE

Drug Product:	Ivermectin Lotion 0.5%
Population:	Male and female patients, 6 months of age and older, with an active *Pediculus humanus capitis* (human head lice) infestation, of which approximately 378 are expected to be index patients.
Study Design:	Randomized, double-blind, placebo-controlled, parallel-design, multiple-site bioequivalence study with clinical endpoints.
Sponsor:	Actavis LLC
Study/Protocol Number:	71691702
Protocol Date:	02/01/2018

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor:	Actavis LLC 400 Interpace Parkway Morris Corporate Center III Parsippany, NJ 07054
CRO:	[redacted]
Sponsor's Representative:	[redacted] Actavis LLC [redacted]
CRO Representative:	[redacted]
Medical Monitor:	[redacted]
Biostatistician:	[redacted]
IWRS Vendor:	[redacted]

3.0 SIGNATURE PAGE

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable FDA regulations, ICH guidelines and Good Clinical Practice standards.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

Actavis LLC

[redacted] Date

Actavis LLC

PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol 71691702 Rev 1 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Actavis LLC) or [redacted], the company managing the study.

_____ _____
Principal Investigator Date

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5.0 SYNOPSIS

Protocol Number	71691702
Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Clinical Study to Evaluate the Therapeutic Equivalence and Safety of Ivermectin Lotion 0.5% (Actavis Laboratories UT, Inc.) to SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) in the Treatment of Human Head Lice Infestation
Objectives	The objectives of this study are to: 1. Evaluate the therapeutic equivalence of the Test formulation, Ivermectin Lotion 0.5% (Actavis Laboratories UT, Inc.) to the Reference product, SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) in the treatment of active head lice infestation. 2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo treatment in patients with active head lice infestation. 3. Compare the safety of Test, Reference and Placebo treatments in patients with active head lice infestation.
Sponsor	Actavis LLC
Study Products	• **Test**: Ivermectin Lotion, 0.5% (Actavis Laboratories UT, Inc.) • **Reference**: SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) • **Placebo**: Placebo (vehicle) lotion (Actavis Laboratories UT, Inc.) Study products will be supplied in 4 oz (117 g) tubes.
Dosage Regimen	Patients will be instructed to administer a single application of study product to the hair on Day 1.
Route of Administration	Topical
Treatment Randomization	[redacted]
Patient Population	Male and female patients, 6 months of age and older, with active *Pediculus humanus capitis* (human head lice) infestation, of which approximately 378 are expected to be index patients.
Study Design	Randomized, double-blind, placebo-controlled, parallel-design, multiple-site bioequivalence study with clinical endpoints
Study Conduct	Eligible patients will be randomized [redacted] to one of three treatments (Test, Reference or Placebo) at Visit 1. All members of the household will be examined for lice, [redacted]

[redacted] Patients [redacted] will be instructed to administer a single application of the study product to the hair on the day of or day after enrollment into the study, leave the study product on the hair and scalp for 10 minutes, and then rinse off with warm water. Patients [redacted] will be instructed to apply the study product at home. The day of dosing will be considered Day 1.

Patients will attend the following four scheduled clinics visits:

- Visit 1 (Day -1 to 1): Screening/Baseline
- Visit 2 (Day 2): Interim Visit
- Visit 3 (Day 8 ± 2): Interim Visit
- Visit 4 (Day 15 ± 2): End of Study

At Visit 2 (Day 2), [redacted] enrolled [redacted] will return the study product to the clinic. Visit 2 must occur the day after dosing. [redacted]. At Visits 2, 3, and 4, patients will be examined for the presence of live head lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. Duration of examination should be recorded. [redacted] Patients who have live lice present at Visits 2 or 3 should be dropped from the study and provided with alternative treatment. Unscheduled visits will be allowed as deemed necessary by the Investigator or Sponsor to ensure patient safety or to perform other study-related procedures.

Definitions

- [redacted]
- [redacted]
- Non-index patient: Any household member who has agreed to participate in the study but is not the youngest member of the

	household. • Index patient: The youngest household member who is randomized into the study.
Inclusion Criteria	1. Signed Institutional Review Board (IRB)-approved informed consent form that meets all criteria of current Food and Drug Administration regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states), the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills. 2. The patient and/or the patient's parent (legal guardian) is willing to apply the study product as directed, comply with study instructions and commit to all follow-up visits for the duration of the study. 3. Male or non-pregnant, non-lactating female, 6 months of age or older. 4. Females of childbearing potential must not be pregnant or lactating at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception. (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before Visit 1 and should not change this regimen during the study. A sterile sexual partner is not considered an adequate form of birth control. 5. Index patients (i.e., the youngest household member) must have an active head lice infestation, defined as ≥ 3 live lice (i.e., live adults and/or nymphs), at Visit 1. 6. Household members participating in the study must have at least one live louse (i.e., live adults and/or nymphs) at Visit 1. 7. All members of the household must be present for examination. Any male head of household who is unable to attend Visit 1 may be assessed by a second member of the household as being lice free.
Exclusion Criteria	1. Females who are pregnant, lactating or planning to become pregnant during the study period. 2. Patients who do 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). 3. Any infested member of the household is unable or unwilling to be treated with the study product. This includes male heads of household who do not attend Visit 1 but report infestation with lice. 4. More than three members of the household infested with lice. 5. Presence of visible skin/scalp condition(s) or open wounds at the application site that are not attributable to head lice infestation and that in the opinion of the Investigator will interfere with safety and/or efficacy evaluations. 6. Presence of eczema or atopic dermatitis at the application site. 7. Use of any prescription, over-the-counter, or home remedies for the treatment of head lice within 7 days before Visit 1. 8. Use of pediculicides within four weeks before Visit 1. 9. Use of systemic anti-parasitic agents within four weeks before Visit 1. 10. Patients with very short (shaved) hair or who are planning to shave head during the study. 11. Use of any hair dye, bleaches, hair straightening or permanent wave solution on the hair within 14 days before Visit 1. 12. History of allergy or sensitivity to pediculicides or hair care products. 13. History of any drug hypersensitivity or intolerance that, in the opinion of the Investigator, would compromise the safety of the patient or results of the study. 14. Significant history or current acute or chronic infectious disease, system disorder, Netherton's Syndrome, organ disorder (e.g., hepatic or renal impairment) or insufficiency, immunosuppression (from medical treatment or disease), organ transplant, uncontrolled diabetes, uncontrolled hypertension, current ocular condition, or other medical condition that, in the Investigator's opinion, would place the study patient at undue risk by participating in the study. 15. Patients or non-infested household members who would act as the primary caregiver who are of intellectually competent age but unable to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study. 16. Receipt of any drug as part of a research study within 30 days before Visit 1.

	17. The patient is a member of the investigational study staff or a member of the family of the investigational study staff. 18. Previous participation in this study.
Efficacy Endpoints	**Primary Efficacy Endpoint** The primary efficacy endpoint is the proportion of index patients in each treatment group who are considered a Treatment Success on Day 15 ± 2. Treatment Success is defined as the absence of live lice. **Secondary Efficacy Endpoint** The secondary efficacy endpoint is the proportion of all randomized patients (i.e., index + non-index) who are considered a Treatment Success on Day 15 ± 2. Treatment Success is defined as the absence of live lice.
Evaluation of Therapeutic Equivalence and Superiority	**Therapeutic Equivalence Analysis** Therapeutic equivalence will be evaluated for both primary and secondary endpoints using the per-protocol (PP) population. If the 90% confidence interval for the absolute difference between the proportion of patients who are considered a Treatment Success in the Test and Reference groups is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated. The same statistical approach will be conducted for analysis of the secondary endpoint in the PP population. To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary endpoint in the PP population. **Superiority Analysis** Superiority of the Test and Reference products against the Placebo for the primary endpoint will be tested at the 5% significance level ($p < 0.05$; two-sided, Cochran-Mantel-Haenszel (CMH) test, stratified by clinical site) in the mITT population using last observation carried forward. If the proportions of patients who are considered a Treatment Success in the Test and Reference groups are numerically and statistically superior to that of the Placebo ($p < 0.05$; using two-sided, CMH test stratified by clinical site), then superiority of the Test and Reference products over Placebo will be concluded. The same statistical approach will be conducted for analysis of the secondary endpoint in the mITT population. To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population. The superiority testing will treat all patients who have no

	data on Day 15 as treatment failure. Treatment-by-Site Interaction and Pooling of Clinical Sites As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population (for equivalence testing). The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Treatment Success rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.
Safety Analysis	Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the study product, action taken, and outcome will be prepared by treatment group. If sufficient data exist, then AE frequencies will be compared among treatments using Fisher's exact test or a similar test. Application site reactions and ocular discomfort will be compared descriptively among treatment groups. Concomitant medication use during the randomized treatment period will be tabulated by patient. Signs and symptoms of head lice will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers to be clinically significant. All patients who are randomized and received study product will be included in the comparative safety analysis.
Sample Size Determination	For the primary endpoint analysis (proportion of index patients in the PP population who are considered to be a Treatment Success on Day 15 ± 2), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. The sample size estimations are based on data reported in the product label for SKLICE® (ivermectin) Lotion, 0.5%.

6.0 STUDY SCHEMATIC

PROCEDURE	VISIT 1 (Day -1 to 1)* Screening/Baseline	VISIT 2 (Day 2)† Interim Visit	VISIT 3 (Day 8 ± 2 Days) Interim Visit	VISIT 4 (Day 15 ± 2 Days) End of Study
Informed Consent/Assent	X			
Medical History and Demographics	X			
Concomitant Medication	X	X	X	X
Adverse Events	X	X	X	X
Vital Signs	X	X	X	X
Pregnancy Test‡	X	X	X	X
Louse Examination	X	X	X	X
Inclusion/Exclusion	X			
Application Site Reactions	X	X	X	X
Ocular Irritation Assessment		X		
Dispense Study Product	X			
Collect Study Product		X		
Provide Patient Diary	X	X	X	
Collect and Review Patient Diary		X	X	X

*Study product will be administered on Day 1.
†Visit 2 must occur the day after patient dosing.
‡For females of childbearing potential

7.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model
AE	Adverse Event
C	Celsius
CDISC	Clinical Data Interchange Consortium
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRO	Clinical Research Organization
eCRF	electronic Case Report Form
F	Fahrenheit
FDA	Food and Drug Administration
g	Gram
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	modified Intent-to-Treat
mL	milliliter
NDA	New Drug Application
OTC	Over-The-Counter
PP	Per-Protocol
RLD	Reference Listed Drug
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDTM	Study Data Tabulation Model

8.0 INTRODUCTION

8.1 Disease Being Treated

Pediculus humanus capitis, the head louse, is an ectoparasite whose only host are humans. The louse feeds on blood several times daily and resides close to the scalp to maintain its body temperature.[1] Head lice infestation is widespread, affecting both children and adults. In the United States it is estimated that between 6 and 12 million infestations occur each year among children 3 to 11 years of age.[2] Head lice infestations can be asymptomatic, particularly with an initial infestation or when the infestation is mild. Itching is the most common symptom associated with head lice infestation and is caused by an allergic reaction to louse bites. Although head lice are not known to transmit any disease, untreated infections can lead to poor sleep and sores on the head caused by scratching. These sores can become infected with bacteria commonly found on a person's hands.[3,4]

8.2 Availability and Efficacy of Already Approved Therapies

There are a number of prescription and over-the-counter (OTC) therapies currently available for the treatment of head lice. Over-the-counter medications contain either pyrethrins or permethrin. Pyrethrins (e.g., A-200®, Rid®) are naturally occurring pyrethroid extracts from the chrysanthemum flower. Pyrethrins can only kill live lice, not unhatched eggs. A second treatment is recommended to kill any newly hatched lice.

Permethrin (e.g., Nix®) is a synthetic pyrethroid similar to naturally occurring pyrethrins. Like pyrethrins, this product only kills live lice. Although it may continue to kill newly hatched lice for several days after treatment, a second treatment is often required.[5]

Prescription treatment options include benzyl alcohol, malathion, spinosad, and ivermectin. Benzyl alcohol (e.g., ULESFIA®) is an aromatic alcohol approved for the treatment of head lice in patients 6 months of age and older. The safety of this product in patients over 60 years of age has not been established. Benzyl alcohol is thought to work by preventing lice from closing their respiratory spiracles, allowing the vehicle to obstruct these spiracles and causing the lice to suffocate. Similar to approved OTC treatments, benzyl alcohol only kills live lice and a second treatment is required.[6]

Malathion (e.g., OVIDE®) is an organophosphate approved in the United States for the treatment of head lice. Malathion acts as a pediculicide by inhibiting cholinesterase activity in vivo. This product kills live lice as well as some lice eggs. Retreatment is recommended if live lice are still present 7-9 days after treatment. Inadvertent transdermal absorption of malathion has occurred from its agricultural use. In such cases, acute toxicity was manifested by excessive cholinergic activity, i.e., increased sweating, salivary and gastric secretion, gastrointestinal and uterine motility, and bradycardia. The potential for transdermal absorption of malathion is unknown, therefore use of this product is limited to children 6 years of age and older. Chemical burns, including second-degree burns, have been reported with use of this product.[7]

Spinosad (e.g., NATROBA) topical suspension is approved for the treatment of head lice in patients 6 months of age and older. Spinosad, which is derived from soil bacteria, causes neuronal excitation in insects. After periods of hyperexcitation, lice become paralyzed and die. Unlike other treatments,

spinosad kills both live lice and unhatched eggs. Most patients require only one treatment with this product.[8,9]

Ivermectin (e.g., SKLICE®) topical lotion is approved for the treatment of head lice in patients 6 months of age and older. Like spinosad, ivermectin is derived from soil bacteria. Ivermectin causes death of parasites by increasing the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell. This results in paralysis and death of the parasite.[10] Although ivermectin is not ovicidal, it appears to prevent newly hatched lice from surviving. Ivermectin is effective in most patients with a single treatment.[5]

Supplemental measures, including nit combing and decontamination of linens and personal items, are recommended along with drug therapy to avoid re-infestation of lice.[5]

8.3 Scientific and Statistical Considerations

Statistical analyses of the clinical data will be based on recommendations in the FDA guidances on malathion lotion, 0.5% and spinosad topical suspension, 0.9%.[11,12]

8.4 Justification for use of Placebo

A placebo group is included to confirm the sensitivity of the study and minimize the possibility of a false positive result of therapeutic equivalence. Therefore, in addition to demonstrating bioequivalence between Test and Reference products, both active products must show statistical superiority to the Placebo.[13,14]

[redacted]

8.5 Risks and Benefits

The risks and benefits to patients enrolled in clinical research studies that include a placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of approved therapies, and the scientific and statistical requirements of the desired outcome of the research study.

Randomized patients will be enrolled in the study for 15 ± 2 days. Although the potential for any drug-related side effects of significance occurring during the study is low, the risk is higher in the two active treatment groups than in the Placebo group.

All patients who do not respond to treatment will be provided with alternative therapy, in some cases within 24 hours.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans.

9.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of the Test formulation, Ivermectin Lotion 0.5% (Actavis Laboratories UT, Inc.) to the Reference product, SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) in the treatment of active head lice infestation.
2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo treatment in patients with active head lice infestation.
3. Compare the safety of Test, Reference and Placebo treatments in patients with active head lice infestation.

10.0 INVESTIGATIONAL PLAN

10.1 Study Design and Plan Description

This randomized, double-blind, placebo-controlled, parallel-design, multiple-site clinical study has been designed to evaluate the efficacy and safety of a generic Ivermectin Lotion 0.5% (Actavis Laboratories UT, Inc.) compared to the Food and Drug Administration (FDA) Reference Listed Drug (RLD) SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC) in patients with active head lice infestation. Additionally, both the Test and Reference (i.e., the RLD) treatments will be tested for superiority to a Placebo.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF). In addition, patients who are considered minors in the state the study is being conducted (< 18 years of age in most states), must have a signed parental/guardian ICF, indicating approval to participate, as well as a signed assent to participate form, as appropriate. Patients 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills.

Males and females, 6 months of age and older with an active head lice infestation will be randomized [redacted] to one of the three study products as follows:

- **Test**: Ivermectin Lotion, 0.5% (Actavis Laboratories UT, Inc.)
- **Reference**: SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC)
- **Placebo**: Placebo (vehicle) lotion (Actavis Laboratories UT, Inc.)

[redacted]

Patients, infested household members, and/or caregivers will be instructed to administer a single application of the study product to the hair on the day of or the day after enrollment into the study,

leave the study product on the hair and scalp for 10 minutes, and then rinse off with warm water. Patients and infested household members will be instructed to apply the study product at home. The day of dosing will be considered Day 1.

Patients will attend the following four scheduled clinics visits:

- Visit 1 (Day -1 to 1): Screening/Baseline
- Visit 2 (Day 2): Interim Visit
- Visit 3 (Day 8 ± 2): Interim Visit
- Visit 4 (Day 15 ± 2): End of Study

At Visit 2 (Day 2), [redacted] enrolled [redacted] will return the study product to the clinic. Visit 2 must occur the day after dosing. [redacted]. At Visits 2, 3, and 4, patients will be examined for the presence of live head lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. Duration of examination should be recorded. [redacted] Unscheduled visits will be allowed as deemed necessary by the Investigator or Sponsor to ensure patient safety or to perform other study-related procedures.

At Visit 2, patients will be questioned about any ocular discomfort associated with the study product. Also at Visits 2, 3, and 4, patients will be questioned about any adverse events (AEs), application site reactions (Appendix A), and any new concomitant medication use.

Definitions

- [redacted]
- [redacted]
- Non-index patient: Any household member who has agreed to participate in the study but is not the youngest member of the household.
- Index patient: The youngest household member who is randomized into the study.

Therapeutic equivalence will be assessed by evaluating the proportion of index patients in each treatment group who are considered a Treatment Success on Day 15 ± 2. Treatment Success is defined as the absence of live lice. The proportion of all patients (i.e., index + non-index) who are considered a Treatment Success on Day 15 ± 2 will be evaluated as a secondary endpoint. The analysis of superiority will compare both active treatment groups to the Placebo group for the same primary and secondary endpoints.

10.2 Selection of Study Design

This protocol is based on procedures and results from studies conducted as part of the New Drug Application (NDA) # 202-736 for SKLICE® (ivermectin) Lotion, 0.5%, recommendations from the FDA industry guidance for the development of topical head lice drugs, and recommendations from the FDA guidances on malathion lotion, 0.5% and spinosad topical suspension, 0.9%, which are products that have a similar indication and usage for treatment of head lice infestation.[11,12,15,16]

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Signed Institutional Review Board (IRB)-approved ICF that meets all criteria of current FDA regulations. For patients who are considered minors in the state the study is being conducted (< 18 years in most states), the parent or legal guardian should sign the consent form and the child will be required to sign a patient "assent" form, as appropriate. Patient 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills.
2. The patient and/or the patient's parent (legal guardian) is willing to apply the study product as directed, comply with study instructions and commit to all follow-up visits for the duration of the study.
3. Male or non-pregnant, non-lactating female, 6 months of age or older.
4. Females of childbearing potential must not be pregnant or lactating at Visit 1 (as confirmed by a negative urine pregnancy test with a sensitivity of less than 50 mIU/mL or equivalent units of human chorionic gonadotropin). Women of childbearing potential must agree to the use of a reliable method of contraception (e.g., total abstinence, intrauterine device, a double-barrier method, oral, transdermal, injected, or implanted non-hormonal or hormonal contraceptive) throughout the study. Female patients using hormonal contraceptives should have been on the same product/dosing regimen for at least 28 days before Visit 1 and should not change this regimen during the study. A sterile sexual partner is not considered an adequate form of birth control.
5. Index patients (i.e., the youngest household member) must have an active head lice infestation, defined as ≥ 3 live lice (i.e., live adults and/or nymphs), at Visit 1.
6. Household members participating in the study must have at least one live louse (i.e., live adults and/or nymphs) at Visit 1.
7. All members of the household must be present for examination. Any male head of household who is unable to attend Visit 1 may be assessed by a second household member as being lice free.

10.3.2 Exclusion Criteria

1. Females who are pregnant, lactating or planning to become pregnant during the study period.

2. Patients who do 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).
3. Any infested member of the household is unable or unwilling to be treated with the study product. This includes male heads of household who do not attend Visit 1 but report infestation with lice.
4. More than three members of the household infested with lice.
5. Presence of visible skin/scalp condition(s) or open wounds at the application site that are not attributable to head lice infestation and that in the opinion of the Investigator will interfere with safety and/or efficacy evaluations.
6. Presence of eczema or atopic dermatitis at the application site.
7. Use of any prescription, OTC, or home remedies for the treatment of head lice within 7 days before Visit 1.
8. Use of pediculicides within 4 weeks before Visit 1.
9. Use of systemic anti-parasitic agents within 4 weeks before Visit 1.
10. Patients with very short (shaved) hair or who are planning to shave head during the study.
11. Use of any hair dye, bleaches, hair straightening or permanent wave solution on the hair within 14 days before Visit 1.
12. History of allergy or sensitivity to pediculicides or hair care products.
13. History of any drug hypersensitivity or intolerance that, in the opinion of the Investigator, would compromise the safety of the patient or results of the study.
14. Significant history or current acute or chronic infectious disease, system disorder, Netherton's Syndrome, organ disorder (e.g., hepatic or renal impairment) or insufficiency, immunosuppression (from medical treatment or disease), organ transplant, uncontrolled diabetes, uncontrolled hypertension, current ocular condition, or other medical condition that, in the Investigator's opinion, would place the study patient at undue risk by participating in the study.
15. Patients or non-infested household members who would act as the primary caregiver who are of intellectually competent age but unable to understand the protocol requirements, instructions, and study-related restrictions, the nature, scope, and possible consequences of the clinical study.
16. Receipt of any drug as part of a research study within 30 days before Visit 1.
17. The patient is a member of the investigational study staff or a member of the family of the investigational study staff.

18. Previous participation in this study.

10.3.3 Restrictions During the Study

The following concomitant medications, products or procedures will not be allowed while enrolled in the study:

- Any prescription, OTC, home remedy, or mechanical/manual methods (e.g., nit combing) for the treatment of head lice. This includes any medicated shampoos specifically used in the treatment of head lice.
- Pediculicides.
- Hair dye, bleaches, hair straightening or permanent wave solution on the hair.
- Topical or systemic anti-parasitic agents.

Patients will be instructed to avoid occlusion of the scalp with any agent (e.g., petroleum) and sleeping at different locations. Patients should not shave their head until after study completion.

Patients will be questioned about all prescription and OTC concomitant medication use (including vitamins or nutritional supplements) at each study visit. All concomitant medications will be recorded in the patient's source documents. Any patient who violates any of the listed restrictions may be dropped from continued participation in the study by the Investigators.

10.3.4 Removal of Patients From the Study

Patients will be advised that they are free to withdraw from the study at any time. If necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. In case of early termination the Investigator will fully document the reason for early termination. The clinical report will include all reasons for early withdrawals. Reasons for removal may include the following:

- Patient withdrew consent.
- Significant AE that led the Investigator or patient to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).
- Presence of live lice at any post-treatment visit.
- Participant enrolls in another clinical trial during the study, or is found to have previously enrolled in this clinical trial.

If a randomized patient terminates from the study early, all efforts will be made to complete the End of Study procedures. Patients who withdraw or are removed from the study will not be replaced.

10.4 Treatments

10.4.1 Treatments Administration

Patients will be provided with verbal and written instructions on how to administer the study product at home. At Visit 1, eligible patients will receive a 4 oz (117 g) tube of randomized study product (i.e., Test, Reference or Placebo). Study product should be applied on the day of or the day after enrollment into the study. The day of dosing will be considered Day 1. Patients, infested household members, and/or caregivers will be instructed to apply the study product to dry hair in an amount sufficient (up to 1 tube) to thoroughly coat the hair and scalp, avoiding contact with the eyes. Study product should be left on the scalp for 10 minutes before rinsing with water only. Patients should wash their hands after application of the study product. Hair should be allowed to dry naturally (pat drying with decontaminated towel is permitted) and left uncovered after application of the study product. Following application and rinsing of the study product, patients may not shampoo, wash, or rinse their hair or scalp until the Day 2 visit has been completed.

If any non-infested household member is pregnant or lactating at the time of the study, this person may not be involved with application of the study product to any household members.

The study product should be applied as a single dose. Patients should not use the product more than once. Tubes of study product will be collected at Visit 2 and the site will verify the product was used and rinsed. If a patient inadvertently does not return a tube of study product at its respective return visit, the patient should be instructed to return it as soon as possible or at the next visit.

On Day 1, before applying treatment, all bedding, hats, clothing, and towels used by infested persons or their household, sexual, and close contacts in the two days before treatment should be decontaminated by machine washing in high temperatures (at least 150°F) and drying in a hot dryer for at least 20 minutes (additional time should be added if large loads are dried). Clothing or items that are not washable can be dry-cleaned or sealed in a plastic bag and stored for two weeks. Personal care items such as combs, brushes, and hair clips should be washed in hot water (at least 135°F) for 10 minutes. Instructions on good hygiene and proper methods of decontamination will be provided to the patient and caregivers.

10.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test**: Ivermectin Lotion, 0.5% (Actavis Laboratories UT, Inc.)
- **Reference**: SKLICE® (ivermectin) Lotion, 0.5% (Arbor Pharmaceuticals, LLC)
- **Placebo**: Placebo (vehicle) lotion (Actavis Laboratories UT, Inc.)

10.4.3 Study Product Shipment, Storage, and Retention

An individual tube of study product (i.e., Test, Reference or Placebo) will be packaged, as a patient kit. Each patient will be assigned to one patient kit. [redacted] The study product will be blinded, packaged and delivered to the site in bulk. The study

products will be shipped to each Investigator's site from a centralized location. The Principal Investigator at each site is responsible for ensuring that all study products are stored in a locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

Study product is to be stored in a secure, locked location, at room temperature between 20-25°C (68°F to 77°F) with excursions permitted to 15º–30ºC (59º–86ºF). Any excursions from the permitted excursion range of 15º–30ºC (59º–86ºF) will require prompt notification to [redacted], and thereafter [redacted] will notify the Sponsor.

For every study product shipment received at the investigative site, the Investigator (or designee) will randomly select study product kits for retention, unless otherwise instructed by the Sponsor and/or [redacted]. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. These kits will be affixed with a label provided by [redacted] to be clearly marked as retention samples and are not to be used for dispensing to study patients. The selected retention samples will be retained at a third party storage facility [redacted] under FDA regulations as study retention samples.[17]

Once the site has been notified that they may do so, all unused study product and empty or partially used tubes of study product, other than that randomly selected for retention samples will be returned to the Sponsor (Actavis) or designee. It is important that retention samples not be returned to [redacted], the Sponsor or the packaging company during or at the end of the study. Sufficient study product tubes must be retained among the sites participating in the study to meet the sample retention requirements as outlined by the FDA.[17]

10.4.4 Method of Assigning Patients to Treatment Groups

The study product will be randomized, packaged and blinded by an independent packaging company [redacted]. The randomization will be pre-planned according to a computer-generated randomization schedule. [redacted].

Using [redacted] (IWRS), all eligible and non-eligible patients who are consented and screened into the study will be assigned a patient number. The patient number is assigned after a patient is consented. It is the only identifier for screened patients. [redacted] The system will also assign a study product kit number (based on the randomization schedule created by an independent biostatistician). The study product kit number is the identifying number listed on the study product dispensed to eligible patients. [redacted]. This will be the identifier used for randomized patients (i.e., randomization number). Both the patient number and randomization number will be entered into the patient's eCRF. At the end of the

study, after all the clinical data have been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

10.4.5 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect study product to/from the patients, maintain dispensing records, and ensure the study product logs are complete and accurate. The patient will be requested not to discuss the appearance of the study product with the Investigator or study staff outside of the Independent Dispenser.

[redacted]. The Test, Reference and Placebo products will be blinded with identical outer cartons and labels. This will allow the study to be conducted under double-blind conditions (i.e., such that neither the patient nor the Investigator nor study staff members will know the identity of the patient's treatment).

To ensure that information that could potentially bias handling of data is not disclosed, the packaging company will hold the randomization scheme until after database lock. During the clinical phase of the study, [redacted] IWRS includes a form for Investigators to complete to determine treatment assignment (i.e., to unblind individual patient) to be completed for a medical emergency only. [redacted] Whenever possible, the [redacted] Medical Monitor should be contacted before breaking the blind for any patient. If the Medical Monitor cannot be reached, then the Vice President Clinical Trials and Data Management or designee will be contacted before unblinding. Investigative sites can use either one of the above methods to unblind a patient, when unblinding is deemed necessary by the Principal Investigator.

In the event the blind is broken for any reason, Sponsor and [redacted] will be notified as soon as possible in writing of the details of the occurrence.

At the conclusion of the study, after the database has been locked, each site will be sent a sealed envelope containing the full study randomization scheme that should be retained with the study documents in the event of an FDA inspection.

10.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications, and AEs. Patients who do not dose as instructed on Day 1 will be considered non-

compliant with dosing, and excluded from the per-protocol (PP) population. Dosing compliance will be checked based on the dosing diary entry and verbal discussion with the patient at Visit 2.

10.5 Study Conduct

Unscheduled visits will be allowed as deemed necessary by the Investigator or Sponsor to ensure patient safety or to perform other study-related procedures.

10.5.1 Visit 1 (Day -1 to 1): Screening/Baseline

1. **Informed Consent**: Patients who are willing to comply with study procedures will read and sign the ICF, as appropriate. Patients who are considered minors will read and sign the assent to participate form, as appropriate, and their parent or legal guardian must sign the ICF. Patient's 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills. All infested members of a household must agree to receive treatment for anyone in the household to be enrolled.
2. **Medical History and Baseline Demographics**: Review the patient's demographic and medical history.
3. **Concomitant Medication**: Review the patient's use of any medications in the last four weeks.
4. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
5. **Pregnancy Test**: A urine pregnancy test will be required of all female patients of childbearing potential before enrollment.
6. **Louse Examination**: An Investigator or staff member, who is experienced and trained in detection and evaluation of head lice, will perform a visual inspection for the presence of live lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. Duration of examination and number of live lice should be recorded in the patient's eCRF.
7. **Inclusion/Exclusion Criteria Review**: Study staff will confirm that the patient meets all inclusion/exclusion criteria.
8. **Application Site Reactions**: The Investigator will grade the individual signs and symptoms presented in Appendix A. This will serve as a baseline for subsequent assessments of application site reactions.
9. **Dispense Study Product**: Eligible patients will receive one tube of study product with instructions for dosing at home. Tubes will be dispensed for all members of a patient's household.

10. **Provide Patient Diary**: A diary will be provided to record date and time of dosing, AEs, including any ocular discomfort, and concomitant medications.
11. **Adverse Events**: Patients will be questioned about any AEs that occurred during the visit.

10.5.2 Visit 2 (Day 2): Interim Visit

Visit 2 must occur the day after patient dosing. All treated household members will return for follow-up at Visit 2 only.

1. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since the last visit.
2. **Adverse Events**: Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
3. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
4. **Pregnancy Test**: A urine pregnancy test will be required of all female patients of childbearing potential.
5. **Louse Examination**: An Investigator or staff member, who is experienced and trained in detection and evaluation of head lice, will perform a visual inspection for the presence of live lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. If any live lice are found during the exam, the patient should be discontinued and provided with alternative therapy. Duration of examination and number of live lice should be recorded in the patient's eCRF.
6. **Application Site Reactions**: Patients will be asked about any application site reactions since last visit (see Appendix A). Any reactions will be recorded.
7. **Ocular Irritation Assessment**: Patients will be questioned about any ocular discomfort resulting from contact with the study product. Any discomfort will be documented as an AE.
8. **Return Study Product**: Patients will return the used study product tube.
9. **Collect and Review Patient Diary**: Study staff will collect previously provided diary and review for compliance with the protocol.
10. **Provide Patient Diary**: A diary will be provided to record AEs and concomitant medications.

10.5.3 Visit 3 (Day 8 ± 2 days): Interim Visit

1. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since the last visit.
2. **Adverse Events**: Patients will be questioned about any health status changes/AEs since the last visit. All AEs will be recorded.

3. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
4. **Pregnancy Test**: A urine pregnancy test will be required of all female patients of childbearing potential.
5. **Louse Examination**: An Investigator or staff member, who is experienced and trained in detection and evaluation of head lice, will perform a visual inspection for the presence of live lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. If any live lice are found during the exam, the patient should be discontinued and provided with alternative therapy. Duration of examination and number of live lice should be recorded in the patient's eCRF.
6. **Application Site Reactions**: Patients will be asked about any application site reactions since last visit (see Appendix A). Any reactions will be recorded.
7. **Collect and Review Patient Diary**: Study staff will collect previously provided diary and review for compliance with the protocol.
8. **Provide Patient Diary**: A diary will be provided to record AEs and concomitant medications.

10.5.4 Visit 4 (Day 15 ± 2 days): End of Study

1. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since the last visit.
2. **Adverse Events**: Patients will be questioned about any health status changes/AEs since the last visit. All AEs will be recorded.
3. **Vital Signs**: The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate).
4. **Pregnancy Test**: A urine pregnancy test will be required of all female patients of childbearing potential.
5. **Louse Examination**: An Investigator or staff member, who is experienced and trained in detection and evaluation of head lice, will perform a visual inspection for the presence of live lice (i.e., live adults and/or nymphs). Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. Duration of examination and number of live lice should be recorded in the patient's eCRF.
6. **Application Site Reactions**: Patients will be asked about any application site reactions since last visit (see Appendix A). Any reactions will be recorded.
7. **Collect and Review Patient Diary**: Study staff will collect previously provided diary and review for compliance with the protocol.

10.6 Study Procedures

10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures all patients will read and sign an IRB-approved ICF. In addition, patients who are considered minors in the state the study is being conducted (< 18 years of age in most states) must have a signed parental/guardian ICF, indicating approval to participate, as well as a signed assent to participate form, as appropriate. Patient's 11-17 years of age will read and sign an IRB-approved assent form and patients 6-10 years of age will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills. If any other language is required, translation will be performed by a certified translator.

10.6.2 Medical History and Demographics

At Visit 1, each patient will be required to provide basic demographic information: date of birth, gender, ethnicity and race. Patients will also be questioned about medical history, including acute and chronic medical history and medical history relevant to their head lice.

10.6.3 Concomitant Medication

At Visit 1, patients will be questioned about current and previous medication use over the last four weeks. At all subsequent visits, patients will be questioned about ongoing or new concomitant medication use.

10.6.4 Adverse Events

At the end of Visit 1, patients will be questioned about any AEs that occurred during the visit. At Visits 2, 3, and 4 patients will be questioned regarding any changes in their medical status since their previous visit. Any significant changes observed after ICF/assent signing will be reported as AEs.

10.6.5 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at Visits 1, 2, 3, and 4.

10.6.6 Pregnancy Test

Urine pregnancy tests on females of childbearing potential will be performed at each visit. The test must be negative for the patient to be eligible for inclusion in the study. If the patient is of non-childbearing potential, the source document must list the reason why she is of non-childbearing potential (e.g., postmenopausal).

Any patient who becomes pregnant during the study must be discontinued and End of Study procedures completed. The outcome of the pregnancy will be followed by the Investigator to birth or early termination as appropriate. The pregnancy will be reported as an AE.

10.6.7 Louse Examination

The Investigator or other qualified staff will perform a visual inspection for the presence of live lice (i.e., live adults and/or nymphs) at each visit. Louse examination should be conducted for 15 minutes or longer, unless any live lice are detected in less time. Duration of examination and number of live lice should be recorded in the patient's eCRF. Patients with live lice present at Visits 2 or 3 should be discontinued from the study and provided with alternative therapy.

Determination of live lice can be aided by the use of a mild magnification (e.g., 5x).

10.6.8 Inclusion/Exclusion Criteria Review

At Visit 1, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study.

10.6.9 Application Site Reactions

At Visit 1, the Investigator will grade the individual signs and symptoms (erythema, pyoderma, excoriation, pain, pruritus, edema) per Appendix A. This will serve as a baseline for subsequent assessments of application site reactions. At Visits 2, 3, and 4, application site reactions will be assessed by clinic staff. Reactions will be scored and recorded.

10.6.10 Ocular Irritation Assessment

At Visit 2, patients will be asked if the study product came into contact with their eyes. If contact is reported, they will be asked to report any signs or symptoms experienced. Any reported signs or symptoms should be recorded as AEs.

10.6.11 Dispense Study Product

[redacted].

10.6.12 Collect Study Product

Tubes of study product will be collected from all patients at Visit 2 and checked for compliance or evidence of tampering with the blind.

10.6.13 Provide Patient Diary

At Visit 1, patients will be provided with a diary to record the time and date of dosing, other concomitant medications and AEs, including any ocular discomfort.

At Visits 2 and 3, patients will be provided with a diary to record concomitant medications and AEs.
An adult member of the household will complete the diary for younger patients who are unable to complete the diary on their own.

10.6.14 Collect and Review Patient Diary

At Visits 2, 3, and 4, patient diaries will be collected and reviewed for compliance with the protocol.

10.7 Adverse Events

Patients will be encouraged to report signs, symptoms and any changes in health to the clinic staff. Severity of each AE will be determined based on observation and questioning of the patient. The Investigator will judge the severity and relationship of the event to the study products.

10.7.1 Adverse Event Definition

An AE is any untoward medical occurrence in a patient, regardless of whether it has a causal relationship with this treatment.

In this study, any AE occurring after the patient has signed the ICF/assent until the end of follow-up period should be recorded and reported as an AE.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study product. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered AEs.

Accordingly, an AE can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event (SAE), or require medical treatment or further diagnostic work up, or are considered by the Investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered AEs.)

A treatment-emergent AE is any AE that occurs after initiation of study product, or any event already present that worsens in either intensity or frequency following exposure to study product.

10.7.2 Serious Adverse Events

An SAE is an AE, regardless of the relationship to study product, that results in any of the following outcomes or actions:

- Death

- A life-threatening AE (i.e., the patient was at immediate risk of death from the event as it occurred; does not include an event that, had it occurred in a more severe form, might have caused death)
- Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered SAEs, unless there was worsening of the pre-existing condition during the patient's participation in this study
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An AE that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious AE.

10.7.3 Other Significant Adverse Events

When tested, marked haematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as SAEs should be collected in the eCRF and summarized in the clinical study report.

10.7.4 Severity

The severity of each AE must be recorded as one of the choices on the following scales:

- Mild: No limitation of usual activities
- Moderate: Some limitation of usual activities
- Severe: Inability to carry out usual activities

10.7.5 Relationship of an Adverse Event to the Study Drug

Adverse events will be assessed for the relationship to the study product (causality) according to the following scale:

TERM	DEFINITION	CLARIFICATION
No Reasonable Possibility (not related)	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those AEs, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): It does not follow a reasonable temporal sequence from the administration of the test drug. It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. It does not follow a known pattern of response to the test drug. It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those AE for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered Reasonable Possibility related if or when (at least two of the following): It follows a reasonable temporal sequence from administration of the drug. It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. It follows a known pattern of response to the test drug.

10.7.6 Expectedness

An AE that is not included in the AE section of the relevant Safety Information Reference by its specificity, severity, outcome or frequency is considered an unexpected AE.

The reference safety information for this study, SKLICE® (ivermectin) Lotion, 0.5% Product Insert, to be used as reference for safety information can be found in Appendix B.

The Sponsor's Pharmacovigilance Department will determine the expectedness for all SAEs. Neither the contract research organization (CRO) nor the Investigators will determine the expectedness.

10.7.7 Recording and Reporting of Adverse Events

In this study, safety will be assessed by qualified study personnel by evaluating reported AEs, application site reactions, ocular safety assessment, vital signs measurements and use of concomitant medication.

For AE recording, the study period is defined for each patient as that time period from signature of the ICF through the end of the study (including any follow-up period).

All AEs that occur during the defined study period must be recorded on the source documentation, regardless of the severity of the event or judged relationship to the study product. For SAEs, the SAE form must also be completed and the SAE must be reported immediately (see section 10.7.8). The Investigator does not need to actively monitor subjects for AEs once the study has ended. However, SAEs occurring in a patient after the treatment of that patient has ended should be reported to the Sponsor if the Investigator becomes aware of them.

At each contact with the patient, the Investigator or designee must question the patient about AEs by asking an open ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the eCRF and, if it is an SAE, on the Serious Adverse Event Form.

The onset and end dates and times, action taken regarding study product, treatment administered, and outcome for each AE must be recorded on the source documentation.

The relationship of each AE to study product treatment and study procedures, and the severity and seriousness of each AE, as judged by the Investigator, must be recorded as described above.

The clinical course of each AE will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the patient is referred for continued care to a health care professional or until a determination of a cause unrelated to the study product or study procedure is made.

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or higher and reported with respect to severity, duration, relationship to study product(s), seriousness and action taken.

10.7.8 Reporting of Serious Adverse Events

To satisfy regulatory requirements, all SAEs (as described in section 10.7.2) that occur during the study period (including any protocol-defined follow-up period), regardless of judged relationship to treatment with the study product, must be reported to the Sponsor or CRO by the Investigator. The event must be reported within 24 hours of when the Investigator learns about it. Completing

the SAE form and reporting the event must not be delayed, even if not all the information is available.

PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.

The CRO should inform the Sponsor's Pharmacovigilance Department if the whole study is discontinued early because of safety reasons.

For studies conducted in USA: It is the responsibility of the CRO to report an SAE to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies- December 2012. Confirmation of submission of this report must then be provided to Teva's study representative as well as their Pharmacovigilance department (contact info below).

Sites outside of the USA will be responsible for reporting the SAE to [redacted] and local regulatory authorities, as appropriate.

The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.

Any serious or unexpected AEs should be reported to [redacted] within 24 hours. Following is the contact information:

[redacted]

Or

[redacted]

All SAEs, whether or not drug-related, will be immediately (within 1 business day) reported by [redacted] to the following Sponsor contact by email and followed by a written report within five (5) working days:

<u>USA Pharmacovigilance Unit</u>

[redacted]

Sponsor's Contact person for this Biostudy (copy of the SAE details for information purposes only):

[redacted]

Actavis LLC
[redacted]

These SAE reports must contain the following information, preferably using the template provided by the Sponsor:

A. Study name/number

B. Study Product

C. Investigator details (name, phone, fax, email)

D. Subject Number

E. Subject Initials when appropriate

F. Subject Demographics

G. Clinical Event

1) Description

2) Date of onset

3) Treatment (drug, dose, dosage form)

4) AE Relationship to study product

5) Action taken regarding study product in direct relationship to the AE

H. If the AE was Fatal:

1) Cause of death (whether or not the death was related to study drug)

2) Autopsy findings (if available)

The SAE form and supportive documents should be filled/written in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report. Patients who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Each report of an SAE will be reviewed and evaluated by the Investigator and the Sponsor's Pharmacovigilance Department to assess the nature of the event and the relationship of the event to the study product, study procedures, and to underlying disease.

10.7.9 Submission of SAEs

Any SAE will be reported to competent authority and ethics committee according to the country specific requirements and the responsibilities defined in section 10.7.8. All AEs will be reported in the clinical study report with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

10.8 Early Termination (Patient, Study)

A patient may terminate from the study early for any reason at any time without any disadvantages. In this case, the Investigator should make every effort to have the patient return to the next scheduled visit to perform all required End of Study / Study Completion / Early Termination visit activities and to collect and reconcile all test articles. If the patient does not return for the End of Study / Study Completion / Early Termination visit, the site should fully document the reason for early termination. All data, including the date and primary reason for termination, must be recorded on the End of Study / Study Completion / Early Termination eCRF, and source document.

Any patient who experiences an AE may be terminated from the study or from study treatment at any time at the discretion of the Investigator. In this case, the patient should be followed at the discretion of the Investigator until the resolution or stabilization of the AE. All applicable data should be recorded in the AE section of the eCRF. If a patient terminates from the study early for multiple reasons that include AEs, the End of Study / Study Completion / Early Termination eCRF should indicate that early termination was related to an AE.

An exception to this requirement will be the occurrence of an AE that in the opinion of the Investigator is not severe enough to warrant early termination but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the AE.

The Investigator must inform the clinical project physician/clinical leader/Principal Investigator as soon as possible of all patients who are being considered for early termination due to AEs. Additional reports must be provided when requested.

The Sponsor reserves the right to terminate the study at any time for administrative reasons. The study may also be terminated by regulatory authorities or by the Investigator for his/her site following consultation with the Sponsor. Following a decision to discontinue the trial, the Investigator will immediately inform both the study patients and the IRB responsible for this trial within 10 working days, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study patients or other persons. It is Sponsor's responsibility to report the premature termination of the study to the regulatory agencies within 15 days providing them with the reasons for the trial discontinuation and advising them in writing of any potential risks to the health of study patients or other persons. The CRO may notify the regulatory agency on behalf of the Sponsor.

10.9 Pregnancy

Non-infested household members who are pregnant at the time of the study may not be involved with the application of the study product to other household members.

Female patients of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female patients are considered to be of childbearing potential unless they are pre-menarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Abstinence is an accepted method of birth control. Alternatively, any of the following methods of birth control are acceptable: oral contraceptives, contraceptive patches/implants (e.g., Skyla® and Mirena®), Depo-Provera®, double-barrier methods (e.g., condom and spermicide) or intrauterine device. Before study enrollment women of childbearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a urine pregnancy test having a minimum sensitivity of at least 50 mIU/mL for hCG should be obtained, before study participation. Pregnancy testing will be performed at all clinic visits (i.e., 1-4) and the results of all pregnancy tests (positive or negative) will be documented.

All pregnancies (of women participating in the study and partners of men participating in the study, if possible) that occur during the study, or within 30 days for unknown half-lives days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Investigator must provide the Sponsor with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a SAE (as above).

Any female patient becoming pregnant during the study will discontinue treatment. All patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the Sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the Investigator becomes aware of after termination from the study will be reported as an AE or SAE, as appropriate.

If the pregnancy does not continue to term, one of the following actions will be taken:

- For a spontaneous abortion, report as an SAE.
- For an elective abortion due to developmental anomalies, report as an SAE.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an AE.

10.10 Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the eCRF, regardless of whether an AE occurs as a result.

Types of medication errors and special situations:

1. Breastfeeding - Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk.
2. Unexpected Benefits of Drug.
3. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
4. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
5. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
6. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
7. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
8. Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.
9. Lack of efficacy.

10.11 Follow-up of Subjects After AE

The staff of the clinical facility has to monitor the clinical trial patient's safety from the occurrence of an AE until satisfactory recovery.

Any AE which remains unresolved at the time point of patient's last visit requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found; in case of AEs related to the study product every effort has to be made to follow-up clinical trial patients in order to determine the final outcome. If follow-up cannot be completed until release of eCRF by the Investigator, follow-up information will be documented separately in the patient's record and outcome, including a short description on follow-up procedures performed, must be sent to the Sponsor.

It is the Investigator's responsibility to assure that patients experiencing adverse reactions will receive definitive treatment for any adverse reaction, if required. Details of follow-up care are to be provided (i.e., if treatment or hospitalization is required). The responsibility to provide adequate follow-up for AEs includes periodically repeating laboratory tests yielding clinically abnormal results at the End of Study evaluation.

11.0 STATISTICAL METHODS

11.1 Statistical Plan

A Statistical Analysis Plan (SAP), including study data report format, detailing the intended statistical analysis of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original statistical plan will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the SAP.

If not otherwise specified, statistical significance is defined as $p < 0.05$, two-sided. Data will be summarized with respect to demographic and baseline characteristics, efficacy variables and safety variables. For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, statistics will include number of observations, mean, standard deviation, median, minimum and maximum values.

All statistical analysis will be conducted using Statistical Analysis Software (SAS®), Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC), Study Data Tabulation Model (SDTM) implementation for human clinical trials, and Analysis Dataset Model (ADaM).

11.2 Sample Size Determination

For the primary endpoint analysis (proportion of index patients in the PP population who are considered to be a Treatment Success on Day 15 ± 2), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. The sample size estimations are based on data reported in the product label for SKLICE® (ivermectin) Lotion, 0.5%.

[redacted] to demonstrate therapeutic equivalence (i.e., the 90% confidence interval (Yates' continuity-corrected) of the absolute difference between the Test and Reference cure rates is within a defined equivalence range [-20% to +20%]).

[redacted]

[redacted]

11.3 Study Populations

11.3.1 Per-Protocol Population

The PP population will include all randomized patients who:

- Meet all inclusion and exclusion criteria.
- [redacted]
- [redacted]
- Have no significant protocol deviations.
- Apply the study product as instructed on Day 1.

[redacted]

11.3.2 Modified Intent-to-Treat (mITT) Population

The mITT population will include all randomized patients who meet all inclusion/exclusion criteria, apply the study product as instructed, and return for at least one post-baseline evaluation visit.

11.3.3 Safety Populations

The Safety population will include all patients who are randomized and received study product.

11.4 Baseline Comparability

Baseline characteristics will be evaluated separately for the PP, mITT and Safety populations.

The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (Male/Female)

- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Number of live lice

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean and standard deviation). Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel (CMH) tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and patient.

11.5 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of index patients in each treatment group who are considered a Treatment Success on Day 15 ± 2. Treatment Success is defined as the absence of live lice.

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of all randomized patients (i.e., index + non-index) who are considered a Treatment Success on Day 15 ± 2. Treatment Success is defined as the absence of live lice.

11.6 Primary and Secondary Endpoint Analyses

Therapeutic Equivalence Analysis

Therapeutic equivalence will be evaluated for both primary and secondary endpoints using the PP population. If the 90% confidence interval for the absolute difference between the proportion of patients who are considered a Treatment Success in the Test and Reference groups is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

The same statistical approach will be conducted for analysis of the secondary endpoint in the PP population.

To declare therapeutic equivalence of the Test product to the Reference product, therapeutic equivalence must be demonstrated for only the primary endpoint in the PP population.

Superiority Analysis

Superiority of the Test and Reference products against the Placebo for the primary endpoint will be tested at the 5% significance level ($p < 0.05$; two-sided, CMH test, stratified by clinical site) in the mITT population using last observation carried forward. If the proportions of patients who are considered a Treatment Success in the Test and Reference groups are numerically and statistically

superior to that of the Placebo ($p < 0.05$; using two-sided, CMH test stratified by clinical site), then superiority of the Test and Reference products over Placebo will be concluded.

The same statistical approach will be conducted for analysis of the secondary endpoint in the mITT population.

To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

11.7 Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population (for equivalence testing). The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Treatment Success rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.

11.8 Safety Analysis

Adverse events will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, date of onset, date of resolution, incidence, severity, relationship to the study product, action taken, and outcome will be prepared by treatment group. If sufficient data exist, then AE frequencies will be compared among treatments using Fisher's exact test or a similar test. Application site reactions and ocular discomfort will be compared descriptively among treatment groups.

Concomitant medication use during the randomized treatment period will be tabulated by patient.

Signs and symptoms of head lice will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers to be clinically significant.

All patients who received randomized treatment and received study product will be included in the comparative safety analysis.

12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, ICF/assent form, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of

the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

12.2 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.[18-21] The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

12.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page.

12.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective study patient before enrollment into the study. In addition, patients 11-17 years of age will read and sign an IRB-approved assent form and patients under the age 6-10 years old will provide verbal assent. Patients 6 months-5 years of age will be exempt from providing assent based on the child's comprehension and cognitive skills. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF or assent, as appropriate. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF and/or assent will be provided to the patient.

12.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICFs will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient's consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

12.2.4 Source Documents and Case Report Forms

All patients will be identified by initials, date of birth, and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete eCRFs. A set of eCRFs will be completed for each patient enrolled in the study. All data and eCRFs will be reviewed, evaluated and signed by the Investigator.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 4 (End of Study) Source/eCRF completed.

12.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (i.e., at the site's close-out visit) all used and unused study product will be returned to Sponsor or designee.

12.2.6 Drug Storage

All study product will be stored at controlled room temperature 20°C to 25°C (68°F to 77ºF) with excursions permitted to 15º–30ºC (59º–86ºF), in a secure place with access by authorized individuals only. Any excursions from the above temperature range, including those within the permitted excursion range of 15º–30ºC (59º–86ºF), will require prompt notification to [redacted], and thereafter [redacted] will notify the Sponsor. The Investigator will be responsible for maintaining accurate records of study product receipt, dispensing, and return. At the end of the study (i.e., at the site's close-out visit), all partially used and unused study product will be returned to Sponsor or designee.

12.2.7 Retention of Reserve Samples

For every study product shipment received at the Investigator site, the Investigator (or designee) will randomly select study product kits for retention, unless otherwise instructed by the Sponsor and/or [redacted]. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. The number of each patient kit kept for retention will be noted on the drug accountability form as a retention sample, in addition to the retention sample log. These retention samples should be stored under the appropriate storage conditions for a minimum of 5 years following the application approval or, if not approved, at least 5 years after the completion of the study. Retention samples should not be returned to Sponsor/CRO/packaging group at any time. The retention samples will be shipped to a third party storage facility:

[redacted]

[redacted]

12.2.8 Return of Clinical Supplies

With the exception of the retention samples, all unused kits of study product will be returned to Actavis's Drug Labeling, Packaging and Shipping Facility:

[redacted]
Actavis Laboratories UT, Inc.
[redacted]

12.2.9 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.[22]

12.2.10 Record Retention

All drug accountability records, eCRFs, source data and related regulatory documents must be retained according to 21 CFR 312.62(c) for a period of 2 years following the date the marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

12.2.11 Study Monitoring and Auditing

[redacted] will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all records associated with the study available to [redacted] representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

12.2.12 End of the Trial

The end of the trial is defined as the time at which the last patient has completed his/her last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at his/her discretion, discuss alternative treatments with the patient.

12.2.13 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to eCTD and International Council on Harmonisation (ICH) formatting standards and guidelines.[23] ANDA summary tables will also be generated. Data sets will be provided in SAS® transport (.xpt) format with appropriate description (Read Me) files as required by FDA.

12.2.14 Termination of the Study

The Sponsor reserves the right to terminate the study at any time for administrative reasons.

13.0 REFERENCES

1 CDC. Head Lice - Biology. (2015).
2 CDC. *Head Lice - Epidemiology & Risk Factors*, <https://www.cdc.gov/parasites/lice/head/epi.html> (2013).
3 CDC. Head Lice - Disease. (2013).
4 Lebwohl, M., Clark, L. & Levitt, J. Therapy for head lice based on life cycle, resistance, and safety considerations. *Pediatrics* **119**, 965-974, doi:10.1542/peds.2006-3087 (2007).
5 CDC. *Head Lice - Treatment*, <https://www.cdc.gov/parasites/lice/head/treatment.html> (2016).
6 Prescribing Information for ULESFIA® Lotion. (2012).
7 Package Insert for OVIDE® (malathion) Lotion, 0.5%. (2011).
8 Prescribing Information for NATROBA Topical Suspension. (2014).
9 Stough, D., Shellabarger, S., Quiring, J. & Gabrielsen, A. A., Jr. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). *Pediatrics* **124**, e389-395, doi:10.1542/peds.2008-3762 (2009).
10 Arbor Pharmaceuticals, LLC. Package Insert for SKLICE® (ivermectin) Lotion, 0.5%. (2012).
11 FDA. Draft Guidance on Malathion. (2012).
12 FDA. Draft Guidance on Spinosad. (2016).
13 ICH. Choice of Control Group and Related Issues in Clinical Trials E10. **20 July** (2000).
14 Penslar. IRB Guidebook, Office for Human Rights Protection. *US Department of Health and Human Services* (1993).
15 FDA. Summary Basis of Approval for SKLICE® (ivermectin) Lotion, 0.5% (2012).
16 FDA. Head Lice Infestation: Developing Drugs for Topical Treatment - Guidance for Industry. (2016).
17 FDA. Guidance for Industry. Handling and Retention of BA and BE Testing Samples *U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER).* **May** (2004).
18 FDA. 21CFR 320 Procedures for Determining the Bioavailability or Bioequivalence of Drug Products. *Department of Health and Human Services, Subchapter D-Drugs for Human Use* **5** (2014).
19 FDA. 21CFR Part 50 Protection of Human Subjects. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
20 FDA. 21CFR Part 56 Institutional Review Boards. *Department of Health and Human Services, Subchapter A-General* **1** (2014).
21 World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* **310**, 2191-2194, doi:10.1001/jama.2013.281053 (2013).
22 FDA. 21CFR 312.32: IND Safety Reporting. (2010).
23 ICH. Structure and Content of Clinical Study Reports E3. **Step 4 version** (1996).

14.0 APPENDICES

14.1 Appendix A: Application Site Reactions

The following application site reactions will be evaluated at each visit based on the scale provided below:

Signs and Symptoms:

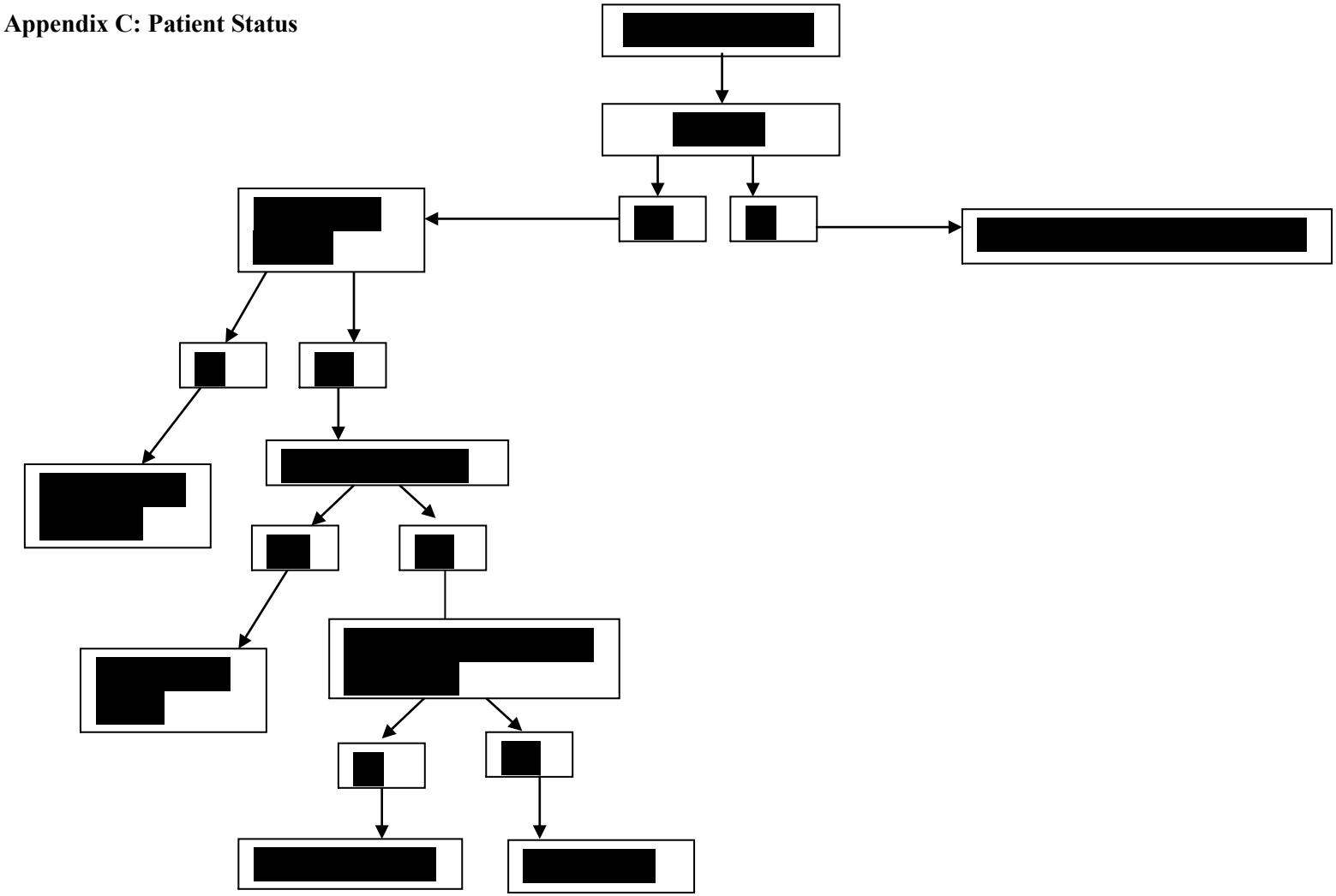
Erythema
Pyoderma
Excoriation
Pain
Pruritus
Edema

Grading Scale:

Absent	0	
Mild	1	(slight, barely perceptible)
Moderate	2	(distinct presence)
Severe	3	(marked, intense)

14.2 Appendix B: SKLICE® (ivermectin) Lotion, 0.5% Product Insert

14.3 Appendix C: Patient Status



[redacted]

14.4 Appendix E: Amendments to the Protocol

Amendment	Date	
1	02/01/2018	

The following revisions were made to the protocol dated 06/21/2017.

- Increased enrollment to approximately 378 index patients.
- Criteria for the PP population were updated.
- Yates' correction removed from analysis methods.