CLINICAL STUDY PROTOCOL

Treatment of infestation with Pediculus humanus capitis in the community using a leave-in spray: A prospective, randomised controlled study

Protocol Identifying Number: ALLI010-0021

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Funded by: Alliance Pharmaceuticals Ltd
Protocol Version 3.0; 27 July 2022

SPONSOR SIGNATURE:

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Date: 27 July 2022

Signature:

Dr. Steve Mann

Digitally signed by Dr. Steve Mann
Date: 2022.07.27 17:19:33 +01'00'

Contents

Abbreviations

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

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INVESTIGATOR SIGNATURE PAGE

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

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INVESTIGATOR SIGNATURE

07/28/2022

DATE

1. Synopsis

Study Title	Treatment of infestation with Pediculus humanus capitis in the community using a leave-in spray: A prospective, randomised controlled study.
Protocol Number	ALLI010-0021
Development Phase	Post-marketing confirmatory
Type of Study	Safety and efficacy
Test Product	Vamousse Spray 'n' Go
Name of Active Ingredient	Natrum Muriaticum 2X (HPUS)
Route, Dose, & Regimen	*Route*: Topical application *Dose*: Spray treatment to completely saturate each section. Work through hair with a comb to ensure full coverage down to the scalp.Thoroughly saturate all hair and scalp. *Regimen*: Allow hair to dry naturally. Leave treatment in for a minimum of 8 hours
Control Product	Nix Creme Rinse Lice Treatment
Name of Active Ingredient	1% Permethrin
Route, Dose, & Regimen	*Route*: Topical application *Dose*: Thoroughly wet the hair and scalp with the permethrin lotion. Be sure to cover the areas behind the ears and on the back of the neck also. Allow the lotion to remain in place for 10 minutes. *Regimen*: Rinse the hair and scalp thoroughly and dry with a clean towel.
Sponsor	Alliance Pharmaceuticals Ltd. Chippenham,Wiltshire , SN15 2BB, United Kingdom
Study Objectives	The primary objective of the study will explore whether treatment with Vamousse Spray 'n' Go is more effective in killing lice & eggs compared to a permethrin-based control product. The secondary objective of the study is to demonstrate the safety and local tolerability of Vamousse Spray 'n' Go in children 2yo+.
Study Endpoints	The primary efficacy endpoint is the proportion of subjects who are lice free (defined as no live lice, adults or nymphs) 14 days after treatment. The secondary efficacy endpoint is the number and percentage of all subjects who are lice-free at Day 2.

Number of Subjects and Site	The planned overall sample size for this Open-Label Clinical Trial is approximately 58 subjects to be enrolled at clinical research center in the United States, specifically Miami, FL. The subjects will be evenly divided between the Spray 'N' Go treatment group and the permethrin control group (29 subjects in each).
Eligibility Criteria	Subjects who satisfy ALL the **inclusion criteria** and have NONE of the **exclusion criteria** may be enrolled in the study.
Inclusion criteria	1. Subjects identified as having an active head lice infestation within the previous 7 days, who have received no treatment at study entry. 2. Subjects must have an active head lice infestation defined as: At least 1 live lice (adults and/or nymphs) present on the scalp and/or hair, as determined by a trained evaluator. 3. Subject is male or female. 4. Subject is at least 2 years and older years of age at time ofenrollment. 5. Subject is in good general health based on medical history. 6. Each subject must have an appropriately signed Informed Consent agreement. A caregiver must sign an Informed Consent agreement for children not old enough to do so. Children ages 6-17 years of age will be administered a child's Assent Form. (The caregiver of a subject must be willing to allow all household members to be screened for head lice. If other household members are found to have an active head lice infestation, they must be willing and able to participate in study or receive the Standard of Care rapid headlice and nit removal with over the counter headlice treatment performed on site.) 7. Subject agrees not to use any other form of lice treatments (commercial, community-anecdotal, or mechanical/manual) while participating in the study. 8. Subject agrees to not cut or chemically treat their hair while participating in the study. 9. Subject agrees to follow all study instructions, including attending all follow-up appointments. Female subjects of childbearing potential must be willing to have a urine pregnancy test prior to inclusion in this study.

Exclusion criteria	1. Subjects with infested household members do not agree to take part in the study or receive the Standard of Care treatment. 2. History of irritation or sensitivity to Natrum Muriaticum 2X (HPUS) or Vamousse Spray 'n' Go components, pediculicides or hair care products. 3. Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation, such as an erythema score and atopic dermatitis that is >2, blisters, vesicles which, in the opinion of the investigative personnel or medical monitor, will interfere with safety and/or efficacy evaluations. 4. Children under two years old. 5. Use of any chemical, physical or mechanical lice removal treatment in any subject following diagnosis. 6. Treatment for head lice (Over the counter [OTC], home remedy and/or Prescription) in the last 7 days. 7. Any condition or illness that, in the opinion of the investigator, may compromise the objective of the protocol. 8. Females who are pregnant, nursing or planning a pregnancy which could include subjects. If a household has a pregnant female who has an active case of lice, the entire household is excluded from participation. 9. Subject of child-bearing potential, and unwilling to use an adequate method of contraception for the duration of the study. Adequate methods of contraception include: abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, Intra uterine devices, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly, surgical sterilization. Subjects and/or their caregivers will be considered non-child-bearing if the following has occurred: full hysterectomy or bilateral oophorectomy is considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization. 10. Participation in a previous investigational drug study within the past 30 days. 11. Does not understand the requirements for study participation and/or may likely exhibit poor compliance, in the opinion of the investigator. 12. Does not have a known household affiliation with their household members (i.e., do not stay in one household consistently, sleeping at one place several nights and then at another place or location). Household is defined as living in a shared area or space (for example the same house or apartment unit).
Withdrawal and Early Discontinuation	*A subject will be discontinued from this study if <u>any</u> of the following criteria are met:* • Withdrawal of consent by the subject is received. • In the opinion of the Investigator or Medical Monitor it is not in the subject's best interests to continue in the study. • Occurrence of an Adverse Event (AE) or Serious Adverse Event (SAE), which, in the opinion of the Investigator, warrants discontinuation of the subject from the study.

	• Pregnancy as informed by the subject or as determined by a positive urine pregnancy test. If found to be positive, subject will be discontinued from the study. • The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. • Head lice treatment product (over the counter [OTC], home remedy and/or Prescription): No medications are contraindicated for use with topical Natrum Muriaticum 2X (HPUS)
Medication/Products and Treatments	Vamousse Spray 'n' Go or Permethrin lotion
Study Product	Natrum Muriaticum 2X (HPUS) or 1% Permethrin lotion
Study Duration	14 Days +/- 3 Day window
Statistical Analysis	**ANALYSIS POPULATIONS** **Safety Population** includes all subjects receiving dispensed treatment. This is the population that will be used for the safety assessments. **Modified Intent-to-Treat (mITT)** population includes all subjects who met all inclusion/exclusion criteria, were randomized, dispensed treatment, and had at least one post-treatment efficacy evaluation. This is the primary population for determination of the kill rate against head lice. **Per-Protocol (PP) population** includes all subjects who received treatment, had no protocol deviations which could have interfered with the accurate assessment of treatment efficacy, and returned for the Day 14 visit within the allowed window. This population is the secondary analysis. **EFFICACY ANALYSIS** **Primary Efficacy Endpoint** The primary efficacy endpoint is the proportion of subjects who are lice free (defined as no live lice, adults or nymphs) 14 days after treatment. **Secondary Efficacy Endpoint** The secondary efficacy endpoint is the number and percentage of all subjects who are lice-free at Day 2. **SAFETY ANALYSIS** Descriptive statistics on the severity and duration of adverse events (AEs) from all subjects will be determined for any AE that occurs in at least 5% of the subjects. Analysis of tolerability will be based on scores of Stinging/Burning and Itching sensations collected during Subject Self-Assessment and Source Document at all follow-up visits between the test and reference treatment groups.
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IRB - Institutional Review Board:	Advarra IRB (Formerly Schulman IRB) 4445 Lake Forest Drive #300 Cincinnati, OH 45242 Phone: 513-761-4100 Fax: 866-377-3359

2. Study Introduction

2.1 Background information

The human head louse Pediculus humanus capitis is an obligate parasitic insect, adapted to life in human hair, that spreads largely through head-to-head contact between infested and uninfested individuals. It is therefore to be expected that infestations spread most readily between people who are in frequent physical contact with each other; typically, younger children in the same school class and close family groups1.

Effective methods for the eradication of an infestation, such as wet-combing and the use of proprietary head lice treatment preparations, are readily available. Most methods are time-consuming, require diligence and some preparations may be expensive. Ineffective application of insecticidal treatments in the past have led to the spread of resistant strains, the so-called "Super Lice". In many cases, the product has to be left in the hair for a set period, then washed out. A product that can be easily applied, then left in the hair for an unspecified period adds the element of convenience when time constraints do not allow the aforementioned approach to be taken.

Vamousse Spray 'n' Go is a member of broad-spectrum antiparasitic products which may have a unique mode of action. Compounds of the class containing IPA 99%, Geraniol and Linalool has potential cause of death primarily through by suffocating lice and/or dissolves the bugs' exoskeletons and dehydrates them.

2.2 Rationale

An effective treatment is much needed to lower patient re-infestations, thus lowering out of pocket cost on lice treatment, multiple pediculicides and/or remedies, as well as nit combs for delousing and nit removal, including loss time spent on doctor's office visits and finally manual delousing and removal of the nits.

The proposed study is aimed to evaluate the safety and efficacy of Vamousse Spray 'n' Go. An Open Label study has been selected

in order to evaluate the efficacy and safety of Alliance Pharmaceuticals Ltd. Vamousse Spray 'n' Go in the treatment of head lice.

Each subject will be selected according to predefined inclusion and exclusion criteria. The study treatment duration of 15 days is expected to be sufficient.

2.3 Potential Risks and Benefits

2.3.1 Known potential risks

SAFETY DATA SHEET Vamousse Spray 'n' Go Date Prepared: 3/03/2021

Information on Toxicological Effects:

Potential Health Effects:

- Eye Contact: May cause mild eye transient irritation with redness and tearing.
- Skin contact: Skin Sensitization, May cause an allergic skin reaction. May cause mild irritation. Prolonged or repeated contact may cause defatting of the skin with dryness and cracking.
- Inhalation: May cause allergy or asthma symptoms or breathing difficulties if inhaled. Breathingvapors or mists may cause irritation of the mucous membranes and upper respiratory tract. Excessive overexposure may cause headache, dizziness, and drowsiness.
- Ingestion: Ingestion is an unlikely route of exposure, this material can be harmful if swallowed. It may cause depression of the central nervous system, nausea, and vomiting. May be fatal ifswallowed and enters airways.

Other Information: A theoretical concern exists about medication errors that might result in the ingestion of the Vamousse Spray 'n' Go product (particularly in young children), therefore it should only be administered under the direct supervision of an adult.

2.3.2 Potential benefits

A demonstration of efficacy and safety with a single treatment application; spraying treatment completely saturate each section in showing safe to leave on overnight allowing hair to dry naturally with 8 hours exposure time. Vamousse Spray 'n' Go represents a significant addition to the current armamentarium for the treatment of head lice.

3. Objectives and Purpose

The study will explore whether treatment with Vamousse Spray 'n' Go is:

- more effective in killing lice & eggs compared to a permethrin-based control product.
- Clinically proven to kill lice & eggs, including super lice,
- Convenient to use - Spray 'n' Go can be left in the hair for the duration of the school day or overnight,
- works with one application or with re-application after 7 days if necessary,
- cosmetically acceptable/smells good/fast-drying,
- safe to use in children 2yo+

4. Study Design and Endpoints

4.1 Description of the Study Design

This is a Study to Evaluate the Safety and Efficacy of Alliance Pharmaceutical Product in Subjects Infested with Pediculosis Capitis. The subject population includes healthy male and female subjects aged 2 years and up who are infested with *Pediculus humanus capitis*. Household members infestation with an active head lice, defined as at least 1 live louse (adult and/or nymph) present on the scalp and/or hair as determined by a trained evaluator, will receive treatment with study product at baseline.

The planned overall sample size for this clinical trial is approximately n=58 subjects, equally divided between treatment and control groups. Potential subjects will be screened for eligibility and if eligible to participate, their infestation level will be rated. Eligible subjects at each infestation level will be assigned alternately to the treatment or control group to ensure that the two groups have approximately equal representations of infestation severity levels. Level of infestation will be rated as heavy, moderate or light described by how quickly lice were found during combing: heavy infestation = >1 louse with one stroke of the comb; moderate infestation =1 louse with one stroke of the comb; light infestation = first louse found only after several strokes of the comb

After assignment to a study group, each eligible subject will receive the application of either the Alliance Pharmaceutical Product Vamousse Spray 'n' Go drug or the Permethrin-based control drug. Infested household members will be treated with the Vamousse Spray 'n' Go or Permethrin lotion on-site (i.e., the household members should be assigned to the same treatment as the index case). During the baseline visit (Day 0), the Investigator and clinical staff members will record subject's demographics; elicit informed consent; obtain medical history; review concomitant medication to identify any prohibited therapies the subject may be receiving; collect vital signs; conduct visual assessment of head lice, specifically counting live lice and nits with stages noted, using a 15 inch led 5x magnifying procedure lamp and if needed for confirmation, laboratory microscopes; perform physical examination; assess local skin/ scalp irritation; assess ocular irritation; perform urine pregnancy test on females; and conduct an adverse event assessment.

At day 7, if live lice are still present, a repeat treatment will be administered. After day 7 if a subject reports clear signs of infestation (i.e., the presence of live lice), they will be regarded as a treatment failure and they will be offered treatment with an alternative product (viz., Vamousse Mousse) by clinical staff.

For the treatment group, Clinical staff will apply Vamousse Spray 'n' Go to fully coat dry hair and scalp, avoiding the eyes and mucus membranes. The Treatment will be left on the hair and scalp for 8 hours, then standard at home shampoo and rinsed off with warm water, followed by combing. The Treatment spray bottle is intended for a single use although it contains a sufficient quantity for two treatments. All household members will be instructed on an overall lice management program, which includes:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash (in hot water) personal care items such as combs, brushes and hair clips.
- Record time and date product shampoo/rinse 8 hours post treatment

For the control group, Clinical staff will first shampoo the hair and scalp using regular shampoo. They will then

thoroughly rinse and towel dry the hair and scalp, and allow hair to air dry for a few minutes. Shaking the permethrin lotion well before applying, they will proceed to thoroughly wet the hair and scalp with the permethrin lotion, being sure also to cover the areas behind the ears and on the back of the neck. After allowing the lotion to remain in place for 10 minutes, they will then rinse the hair and scalp thoroughly and dry with a clean towel.

The site will provide Subject with lice management instructions. Subjects will return for post-baseline visits assessments at Day 2, Day 7, and Day 14.

Day 2: The Investigator and medical staff will collect medical history, collect vital signs, perform physical examination, scalp irritation assessment, ocular irritation assessment and adverse events assessment, perform a visual assessment for the presence or absence of head lice, (Lice will be counted, each stage examined and noted live or dead; 15in led 5x magnifying procedure lamp or laboratory microscopes are used for confirmation if needed, Without clipping hair strands, nits will also be examined, each stage examined and noted hatched or unhatched), and adverse events assessment Urine pregnancy testing will be performed on each Visit, with interim visits confirming pregnancy has not occurred through questioning participating subject and legal guardian.

Day 7: The Investigator and medical staff will collect medical history, collect vital signs, perform a physical examination, assess scalp irritation, assess ocular irritation and adverse events, perform a visual assessment for the presence of head lice (lice will be counted, each stage identified, and noted live or dead; 15in led 5x magnifying procedure lamp or laboratory microscopes will be used for confirmation if needed; without clipping hair strands, nits will also be examined, each stage examined, and noted hatched or unhatched). Urine pregnancy testing of females will be performed on each visit, with interim visits confirming pregnancy has not occurred through questioning participating subject and legal guardian. If, at day 7, live lice are still present, a repeat Vamousse Spray 'n' Go or Permethrin (depending on study group) shampoo treatment will be administered.

Day 14:The Investigator and medical staff will collect medical history, concomitant and prohibited medication review, perform vital signs, urine pregnancy testing if applicable, perform physical examination, record local application site reactions, ocular irritation assessment, perform a visual assessment for the presence of head lice (lice will be removed, counted, each stage examined and noted live or dead; 15 inch led 5x magnifying procedure lamp or laboratory microscopes are used for confirmation; nits will also be removed by clipping hair strands, examined, each stage counted, and noted as hatched or unhatched) and adverse events assessment. By day 14 if a subject reports clear signs of infestation (i.e., the presence of live lice) they will be regarded as a treatment failure and will be offered treatment with an alternative product (Vamousse Mousse) by clinical staff.

4.2 Study outcome measures and endpoints

4.2.1 Outcome measures

Primary outcome measure: the proportion of subjects in a study group who are completely lice free, meaning no live adults or nymphs.

Secondary outcome measure: the decline in total number of live adult lice and nymphs from the baseline count.

4.2.2 Primary Endpoint

The proportions of participants in each of the study groups (i.e., treatment and control) who are completely free of live adult lice and nymphs at day 14

4.2.3 Secondary Endpoints

- Assessment of infestations detected: number of live adult and nymph forms at the 7-day visit confirmed by investigator inspection during detection combing.
- Proportion of subjects requiring re-treatment at 7 days.
- Proportion lice free at day 2 (i.e., 24 hours after first treatment)
- Volume of product used in relation to hair type (Volume will be weighted pre and post and weight will be recorded on the product log. Hair type will be recorded as fine, medium or coarse on source document.)
- Safety of the product – as determined by reported adverse events during the study and recalled at the end of the treatment period.
- Cosmetic acceptability of the product in daily use as determined by consumer assessment questionnaire at the 14-day visit.
- The mean change between day 14 and baseline in the counts of live lice (i.e., total of live adult lice and nymphs) in each study group (i.e., treatment and control).

5. Study Enrollment and Withdrawal

5.1 Inclusion criteria

1. Subjects must have an active head lice infestation defined as: At least 1 live lice (adults and/or nymphs) present on the scalp and/or hair, as determined by a trained evaluator.
2. Subjects must be at least two (2) years of age through 75 years of age, presenting with an active head lice infestation.
2. Subject is male or female.
3. Subject is at least 2 through 75 years of age at time of enrollment.
4. Subject is in good general health based on medical history.
5. Each subject must have an appropriately signed Informed Consent agreement. A caregiver must sign an Informed Consent agreement for children not old enough to do so. Children 6-17 years of age will be administered a child's Assent Form.
6. The caregiver of a subject must be willing to allow all household members to be screened for head lice. If other household members are found to have an active head lice infestation, they must be willing and able to participate in receiving study product or Standard of Care.
7. Subject agrees not to use any other form of lice treatments (commercial, community-anecdotal, or mechanical/manual) while participating in the study.

8. Following application of the test product, subject agrees not to shampoo, wash, or rinse their hair or scalp until 8-hour post-treatment time has been reached and documented.
9. Subject agrees to not cut or chemically treat their hair while participating in the study.
10. Subject agrees to follow all study instructions, including attending all follow-up appointments.
11. Female subjects of childbearing potential must be willing to have a urine pregnancy test prior to inclusion in this study.

5.2 Exclusion criteria

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

1. History of irritation or sensitivity to Vamousse Spray 'n' Go or the components, pediculicides or hair care products.
2. Presentation at the treatment site with visible skin/scalp condition(s) that are not attributable to head lice infestation, such as an erythema score that is >2, blisters, vesicles which, in the opinion of the investigative personnel or medical monitor, will interfere with safety and/or efficacy evaluations.
3. Presentation at the treatment site with eczema or atopic dermatitis.
4. Treatment for head lice (Over the counter [OTC], home remedy and/or Prescription) in the last 30 days.
5. Any condition or illness that, in the opinion of the investigator, may compromise the objective of the protocol.
6. Is receiving any other treatment which, in the opinion of the investigator or medical monitor, may interfere with the study results.
7. Females (including caregivers who come in contact with the investigational product) who are pregnant, nursing or planning a pregnancy which could include household subjects. If a household has a pregnant female who has an active case of lice, the entire household is excluded from participation and provided Standard of Care.
8. Household members of child-bearing potential, including subjects, and unwilling to use an adequate method of contraception for the duration of the study. Adequate methods of contraception include: abstinence, vasectomized partner, oral birth control pills, birth control injections or patches, Intra uterine devices, condoms with a spermicidal jelly or a diaphragm with spermicidal jelly, surgical sterilization. Subjects and/or caregivers will be considered non-child-bearing if the following has occurred: full hysterectomy or bilateral oophorectomy is considered surgically sterile. Tubal ligation is not considered equivalent to female sterilization.
9. Participation in a previous investigational drug study within the past 30 days.
10. Does not understand the requirements for study participation and/or may likely exhibit poor compliance, in the opinion of the investigator.
11. Does not have a known household affiliation with their household members (i.e., do not stay in one household consistently, sleeping at one place several nights and then at another place or location). Household is defined as living in a shared area or space (for example the same house or apartment unit).

5.3 Criteria for Inclusion of Minor Subjects

Subjects aged 6 years through 17 years of age must sign the Assent Form that will be written in such a way as to be understandable to a child and to obtain parental or legal guardian consent prior to enrollment in this study.

5.4 Strategies for recruitment and retention

- Expected total number of screened subjects will be 64.
- Given a 10% screen failure rate, an anticipated number of enrolled subjects will be 58.
- Assumed dropout rate is 10%, an expected number of 52 subjects will complete the study.
- Source of subjects will be primarily from established patient data base, community at large, area schools and daycares, along with referrals by local healthcare centers to research site.
- Retention of subjects will be supported by thorough visit reminders and proper education on the study itself, including study duration, activities and responsibilities.

5.5 Subject withdrawal and termination

5.5.1 Potential reasons for withdrawal

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

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

1. Withdrawal of consent by the subject is received. In the opinion of the Investigator or Medical Monitor it is not in the subject's best interests to continue in the study.
2. Occurrence of an Adverse Event (AE) or Serious Adverse Event (SAE), which, in the opinion of the Investigator, warrants discontinuation of the subject from the study.
3. Pregnancy as informed by the subject or as determined by a positive urine pregnancy test.
4. Significant non-compliance with study procedures that would interfere with the study results or increase the subject's risks in the study, as determined by the Investigator.
5. Subject is deemed to be a treatment failure if upon revisit it is determined that they are still infested having live lice. They will be terminated from the study and provided the standard of care at that point in the study.
6. Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
7. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

5.5.2 Handling of Subject Withdrawals or termination

The Sponsor reserves the right to discontinue the trial prior to inclusion of the intended number of subjects. After such adecision, the Investigator must contact all participating subjects within a time period specified by the Sponsor to inform them of the decision to discontinue the trial.

5.6 Premature suspension or Termination of Study

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

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

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

Criteria for Premature Termination or Suspension of Investigational Sites:

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

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

- In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational site during the course of termination or study suspension.
- Appropriate therapy and follow-up should be ensured for any study subject by the sponsor.
- Ensure where required by applicable regulatory requirements that the regulatory authority is properly informed.
- If the sponsor terminates the study or the subject withdraws, the end of treatment visit and/or discontinuation Visit should be conducted.

6. Study product

6.1 Study product and control description

6.1.1 Acquisition

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

6.1.2 Formulation, appearance, packaging and labeling

Document Attached: Alliance Pharma - Vamousse Spray 'n' Go 4oz Label

The test product is Vamousse Spray 'n' Go manufactured by Alliance Pharmaceuticals Ltd., supplied in 4 oz. tubes.

Study product Spray:

Active ingredient: Natrum Muriaticum 2X (HPUS)

Inactive ingredients: Benzyl Alcohol, Geraniol, Glycerin, Isopropyl Alcohol, Linalool, Potassium Cocoate, Water.

The control product is Nix Creme Rinse Lice Treatment manufactured by Prestige Consumer Healthcare Inc., supplied in 2 oz. bottles.

Control product Shampoo:
Active ingredient: Permethrin 1% shampoo

Inactive ingredients: balsam canada, cetyl alcohol, citric acid, FD&C yellow no. 6, fragrance, hydrolyzed animal protein, hydroxyethylcellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methylparaben 56 mg (0.2%), and propylparaben 22 mg (0.08%).

6.1.3 Product Storage and Stability

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

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

6.1.4 Preparation

Shake the bottle to ensure the product is fully mixed. Neither Vamousse Spray 'n' Go nor the Nix requires no additional preparation prior to use.

6.1.5 Dosing and administration

Lice and nit removal is not performed prior to nor during dosing and administration. For the study drug (Vamousse Spray 'n' Go), separate hair into 3-4 sections with clips. Part hair in 1-inch sections, spray treatment to completely saturate each section. Work through hair with a comb to ensure full coverage down to the scalp. Pay special attention to the nape of the neck and behind ears. Thoroughly saturate all hair and scalp. To be effective, all lice and nits must come in contact with the product. Allow hair to dry naturally. Leave treatment in for a minimum of 8 hours. Avoid contact with eyes. Do not swallow. Thoroughly wash hands after applying study product. Vamousse Spray 'n' Go should be used in the context of an overall lice management program:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding and towels.
- Wash (in hot water) personal care items such as combs, brushes and hair clips.

For the control drug (Nix Creme Rinse Lice Treatment), first shampoo the hair and scalp using regular shampoo. Then thoroughly rinse and towel dry the hair and scalp, and allow hair to air dry for a few minutes. Shaking the permethrin lotion well before applying, proceed to thoroughly wet the hair and scalp with the permethrin lotion, being sure also to cover the areas behind the ears and on the back of the neck. After allowing the lotion to remain in place for 10 minutes, rinse the hair and scalp thoroughly and dry with a clean towel.

6.1.6 Route of Administration

Vamousse Spray 'n' Go, is for topical use only. It is not for oral, ophthalmic, or intravaginal use.

6.1.7 Duration of therapy

The study is comprised of three phases: Screening, Treatment (3) Follow-Ups. The duration of this study is 14 days (+/- 3). The Screening and Treatment Phase (baseline) will be Day 0 (visit 1). Screening and treatment will occur on the same day.

6.1.8 Tracking of at home compliance

Subject Home Instructions will be distributed and accounted for. Subjects will fill out their Subject Home Instructions noting the following:

- Time and date of removal (washing off the study drug in 8 hours, followed by thorough combing)
- Confirmation that subject disinfected personal items; worn clothing, hats, used bedding and towels
- Confirmation Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding, towels including combs, brushes and hair clips.

Subjects will return their Subject Home Instructions to the clinical site for compliance review at Follow-up Day 2, Day 7, and Day 14. The Investigator will verify that the subject complied with disinfection regimen. Both the subject and the study staff will sign off on completed Subject Household Instructions. If the subject has missed the disinfection notation, this is considered a protocol deviation and must be reported.

6.2 Study drug accountability

The Sponsor will supply sufficient quantities of the study drug for the completion of this study. The study pharmacist or designated study personnel will maintain a Drug Application Log. All product bottles must be accounted for, and any discrepancies explained. Study site should contact site Clinical Research Associate (CRA) in case of any dispensing errors or if discrepancies are discovered.

At the end of the study, the Investigator will retain all the original documentation regarding study drug accountability, return, and copies will be sent to the Sponsor. All unused and used Study Drug bottle will be returned to the Sponsor or its designee for destruction at the end of the study. Retention is stored on site with Sponsor instructions.

7. Study procedures and schedule of events

7.1 Study procedures and evaluations

Informed Consent, Eligibility Criteria, Subject Demographics, hair type and Investigational Product Dispensation/ Application on Day 0.

Medical History, Vital signs, Physical Examination, Head Lice Visual Assessment, Local Skin/Scalp Irritation Assessment, Ocular Irritation Assessment and Adverse Events Assessment will be collected at Baseline Visit 1 (post treatment), Visit 2, visit 3 and Final Study Visit 4.

Basic demographic information, including date of birth, sex, ethnicity, and race will be recorded at the Screening /Baseline Visits. Relevant medical history, and past history of head lice will be documented. All medications (both prescription and

nonprescription), including vitamins, herbals, topical, inhaled, and intranasal taken within 30 days prior to the start of the Study Drug and through the final study visit will be recorded on the appropriate source document (using their generic and/or brand names), if known with the corresponding indication, start and stop dates. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed medication use).

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

Physical examination, including height, weight, and evaluation of organs and systems (General Appearance, Heart/Cardiovascular, Lungs, Gastrointestinal, Ears / Nose / Throat, Extremities, and Skin) will be assessed at Visit 1 Day 0, Visit Day 2, Visit Day7, and Final Study Visit Day 14

Urine Pregnancy Test and Concomitant/ Prohibited Medication Review will be performed on all Visits.

7.1.1. Study specific procedures

In addition to the regular standard of clinical care, the following study specific procedures will

be included as part of the study.

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

- Visual Assessment of Head Lice:
  Subjects and their household members will be thoroughly assessed for the presence or absence of live head lice, including adult lice, nymphs, and nits. Results will be recorded on Source Document.

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

- Ocular Irritation:
  Subjects will be assessed for eye irritation, conjunctivitis, and ocular hyperemia. Results will be recorded on the Source Document.

- Subject Household Instructions:
  Administration of a checklist for rinse/ shampoo time and date; and daily laundry and disinfection measures will be collected at all follow-up visits.

- Subject Assessments:
  Administration of questionnaire for subject-reported outcomes. The site will complete a Subject Self-Assessment Worksheet to record the grading of Itching and Stinging/Burning sensations. Analysis of tolerability will be based on a 7 point scoring scale of Stinging/Burning and Itching sensations collected during Subject Self-Assessment at all follow-up visits.

7.2 Laboratory procedures and evaluations

7.2.1 Clinical laboratory evaluations

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

7.3 Study schedule

7.3.1 Screening/randomization

Screening Visit Day 0 (Visit 1)

- Obtain informed consent of potential participant verified by signature on written informed consent.
- Record demographic information, obtain medical history, and history of head lice.
- Review medications history and concomitant/prohibited medications to determine eligibility
- Verify inclusion/exclusion criteria.
- Collect urine sample for pregnancy testing for all subjects of childbearing potential.
- Perform assessment for living head lice on subjects and household members for a minimum of 15 minutes. Each subject must have at least 1 live louse. Rate severity of infestation. After each subject has been identified, additional infested household members will also be assessed for infestation.
- Level of infestation will be rated as heavy, moderate or light described by how quickly lice were found during combing: heavy infestation = >1 louse with one stroke of the comb; moderate infestation =1 louse with one stroke of the comb; light infestation = first louse found only after several strokes of the comb
- Household members must have an active head lice infestation defined as: At least 1 live lice (adult and/or nymph) present on the scalp and/or hair, as determined by a trained evaluator. Household members will be assigned to the same study group as index case.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Randomly assign subjects to treatment or control group based on infestation severity alternation system (i.e., randomly assign pairs of equal severity levels to treatment and control groups, a form of stratified random sampling) to achieve balanced representation of severity in the two groups.
- Investigational Product Dispensation/ Application for subject.
- Provide each subject with homecare instructions including combing after first wash out.
- Inform subject when to come back for each follow-up visit.
- Provide Standard of Care treatment on-site to unqualified infested household members.

7.3.2 Follow up

Follow-up Visit (Day 2) Visit 2 (+24hrs.)

- Medical History, Vital Signs, Physical Examination, Head Lice Visual Assessment, Local Skin/Scalp Irritation, Assessment, Ocular Irritation Assessment. Record results on Source Document.
- Record adverse events as reported by participant or observed by investigator.
- Record subject's adherence to homecare instructions.
- Perform assessment for living head lice on subject for visual confirmation of infestation.
- Record subject's adherence to homecare instructions.
- Inform each subject when to come back for their visit (Day 7) Visit 3 ± 1 days

7.3.3 Follow up study visits

Follow-up Visit (Day 7) Visit 3 (+/- 1 day)

- Medical History, Vital Signs, Physical Examination, Head Lice Visual Assessment, Local Skin/Scalp Irritation, Assessment, Ocular Irritation Assessment.
- Record results on Source Document.
- Record adverse events as reported by participant or observed by investigator.
- Record subject's adherence to homecare instructions.
- Perform assessment for living head lice on subject for visual confirmation of infestation.
- Record subject's adherence to homecare instructions.
- If, at day 7, live lice are still present, a repeat treatment will be administered followed by thorough combing
- Inform each subject when to come back for their Final visit (Day 14) Visit 4 +-2 days.

7.3.4 Final study visits

Visit Day 14 (Visit 4) (+/- 2 days)

- Medical History, Physical Examination, Vital Signs, Urine Pregnancy Test, Head Lice Visual Assessment, Local Skin/Scalp Irritation Assessment, Ocular Irritation Assessment,
- Concomitant and Prohibited Medication Reviewand record results on Source Document.
- Record adverse events as reported by participant or observed by investigator.
- Perform assessment for living head lice on subject for visual confirmation of infestation for a minimum of 15 minutes.
- If, after day 14, a subject reports clear signs of infestation i.e., the presence of live lice, they will be regarded as a treatment failure and they will be offered treatment with an alternative product, Vamousse Mousse.

7.3.5 Unscheduled visit

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

7.3.6 Rescreening

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

7.4 Concomitant/precautionary medication, treatment and procedures

As part of standard medical history, all medications (both prescription and nonprescription, and including vitamins, herbals, topical, inhaled, and intranasal) taken within 30 days prior to the start of the Study Drug and through the final study visit will be recorded on the appropriate source document (using their generic and brand names, if known) with the corresponding indication, start and stop dates. At each study visit, subjects will be asked whether they have started or discontinued any medication since their previous study visit. This includes single use or PRN (as needed) medication use.

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

7.5 Prohibited medication, treatment and procedures

Head lice treatment products (over the counter [OTC], home remedy and/or Prescription) are prohibited 30 days prior to and during the study. These include, but are not limited to:

- Nix Ultra
- Rid Max
- LiceMD

7.6 Rescue medication, treatment and procedures

If live lice are present on Day 14, the subject will receive the over-the-counter (OTC) rescue treatment, Vamousse Mousse, for head lice and their study participation will be considered complete and will be considered a treatment failure.

7.7 Participant access to study product at study center

Participants will receive the study product at their Enrollment/Baseline Visit/ Day 0.

8. Assessment of Safety

8.1 Specification of study parameters

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

8.1.1 Definition of adverse events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the investigational product. Treatment-emergent AEs (TEAE) will include any AEs reported beginning with the application of study drug on Day 0.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. I.e., if a new signs or symptom or worsening of a sign or symptom was believed by the investigator to be related to the study drug and not the disease, then it was recorded as an AE. Clinically significant abnormalities are to be followed to resolution (i.e. become stable, return to normal, return to baseline, or become explainable). Changes in vital signs are considered to be AEs only if they necessitate therapeutic medical intervention, and/or if the Investigator considers them to be AEs.

8.1.2 Definition of serious adverse events (SAE)

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

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

8.1.3 Definition of unanticipated problems

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

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

8.2 Classification of an adverse event

8.2.1 Severity of event

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

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

8.2.2 Relationship to study product

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

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

8.2.3 Expectedness

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

8.3 Time period and frequency for event assessment and follow up

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

8.4 Reporting procedures

8.4.4 Adverse event reporting

8.4.4.1 Serious adverse event reporting

In the event of a SAE, whether related to study drug or not, the Investigator or representative must make an accurate and adequate report consisting of at least the minimum criteria (Site and Subject ID, Date site became aware of the event, SAE Term, Seriousness criteria, Study Drug information, Investigator/Reporter and site address) within 24 hours by email, or telephone to the Sponsor's (Alliance Pharmaceuticals Ltd) US-based Scientific Affairs Team (NorthAmericanScientificAffairs@allianceph.com, tel: +1-984-204-1543.). Alliance Pharmaceuticals Ltd. Personnel will complete the SAE report onto a MedWatch 3500A form for evaluation and convey for review by the Medical Monitor and Site Investigator. Accurate Completion of the MedWatch 3500A form will consist of all data supplied such as Subject's demography, SAE narrative, concomitant medication, laboratory parameters and relevant medical history. In addition, if required by the applicable IRB/source document, the Investigator will submit the SAE reports to the IRB/source document within 15 calendar days of discovering the SAE, or alternatively, within accordance of applicable regulations or IRB/source document requirements.

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

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

MEDICAL MONITOR
Alliance Pharmaceuticals Ltd.
E-mail: Steve.Mann@allianceph.com
Alliance Pharmaceuticals Ltd. Chippenham, Wilshire, SN15 2BB, United Kingdom

8.4.5 Unanticipated problem reporting

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

8.4.6 Reporting of pregnancy

If a subject, or female partner of male subject becomes pregnant during the participation in the study, the Investigator will immediately discontinue the subject from the study and contact the Medical Monitor and the Sponsor. Diligent efforts will be made to determine the outcome for all pregnancy exposures in the clinical trial. Information on the status of the mother and the child will be forwarded to the Sponsor's Safety Team using the Pregnancy Data Collection Form. Generally, follow-up will occur within 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported. Detailed guidance on the reporting of Pregnancies will be provided in SAE and Pregnancy Reporting Guidance.

8.5 Safety oversight

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

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

9 Clinical Monitoring

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

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

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

10 Statistical considerations

The sections below summarize the intended statistical methods and analyses of data for the study.
Descriptive statistical methods will be used to summarize the data from this study, with confidence intervals calculated for the primary and secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum, and maximum for continuous data and frequencies and proportions for categorical data. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment, subject number, and then by date within each subject number.

10.1 Statistical analysis plans

Treatment and control groups will be compared at the primary and secondary endpoints using the proportion of subjects in each group who are lice-free (i.e., no adults or nymphs) as the dependent outcome measure. The proportions for the two groups will be compared using the Z test for independent proportions. In either analysis if the numbers of subjects in the no lice category of either group is less than 10, an alternative estimate of the standard error will be used (e.g., Fisher's Exact or bootstrapping).

10.2 Data sets to be evaluated

The subject populations are defined as follows:

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

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

Per-Protocol (PP) population includes all mITT subjects who were administered treatment, had no protocol deviations which could have interfered with the accurate assessment of treatment efficacy, and returned for the Day 14 visit within the allowed window. This is the primary population for the efficacy comparisons between the two active treatment groups.

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

Efficacy analyses will be performed on both the per-protocol population and the mITT population. Safety analyses will be performed using the Safety population as defined.

10.3 Statistical hypotheses

Primary Efficacy Endpoint:

Primary Outcome:

The proportion of subjects who are lice free (defined as no live lice, adults or nymphs) at day 14 will be greater in the treatment group than in the control group.

Secondary Outcome:

The mean change between day 14 and baseline in the counts of live lice (i.e., total of live adult lice and nymphs) will be greater in the treatment group than in the control group.

Secondary Efficacy Endpoint:

Primary Outcome:

The proportion of subjects who are lice free (defined as no live lice, adults or nymphs) at day 7 will be greater in the treatment group than in the control group

Secondary Outcome:

The mean change between day 7 and baseline in the counts of live lice (i.e., total of live adult lice and nymphs) will be greater in the treatment group than in the control group.

10.4 Description of statistical methods

10.4.1 Subject disposition and demography

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

10.4.2 Assessment of primary and secondary endpoints

Primary Outcome:

To test the hypotheses for this outcome for each of the two endpoints, the counts of subjects in the treatment and control groups who were lice free at each endpoint will be converted into proportions of the respective group. These proportions along with the group sample sizes will be used to compute the necessary Z statistics for independent proportions.

Secondary Outcome:

To test the hypotheses for this outcome for each of the two endpoints, the difference between the day 14 and baseline counts of live lice (i.e., total of live adult lice and nymphs) will be computed for each participant. The mean difference in counts for the treatment and control groups will be tested using the *t*-test for independent means.

10.4.3 Safety analyses

The reporting of safety data is descriptive, and will include all subjects in the Safety population. The variables for safety endpoints are AEs. AEs will be summarized based on their frequency and their severity. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group. Data will be summarized using preferred term and primary system organ class.

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

Summaries of treatment-emergent AEs will include any AEs reported beginning with the first dose of study product on Day 0. The occurrence of treatment-emergent adverse events will be summarized by treatment group using preferred terms, system organ classifications, and severity. Separate summaries of treatment-emergent serious adverse events, treatment-emergent adverse events related to study drug, and events leading to the discontinuation of study drug will be generated. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms.

Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary. These data will be summarized for all subjects. Previous and concomitant medications will be presented in a data listing.

10.5 Sample Size

Sample size is 52. The requisite sample size for the *t*-test of the means of independent samples, assuming a Cohen's *d* of .40, alpha .05 two-tailed, and a power of .80, was smaller at 44. Thus, the larger requisite sample size for the z-test will also suffice for the t-test and will provide a cushion for the application of the Holm correction for Type I error. The sample size of 52 should be increased to account for a 10% expected dropout rate, resulting in a total sample size, rounded to an even number, of 58 (26 per group).

Expected difference:

40% difference between treatment groups, based on results of LiceFreee Spray (1% Sodium Chloride) compared to Permethrin; the results showed significantly higher pediculicidal activity for Sodium Chloride spray (85%) as compared to Permethrin (45%) at Day 15 ($p < 0.05$)[1].

A pilot study using Vamousse Spray 'n' Go as a once only treatment, showed high early lice kill (88% lice free at day 0 after treatment) but low efficacy at day 14 (12% lice free). It is anticipated that repeat dosing after 7 days, if live lice are present, will boost day 14 efficacy to levels similar to those at day 0.

Assumptions:

80% power, 0.05 alpha
Allocation ratio 1:1

Methods:

Calculations performed in Stata/IC 16.1
Binary data (lice free – Y/N) – proportions
Independent samples
Chi Squared, two-sided test

Sample:

Estimated sample sizes for a two-sample proportions test
Pearson's chi-squared test
Ho: p2 = p1 versus Ha: p2 ≠ p1
Study parameters:

alpha = 0.0500
power = 0.8000
delta = 0.4000 (difference)
p1 = 0.4500
p2 = 0.8500

Estimated sample sizes:

N = 52
N per group = 26
Allowance for drop out: 10% per group, 3
Total sample: 29 per group (58)

References:

[1] Serrano, L. et al. Evaluation of the Efficacy and Safety of 1% Sodium Chloride (LiceFreee Spray) against 1% Permethrin Crème Rinse on Head Lice Infested Individuals. *Pharmacology & Pharmacy*, 2013, 4, 266-273.

11 Source documents and access to source data/documents

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

12 Ethics/subject protection

12.1 Ethical standard

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

12.2 IRB

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

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

12.3 Informed Consent Process

12.3.1 Other information documents provided to participants

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

12.3.2 Consent procedures and documentation

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

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

The informed consent form will be in compliance with ICH GCP, local regulatory, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and the Sponsor before use, and shared with the subject and/or their representative for continued inclusion in the study

12.4 Participant and data confidentiality

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

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigatorto permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process.
Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's source documents).

13 Data handling and record keeping

13.1 Study records retention

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

meeting minutes, telephone calls reports) for a duration of five (5) years.

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

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

13.2 Protocol deviations

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

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

Protocol Compliance review:

- Verify that the Investigator and Investigational Site personnel are adhering to the IRB/IEC approved Protocol and all amendments. In addition to the Protocol, the Monitoring Plan may include (or reference) verification strategies which define a percentage of data points to be reviewed or other methodologies for verification of Investigational Site compliance. The Monitoring Plan should be followed regarding verification and study specific problem escalation, and Protocol compliance is often reviewed by checking adherence to the correct Protocol-defined procedures, assessments, and sampling requirements (if applicable).
- Verify that the Investigator is enrolling only eligible Study participants and all entry criteria are satisfied for each Study participant verified, as per the current approved Protocol. Documentation and verification of participant status in the study.
- Verify that no prohibited medications or changes in dose for indication-related medications are being used without prior approval from Medical Monitor or Sponsor Designee.
- Address any protocol deviations with site personnel during the IMV and identify ways to prevent the recurrence of similar issues e.g. training the site team on that particular issue.

13.3 Publication and data sharing policy

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution.

The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

14 Conflict of interest policy

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

15 References

(1) Head Lice infestation: Developing Drugs for Topical Treatment – Guidance for Industry. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research October 2016 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/head-lice-infestation-developing-drugs-topical-treatment-guidance-industry
(2) Barker, S.C. et al. International guidelines for clinical trials with pediculicides. Int. J. Dermatol. 2012; 51: 853-858
(3) Birkemoe, T. et al. Head Lice predictors and infestation dynamics among primary school children in Norway. Family Practice, 2016; 33(1): 23-29

16 Appendices

16.1 Schedule of events

Visit Number	Visit 1	Visit 2	Visit 3	Visit 4
Visit Day	Day 0	Day 2	Day 7	Day 14
Informed Consent	X			
Eligibility Criteria	X			
Subject Demographics	X			
Medical History	X	X	X	X
Physical Examination	X	X	X	X
Combing		x	X (if treatment needed)	
Investigational Product Dispensation	X		X (if necessary)	
Vital Signs	X	X	X	X
Urine Pregnancy Test	X	X	X	X
Head Lice Visual Assessment	X	X	X	X
Local Skin/Scalp Irritation Assessment	X	X	X	X
Ocular Irritation Assessment	X	X	X	X
Concomitant and Prohibited Medication Review	X	X	X	X
Adverse Events Assessment	X	X	X	X

16.2 Subject household information

SUBJECT DIARY

Protocol Number: ALLI010-0021

Study Title: **A Study to Evaluate the Safety and Efficacy of Alliance Pharmaceutical Product Vamousse Spray 'n' Go in Subjects Infested with Pediculosis Capitis.**

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

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

SUBJECT HOUSEHOLD INFORMATION			
Study Visit	**Visit 1**	☐	
HOUSEHOLD MEMBERS TREATMENT INFORMATION			
Number of Infested Household Members			
Number of Non-Infested Household Members			
Total Number of Household Members			
Infested Household Member # 1 Standard of Care Treatment	**Yes**	**No**	**Circle (Yes) or (No)**
Infested Household Member # 2 Standard of Care Treatment	**Yes**	**No**	
Infested Household Member # 3 Standard of Care Treatment	**Yes**	**No**	
Infested Household Member # 4 Standard of Care Treatment	**Yes**	**No**	
Infested Household Member # 5 Standard of Care Treatment	**Yes**	**No**	
Infested Household Member # 6 Standard of Care Treatment	**Yes**	**No**	
Infested Household Member # 7 Standard of Care Treatment	**Yes**	**No**	

16.3 Subject home instructions

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

Subjects Home Instructions		
Activity	Application of study drug – Day 0	Complete
To be completed by Study staff	• Was product Applied Onsite?	Yes No **Date of Application** D D M M M Y Y Y Y **Time of Application** H H M M
To be completed by subject/or caregiver	• Was the hair wash, or rinse 8-hours post-treatment?	Yes No **Date to Shampoo Hair** D D M M M Y Y Y Y **Time to Shampoo Hair** H H M M
LAUNDRY DISINFECTION:	• Was all recently worn clothing, hats, used bedding & towels washed at home?	Yes No

Subject and/or Caregiver (Initials): _____ Date: _____

Completed & Reviewed By (Initials): _____ Date: _____

16.4 Subject self-assessment

SUBJECT SELF ASSESSMENT

SITE PERSONELL TO COMPLETE:

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

Visit Number	*Visit 1 [Baseline]*	*Visit 2 [Follow Up]*	*Visit 3 [Follow Up]*	*Visit 4 [Final Visit]*
Visit Day	*Day 0*	*Day 2*	*Day 7*	*Day 14*

TO BE COMPLETED BY SUBJECT AND/OR CAREGIVER:

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

ITCHING

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

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

STINGING/BURNING

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

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

Subject and/or Caregiver (Initials): _____ Date_____

Completed & Reviewed By (Initials):_____ Date: _____

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Version 3.0
27 July 2022