Prevention of infestation with *Pediculus humanus capitis* in the family group using a pediculicidal shampoo: A prospective, randomised controlled study.

VAM2301

Version: 2.1 dated 3rd November 2021

Prevention of infestation with *Pediculus humanus capitis* in the family group using a pediculicidal shampoo: A prospective, randomised controlled study.

VERSION NUMBER:	Version: 2.1 3rd November 2021
PRODUCT NAME:	Vamousse Lice Defence Shampoo
COUNTRY:	UK
CLINICAL STUDY NUMBER:	VAM2301
CHIEF/PRINCIPAL INVESTIGATOR:	Ian Burgess – Director Medical Entomology Centre, Insect Research and Development Ltd, 6 Quy Court, Colliers Lane, Stow-cum-Quy, Cambridge, CB25 9AU Tel: 01223 813696
CLINICAL RESEARCH MANAGER/MONITOR:	Onorach Limited Unit 20, Prospect Business Centre Dundee Technology Park Dundee DD2 1TY
STUDY ALLIANCE PHARMACEUTICALS LTD. REPRESENTATIVE:	Jonathan Ormerod ALLIANCE PHARMACEUTICALS LTD AVONBRIDGE HOUSE BATH ROAD CHIPPENHAM WILTSHIRE SN15 2BB Tel: 01249 705119

ESTIMATED START DATE: January 2022

ESTIMATED COMPLETION DATE: March 2022

Investigator's Agreement

We have read this Alliance Pharmaceuticals Ltd. approved protocol, number VAM2301, version 2.1, dated 3rd November 2021, entitled "Prevention of infestation with *Pediculus humanus capitis* in the family group using a pediculicidal shampoo: A prospective, randomised controlled study"**, and have discussed it to our satisfaction with Alliance Pharmaceuticals Ltd.**

We agree to conduct the study according to this protocol and to comply with its obligations, subject to ethical and safety considerations.

We understand that should we be in breach of any of the terms of this protocol, or if we are negligent, that Alliance Pharmaceuticals Ltd., would not be held responsible for any resulting losses, damages, costs and expenses of whatever kind made by or on behalf of a participant.

Insect Research and Development Limited

Chief Investigator: Ian F Burgess Digitally signed by Ian F Burgess Date: 2021.11.04 15:37:38 Z _____Dated ___/___/___

Ian Burgess

Onorach Limited

Managing Director:

_____Dated ___/___/___

Christene Leiper

Alliance Pharmaceuticals Limited

Clinical Research Manager: Jonathan Ormerod Digitally signed by Jonathan Ormerod Date: 2021.11.04 15:45:38 Z _____Dated ___/___/___

Jonathan Ormerod

Should the decision be made by Alliance Pharmaceuticals Ltd. to terminate the study at any time, such decision will be communicated to the Investigator in writing, and appropriate arrangements will be agreed upon and specified in writing. Conversely, should the Investigator decide to withdraw from execution of the study he/she will communicate immediately such decision in writing to Alliance Pharmaceuticals Ltd.

CONTENTS

Investigator's Agreement 4

1.1 Summary of the Study 9

1.2 Rationale 11

1.3 Aims (Objectives) 11

1.4 Design in Brief 11

2. Materials and Methods 13

2.1 Participant Selection 13

2.1.1 Total Numbers of Participants, and Study Duration 13

2.1.2 Inclusion Criteria 13

2.1.3 Exclusion Criteria 14

2.2 Clinical Supplies and Materials 15

2.2.1 Physical Forms of the Study Supplies 15

2.2.2 Packaging and Labelling 16

2.2.3 Care of Supplies 16

2.2.4 Study Materials 17

2.2.5 Compliance 17

2.3 Procedures and Investigations 17

2.3.1 Treatment Regimen/Allocation 17

2.3.2 Randomisation 17

2.3.3 Study Methodology 18

2.3.3.1 Pre-recruitment 18

2.3.3.2 Recruitment (Day 0) 18

2.3.3.3 Follow up Assessments (Days 1, 7, 9, and 14) 21

2.3.3.4 Final Follow up Assessment (Day 14, +1 day). 21

2.3.3.5 Use of Patient Diaries During the Study 14

2.3.3.6 Assessment Analysis 21

2.3.4 Concomitant Medication 22

2.3.5 Adverse Events 22

2.3.6 Serious Adverse Events 22
2.3.7 Withdrawals 23
3. Analysis and Reports 24
3.1 Definition of End Points 24
3.1.1 Safety 24
3.1.2 Efficacy 25
3.2 Definition of Populations to be analysed 25
3.3 Proposed Primary and Secondary Analyses 25
3.4 Statistical Methods 26
3.5 Final Study Report 28
4 Administrative Procedures 28
4.1 Regulatory Documentation 28
4.2 Ethics Committee Approval 28
4.3 Informed Consent 28
4.4 Insurance Policy 29
4.5 Compensation 29
4.6 Investigator's Responsibilities 29
4.7 Curriculum Vitae 30
4.8 Case Record Form 31
4.9 Monitoring of the Study 31
4.10 Quality Assurance 31
4.11 Protocol Appendices 32
4.12 Protocol Amendments 32
4.13 Research Registration and Publication Policy 32
4.14 Early Termination of the Study 32

Appendices

Appendix 1: Declaration of Helsinki.

Appendix 2: ISO 14155:2020 Clinical Investigations of medical devices for human use – good clinical practice

Appendix 3: General Data Protection Regulations (GDPR) statement

Introduction

1.1 Summary of the Study

Title:	Prevention of infestation with *Pediculus humanus capitis* in the family group using a pediculicidal shampoo: A prospective, randomised controlled study.
Chief Investigator:	Ian F Burgess
Study Monitoring:	Onorach Limited
Estimated Study Start:	January 2022
Estimated Study Finish:	March 2022
Participants:	Eighty-four (84) participants (the Index Cases) with evidence of an active head louse infestation and their Households as the unit of randomisation will be recruited to the study. All Index Cases will be treated with Vamousse Treatment Mousse. Forty-two (42) participants and their Households will be treated with Vamousse Lice Defence Shampoo and forty-two (42) with The Control Shampoo. All participants will use the randomly assigned shampoo for fourteen (14) days and will be assessed for active head lice infestation at the end of that time.
Type:	Eligible children and adults
Products:	Vamousse Lice Defence Shampoo and The Control Shampoo.

Methods of Application:	Both preparations will be applied to wet hair, massaged into the scalp and left in the hair for 3 minutes and no more than 5 minutes before rinsing with water and towel-drying. (see Section 2.3.3.2).
Study Design:	Participants will be recruited into the study by household and randomised to receive either Vamousse Lice Defence Shampoo or The Control Shampoo. Index cases will be assessed for presence of head lice at their day of recruitment (Day 0) in order to ensure that all participants have live lice present at the start of the study. Other family members who proactively complain of head lice infestation will be treated as though they are an index case. All index cases will be treated the same day with Vamousse Treatment Mousse following confirmation of their eligibility. A member of the Medical Entomology Centre (MEC) study team will apply the treatment. All members of the household will commence using Vamousse Lice Defence Shampoo on Day 0 and will continue to use the shampoo daily for fourteen (14) days. On Day 3, the index case will be assessed for lice infestation; if necessary, a second treatment with Vamousse Treatment Mousse will be applied. Index cases with active infestation on Day 3 will be assessed again on Day 6 and treated again if the infestation is still active. All participants will be assessed for the presence of live head lice by dry detection combing on Day 14. No other active assessments will take place during the course of the study. If, however, a member of the household complains of infestation, a member of the MEC team will confirm the presence of live lice and they will be offered treatment with Vamousse Treatment Mousse.
Aims of the Study:	To demonstrate superiority of Vamousse Lice Defence Shampoo to The Control Shampoo in the prevention of lice infestation among close family members.

1.2 Rationale

Despite the introduction of physically acting treatments for head louse infestation that are not affected by resistance, infestation with the human head louse (*Pediculus capitis*) is still of widespread concern, partly because most families act individually and there are no coordinated efforts to eliminate infestation in most communities and partly because not all products are fully effective to eliminate infestation.

It has long been known that infestations of head lice occur most frequently in young children, but that the wider family can be a source of spreading the infestation and of re-infestation. Detection combing is a skilled procedure and may not be effective in the hands of the general public and over-use of neurotoxic insecticidal lice treatments has led to the evolution of resistant strains of head lice. The active ingredients in Vamousse Shampoo have been demonstrated in vitro to dissolve the waxy cuticle of the louse, which then dies from dehydration. As the shampoo is less effective at killing lice eggs, the shampoo needs to be used for approximately two weeks, in order that all nymphs, hatching from viable eggs, can be exposed to the shampoo.

The rationale behind this study is that treatment with a cosmetically acceptable, daily use lice-killing shampoo can help to prevent the spread of an infestation among close family members, prevent re-infestation of the index case and therefore reduce the impact of the infestation. To this end, the study will evaluate the superiority of Vamousse Lice Defence Shampoo used daily for 14 days in preventing the spread of infestation in the household, compared to a control shampoo with no active ingredients.

1.3 Aims (Objectives)

1. To compare efficacy of Vamousse Lice Defence Shampoo and The Control Shampoo with the aim of demonstrating the superiority of Vamousse Lice Defence Shampoo compared to The Control Shampoo in preventing the spread of infestation in a household.

2. To confirm the safety and acceptability in use of Vamousse Lice Defence Shampoo.

1.4 Design in Brief

This trial will be a randomised, parallel group study of a topical treatment for head lice (Vamousse Lice Defence Shampoo) in comparison with a control preparation (The Control Shampoo). At least eighty-four (84) index cases and their households will be recruited, randomised by household and stratified by family size (see Section 3.4 for

details).

At the first visit (Day 0), verbal consent will be obtained to check for the presence of live head lice in the index case, using a fine-toothed plastic detection comb. Any other family member who proactively complains of infestation will also be checked and thereafter will receive treatment as though they are an index case, but will still count as a member of the household. Other household members will not be assessed for the presence of lice.

After the preliminary assessment, participants can be enrolled to the study, provided the index case has an active infestation, all individuals comply with the inclusion/exclusion criteria and any further questions they may have are fully dealt with.

Participants (or their parents/guardians if they are younger than 16 years) will be asked to give written informed consent and sign a Consent Form before participation in the study. There will be a separate Assent Form for children capable of giving written assent. Assent Forms will be witnessed by the parent/guardian and signed by the Investigator.

All prospective index cases who fit the selection criteria (see section 2.1.2 and 2.1.3) will be confirmed as having an active head louse infestation prior to commencement of treatment (see below).

The household of the index cases enrolled on to the study will be randomly allocated to receive one of the two study preparations with at least forty-two (42) individuals allocated to each (see Section 3.4 for details). The Investigator will assign each Initial index case a study number, this being the next available number from a randomised treatment allocation sequence. The treatment allocations will be made double blinded, identified only by a code. Instructions for use will be held in sealed envelopes and will only be opened after consent has been received. Assignment will continue until there are at least forty-two (42) initial index cases in each group.

The population will be stratified according to the following criteria:

Number of children <3/≥3 and number of overt infestations on Day 0 =1/>1.

Index cases will be treated with Vamousse Treatment Mousse at Day 0. A member of the MEC study team will apply the treatment. This treatment is designed to eliminate infestation. Combing to remove lice or louse eggs, in addition to the shampoo treatment, will not be given in this study.

Starting on Day 0 and ending on Day 14, all participants will commence using the shampoo as part of their daily routine. As appropriate, reminders can be issued by SMS text.

The index case will be assessed for active infestation on Day 3 ±1. If live lice are present, Vamousse Treatment Mousse will be applied again. Index cases with active infestation on Day 3 will be screened again on Day 6 ±1 and re-treated if live lice are detected.

On day 14 ±1, all participants will be assessed for infestation by dry detection combing. Those with signs of an active infestation will be recorded as treatment failures. Anyone who has a head louse infestation at the end of the study will be provided with the standard of care treatment (Vamousse Treatment Mousse), as will any infested household member who is a non-participant.

It is possible that a participant may complain of infestation during the course of the study, although participants should be discouraged from taking active steps to detect the presence of lice. If this does occur, the individual should contact the MEC study team, who will confirm the presence of live lice and offer treatment. The individual will be recorded as a treatment failure in the CRF.

All adverse events will be monitored during the study (see sections 2.3.5 and 2.3.6) and all changes in concomitant health conditions and/or medication will be recorded (see section 2.3.4). A Completion/Withdrawal Form will be completed at the end of the study period.

2. Materials and Methods

2.1 Participant Selection

2.1.1 Total Numbers of Participants, and Study Duration

Randomisation will continue until each arm of the study consists of at least forty-two (42) index cases, plus their households. The study population will also be stratified according to family size. The duration of the study for each participant will be 2 weeks.

2.1.2 Inclusion Criteria

1. Males and females, minimum age 4 years, with no upper age limit who are family members of an eligible index case (as defined below).
2. People who upon examination, are confirmed to have an active infestation with head lice, as shown by presence of at least one live louse on Day 0 are eligible as index cases. For the purposes of randomisation, only the first presenting case in a household shall be considered a Primary index case.
3. People who give written informed consent or, if the prospective participant is under

16 years of age, whose parent/guardian gives written informed consent to participate in the study.

4. People who will be available for home visits by MEC study team members over the 15 days of the study.
5. Primary Index cases should preferably be children between the ages of 5 & 11 years but not adults, although adults may be secondary index cases, and must have at least one sibling of similar age, with at least one responsible adult living under the same roof.

2.1.3 Exclusion Criteria

1. Anyone with a known sensitivity to any of the ingredients in Vamousse Lice Defence Shampoo, or The Control Shampoo (see **Section 2.2.1**).
2. Anyone with a secondary bacterial infection of the scalp (e.g. impetigo) or who have a long-term scalp condition (e.g. psoriasis of the scalp).
3. Anyone who has used a treatment for head lice infestation within the previous 7 days.
4. Anyone who has been treated using a trimethoprim-based antibiotic product during the past 4 weeks or who is currently under such treatment.
5. Pregnant or breast-feeding mothers.
6. Anyone who has participated in another clinical study within 1 month before entry to this study.
7. Anyone who has already participated in this clinical study.

2.2 Clinical Supplies and Materials

2.2.1 Physical Forms of the Study Supplies

Vamousse Lice Defence Shampoo:

Ingredients:

		%w/w
Water		55.815
Sodium C14-16 Olefin Sulfonate		20
Cocamidopropyl Betaine		10
Sodium Cocoyl Isethionate*		3
Cocamide DIPA		2
Benzyl Alcohol		1.5
Butyl Lactate		1.25
Citric Acid Anhydrous		0.1
Polyquaternium-10		0.25
Tetrasodium EDTA		0.1
Liquid Germall Plus	Propylene Glycol	0.6
	Diazolidinyl Urea	
	Iodopropynyl Butylcarbamate	
Crothix Liquid	PEG-150 Pentaerythrityl Tetrastearate	3.5
	PEG-6 Caprylic/Capric Glycerides	
	Water	
Tea Tree Oil		0.01
Eucalyptus Oil		0.01
Vamousse Shampoo Oil B6160 IV (same as B-6160 but different fragrance) - Lebermuth	Geraniol	1.865

The Control Shampoo:

Ingredients:

Water
SLS
Cocamidopropyl betaine
NaCl
Litchi chinensis Fruit Extract
Cocamide MEA
Cocos Nucifera Oil
Panthenol
Parfum
Glycol Diastearate
Polyquaternium-10
Sodium Benzoate
Citric Acid

Disodium EDTA
Glycerin
Propylene Glycol
Sodium Acetate
Pantolactone
PPG-6
Sodium Hydroxide
Benzyl Alcohol
Coumarin
Limonene
Linalool

2.2.2 Packaging and Labelling

Packaging – both preparations

The product will be packed in plastic bottles with each container holding 400mL of material. The bottles will be made from polyethylene terephthalate (PET) containers.

Labelling – both preparations:

The bottles of both preparations used in the study will be numbered and weighed on calibrated scales before use. A clinical trial label will be affixed identifying the individual bottle number of the anonymized treatment. A blank section will be provided for completion of Household number and initials of the Primary Index case. Both products will be labelled with appropriate clinical trial labelling that will also state that they are "For Clinical Trial Use Only".

2.2.3 Care of Supplies

All supplies used in the study must be maintained securely under the direct responsibility of the Chief Investigator or under that delegated by the Investigator.

All supplies shall be dispensed in accordance with the Investigator's direction and it is the Investigator's responsibility to ensure an accurate record of supplies issued and returned is maintained.

All supplies should be stored at room temperature, out of direct sunlight, and protected from extremes of environmental conditions.

All supplies will be used only while participating in the study and returned to MEC at the end of the study for weighing before being returned to Alliance Pharmaceuticals Ltd.

2.2.4 Study Materials

Alliance Pharmaceuticals Ltd. will supply all the clinical study materials required for the duration of the study. In addition, numbered CRFs, patient diaries and other documentation will be prepared for each participant on behalf of the Sponsor by the Clinical Research Organisation or Insect Research and Development Limited.

2.2.5 Compliance

All supplies used, partly used, or unused will be maintained for collection by the investigators.

2.3 Procedures and Investigations

2.3.1 Treatment Regimen/Allocation

This is a randomised, double-blinded, parallel group study of Vamousse Lice Defence Shampoo and The Control Shampoo in the prevention of the spread of head louse infestation. Each household which satisfies the inclusion/exclusion criteria will be randomised into one of two equal sized study arms, stratified by family size. As there may be households where the index case is not the only overt infestation on Day 0, the population will also be stratified on this criterion (overt infestation on Day 0 =1 or >1). Following treatment of the index case, participants in one arm will be treated with Vamousse Lice Defence Shampoo and in the second arm with The Control Shampoo. Anyone found to be infested at the end of the study (Day 14) will be treated using the standard of care product (Vamousse Treatment Mousse).

2.3.2 Randomisation

The randomised treatment allocation code will be generated using the free online randomisation service provided at http://www.randomization.com/. The treatment allocation will be made in 22 balanced blocks of 8 treatments, which will provide sufficient numbers for the randomisation allocations together with enough additional allocations as may be required to address any overruns or replacements. The Seed number and date of randomisation will be recorded on the randomisation plan. The randomisation sequence will be held by the packaging company responsible for clinical trial supply and, in order to maintain blinding, will not be revealed to the sponsor, investigators or other study personnel until the end of the study.

The individual treatment allocations will be prepared as sheets bearing the anonymous identification of the product to be used (bottle number) and instructions for application. The product identification/instruction sheets will be sealed in opaque envelopes numbered sequentially on the outside with the participant number taken from the randomisation schedule. Each envelope will be enclosed in a CRF prior to use. Each investigator delegated to enrol participants will allocate the numbered CRFs to participants in numerical sequence. However, where two or more investigators, each allocated separate blocks of numbers, enrol participants in parallel the overall chronological sequence will not necessarily follow the numerical sequence.

Only after written informed consent has been obtained will the investigator allocate a study number and open the randomisation envelope for that number. As detailed above, the envelopes will contain no other information that could compromise blinding. The investigating team will keep a copy of the randomisation code also in a sealed envelope, in case an adverse event, reaction, or any other emergency circumstance necessitates that the code be broken.

2.3.3 Study Methodology

2.3.3.1 Pre-recruitment

Some participants may be obtained via schools and/or school nurses with whom MEC collaborates in screening for head louse infestation. Primarily recruitment will be via radio advertising. Respondents to advertising will be put in contact with MEC via a "text-back" service. When contact is made, a detailed Participant Information Booklet (PIB) will be provided by post or email to explain the purpose of the study. This will include a children's section explaining what will happen if the person enters the study. It will also contain a General Data Protection Regulation (GDPR) statement relating to protection of the integrity of personal data.

On first contact a member of the study team will conduct a brief interview to establish whether the person(s) will be suitable for entry into the study. If they wish to enter the study, they will be visited and conducted through a consent process, which includes explanation of study procedures and answers to any questions about the study. Potential participants must have had access to the PIB for at least 24 hours before the recruitment visit takes place.

2.3.3.2 Recruitment (Day 0)

Screening:

Each potential index case will be asked for permission to assess their hair to determine

whether live head lice are present at the start of the study. The assessment will be made by dry combing the hair with a plastic fine-toothed head louse detection comb. Any family member complaining of symptoms of infestation will also be assessed and if confirmed, will be recorded in the CRF. Thereafter, they will receive treatment as though they are an index case. Other family members will not be assessed.

Details will be recorded of how many people share the place of residence with the index case(s).

Consent/Assent:

Potential participants and/or parents/guardians will be asked if they understand the requirements of the study, as set out in the PIB, and if they have any further questions concerning it. Provided they still wish to enter the study and meet the inclusion/exclusion criteria for entry, the participant or parent/guardian (when the participant is below the age of 16) will read and sign the Consent Form. The Investigator will countersign the Consent Form.

A separate Assent Form will be available for those under the age of 16 provided they are capable of signing their name. The Investigator and the parent/guardian will countersign the Assent Forms. A copy of the Consent Form and, if appropriate the Assent Form, will be given to the individual or the carer.

Should an adult member of the household not meet with the inclusion/exclusion criteria, it may not necessarily mean the entire household is ineligible. At the discretion of the investigator, the household may be enrolled and the excluded family member will recorded as a non-participant.

Case Record Form completion:

Personal data allowing identification of an individual will not be recorded in the CRF. However, as there are no source medical documents (i.e. patient medical records) available to the investigators, a Source Data Verification Sheet will be completed for each participant that will be maintained separately from all other study documentation. This Sheet will include information such as name, date of birth, address, and contact details for the General Practitioner. A copy of the GDPR statement covering security of personal data collected during the course of the study will be given to the carer.

The following information will be recorded in the CRF:

1. **Declaration of Receipt of Informed Consent and GDPR statement**: Confirmation that informed consent and assent (where relevant) was obtained by the investigator, that a copy of the consent has been given to the participant and/or parent guardian, and that the original will be retained. Confirmation that the participant was in receipt of the GDPR statement outlining their rights with respect to personal data held as a result of participation in the study.
2. **Identification**: Participant's study number, gender, age.
3. **Hair Characteristics**: Characteristics will be recorded of the participant's hair:
    a) Length: closely cropped, above ears, ears to shoulders, below shoulders
    b) Thickness: fine, medium, thick
    c) Degree of curl: straight, wavy, curly
    d) Type: dry, normal, greasy
4. **Head Lice Details**: The investigator will make a subjective assessment of the severity of the current louse infestation in the index case using the following scale:
    a) Light infestation: lice only found after several combs of the hair
    b) Moderate infestation: single louse found on the first comb of the hair
    c) Heavy infestation: more than one louse found on the first comb of the hair
5. **Medication Current at Entry**: Any medication being taken along with the date the medication started the total dose and the reason for the medication.
6. **Medical History**: Medical history and any current illnesses will be recorded.
7. **Inclusion/Exclusion Criteria**: Confirmation that the participant meets the inclusion/exclusion criteria for entry into the study.

<u>Procedure:</u>

All Index Cases will be treated using Vamousse Treatment Mousse on Day 0. The product will be applied directly to dry hair. Sufficient product will be applied to saturate the hair and scalp. The product will be left in place for 15 minutes and then it will be washed off by rinsing with the treatment shampoo and water. Hair can be dried in the usual way following hair washing after treatment. Full instructions for use are provided.

All other participating household members will commence using the treatment shampoo on Day 0. The shampoo should be applied generously to wet hair, lathered and massaged into the scalp. It should then be left in the hair for at least 3 minutes but not more than 5 minutes before it is thoroughly rinsed out of the hair. The shampoo should be used once a day for the duration of the study.

The Investigator will issue participants with the patient diary and give them instruction in its use.

2.3.3.3 Follow up Assessments (Days 3 & 6 ±1 day)

Index cases will be assessed for continued active lice infestation on Day 3. If live lice are present, a second treatment with Vamousse Treatment Mousse will be applied. Those index cases with evidence of active infestation on Day 3, will be assessed again on Day 6 and treated again if the infestation is still active.

2.3.3.4 Use of Patient Diaries During the Study (Days 1-14)

During the study, participants or their care givers will record information in the patient diary on when the shampoo was used. They will also record any adverse events at the time of occurrence.

2.3.3.5 Final Follow up Assessment (Day 14, ±1 day).

At the end of the 14 day follow up period, the investigator will conduct the final assessment, unless the participant is withdrawn sooner, i.e. they choose to withdraw or are withdrawn on safety grounds. At the final assessment, all participants' hair will be combed with the head louse detection comb and any lice found will be taped (with clear tape) into the participant's CRF. If any participants, or non-participating household members, have live lice at the end of the study they will be offered a standard of care treatment (Vamousse Treatment Mousse).

All adverse events and changes in concomitant medication at any point during the study will be recorded in the CRF. Patient diaries will be collected.

Any remaining supply of investigational product will be collected by the investigator.

The Completion/Withdrawal Form will then be completed.

2.3.3.6 Assessment Analysis

Any lice fixed into the CRF during the course of the study will be examined under the microscope to establish the sex and/or stage of development of the insects. It is expected that if lice are found during the monitoring period, and the product was

initially successful in eliminating the infestation, they are likely to be adult or third stage nymphs that have newly migrated to the head. The presence of small lice (nymphs) will be evidence that louse eggs had not been sufficiently affected by the treatment regimen and were not prevented from developing to the point of hatching. All CRF pages bearing lice will be archived along with the other CRF documents, the lice fixed with tape constituting a permanent record, in much the same manner as a microscope slide.

2.3.4 Concomitant Medication

The participant should not use any other form of pediculicide or physical treatment, including lice combing, for head lice while taking part in the study. If the use of such treatment occurs, the participant will be withdrawn from the study. Participants will also be instructed not to use other hair care products, such as conditioners, hair gels and sprays for the duration of the study.

Other medication can be prescribed in the normal way although participants requiring Co-Trimoxazole or Trimethoprim should also be withdrawn from the study.

All concomitant medicines should be listed in the CRF and any changes to such medicines, during the course of the study, recorded.

2.3.5 Adverse Events

Space will be provided in the CRF specifically for recording observed and reported adverse events. All unwanted effects, whether considered to be caused by the study medication or not, will be reported to Alliance Pharmaceuticals Ltd. by completing the Adverse Event form.

Where an adverse event occurs, it will be recorded by the member of the study team to whom it was first notified and discussed with the CI to evaluate for seriousness, causality, and expectedness. Adverse events considered to be related to any of the study interventions will be referred to the study Local Medical Contact for review prior to any notification to the Sponsor. Commonplace childhood complaint and accidents will be included in any adverse event reviewing.

2.3.6 Serious Adverse Events

If the adverse event is serious, it shall be reported immediately, by e-mail and telephone to the Medical Contact and Alliance Pharmaceuticals Ltd. A full written report will be forwarded to Alliance Pharmaceuticals Ltd. within 3 working days.

Serious adverse events are defined as events that are fatal, life threatening, disabling or incapacitating, cause or prolong hospitalisation, overdose (of any kind, with or without symptoms), newly diagnosed cancer or clinically abnormal laboratory values (with or without symptoms).

The contacts for all serious adverse events are as set out below:

Study Sponsor contact:

Dr. Asim Shafiq, Qualified Person for Pharmacovigilance

Alliance Pharmaceuticals Limited

Avonbridge House

Bath Road

Chippenham

Wiltshire SN15 2BB

Tel: 01249 466966

Email: asim.shafiq@alliancepharma.co.uk

Local Medical contact:

Dr. Paul Silverston

The Walled Garden,

9 Church Lane,

Snailwell,

Cambridgeshire, CB8 7LZ

Tel: 01638 57772

Email: paul.silverston@btinternet.com

2.3.7 Withdrawals

Participants may be withdrawn from the study at any time for the following reasons:

Adverse Event:

The participant is withdrawn from the study by the Investigator because of an adverse event, whether or not the Investigator believes it to be serious or caused by the study medication, and provided that the Investigator considers it is in the participant's best interest to be withdrawn. There must be a corresponding entry on the Adverse Events and/or the Serious Adverse Events Form in this instance.

Non-compliance:

The participant is withdrawn because of failure to comply with the treatment regimen, or comply with the investigations as required, but is still accessible to the Investigator.

Drop Out:

The participant withdraws consent to continue in the study, but the Investigator would otherwise consider it appropriate for him/her to continue. The participant remains accessible to the Investigator.

Lost to Follow-up:

The participant, without explanation, fails to keep appointments as scheduled for study assessments and is not seen again despite the Investigator's effort (letter, telephone, home visit etc.) to re-establish contact.

Death:

All deaths will be treated as Serious Adverse Events and Alliance Pharmaceuticals Ltd. must be informed within 24 hours. All associated documentation must be completed within 3 working days. Full details will be required including a post-mortem examination if possible.

Lack of Efficacy:

The participant elects to withdraw because the medication is not adequately effective.

Data from all participants will be collected and missing data will be imputed as described in section 3.4.

3. Analysis and Reports

3.1 Definition of End Points

3.1.1 Safety

Participants will be observed and all untoward effects will be recorded, whether or not they are thought to be related to the study treatment.

Details of the recording of adverse events are shown in section 2.3.5 and 2.3.6.

3.1.2 Efficacy

The primary outcome of the study is the proportion of individuals in each household with active head lice infestation at day 14.

Secondary objectives are:

To demonstrate the safety of Vamousse Lice Defence Shampoo in clinical use.

To demonstrate the acceptability of Vamousse Lice Defence Shampoo in daily use.

3.2 Definition of Populations to be analysed

The Per-protocol Population:

Includes all randomised participants who complete the study and are treated and followed up strictly according to the study protocol. For the purposes of the per protocol analysis, a study participant will be deemed to be non-compliant if the shampoo is not applied for at least seven (7) days during the study period and/or is not applied for four (4) consecutive days.

"Intention-to-treat" Population:

Includes all participants who consented and were treated at least once. Premature terminations due to drop out, treatment failure, adverse events etc., are included.

3.3 Proposed Primary and Secondary Analyses

1. To compare the efficacy of Vamousse Lice Defence Shampoo with that of The Control Shampoo and to test for superiority in the intention-to-treat population.
2. To compare Vamousse Lice Defence Shampoo with The Control Shampoo in terms of safety.
3. To compare the cosmetic acceptability of Vamousse Lice Defence Shampoo with The Control Shampoo.
4. To compare the efficacy of Vamousse Lice Defence Shampoo with that of the Control Shampoo in the per-protocol population.

3.4 Statistical Methods

Sample size determination

The study has been designed to detect superiority of the test product (Vamousse Lice Defence Shampoo) (the treated group) to the comparator product (The Control Shampoo) (the placebo group) in clinical use.

The primary analysis proposed (see **Analytical Methods** below) is a comparison of the efficacy of the products with the aim to detect for superiority of Vamousse Lice Defence Shampoo to The Control Shampoo in the prevention of spread of infestation in a close household. The primary parameter on which this will be based is the proportion of individuals with active infestation at Day 14 in each household.

Stratifications – 1: <3 children in a household versus ≥3 children in a household and 2: overt infestations on Day 0 =1 Index Case versus >1 Index Case.

The principal analysis will be a stratified Kruskal-Wallis test using the Fry-Lee Test[1].

Significance will be declared at a level of 5%, using a two-sided test for greater percentage of infected family members in the placebo group versus the treated group.

To work out the numbers required to treat the code for calculating the probability of rejecting using the Fry-Lee Test[1] was put into an R routine, with the results validated against results from the proprietary package RoeLee[2].

From previous studies it was estimated that the infection rate in untreated families would be about 0.7 with standard error 0.367. The treatment is intended to lower the rate by 30%, so the rate in the treated group should be about 0.4 with standard error 0.367.

For a given number of families in each arm a random set of rates was then simulated using these mean and standard errors, using the R routine pnormal, truncating the values so that values less than zero were given the value zero, and values greater than one were given the value one.

The values were then checked to see if they would reject on a two-sided test at the significance level of 5%.

This process was repeated 5000 times and the rate of rejection used to estimate the power of the test.

If the power of the test was less than the required power, in this case 90%, the number of observations was increased and the process repeated.

To deal with stratification, two extra variables were simulated in each run, the first with a probability of being positive set at 0.5, and the second set at 0.7. The result of the test was calculated allowing for these strata.

Starting from a default value of 30 families per group the following results were found:

Kruskal Wallis Analysis of Data
Study Size calculations based upon 5000 replicates

Normal Distribution. Test of Mean2 - Mean1 (Std.Dev. known). 2-sided . Wilcoxon-Mann-Whitney
Use Truncated Normal Distribution - x<0 -> 0, x>1 -> 1
Stratify data, (Fry-Lee Test). Two strata vars, 1:prob of strata level 2 = 0.7 2:prob of strata level 2 = 0.5
Sample Size 1 as a function of Power and Significance Level.
H0: Mean 2 - Mean 1=0 H1: Mean 1= 0.7 H1: Mean 2= 0.4
Std.Deviation 1= 0.367 Std.Deviation 2= 0.367 , Sample Size 2 / Sample Size 1=1

	Significance Level		
Number	.001	0.01	0.05
	Power Required: 90		
30	19.24	49.50	74.86
31	22.46	52.30	76.48
32	23.66	55.14	78.36
33	25.38	56.24	79.72
34	28.10	58.80	81.88
35	29.62	61.04	82.66
36	30.62	62.12	83.74
37	34.30	65.80	85.58
38	36.32	66.50	85.74
39	38.36	68.88	87.64
40	39.66	70.90	88.74
41	41.42	72.34	89.68
42	44.18	74.44	90.56

Thus 42 families per group should be sufficient to give a 90% power to detect a difference at two-sided significance level of 5%. Experience from previous studies of this kind suggests that drop-outs are infrequent. As described in section 3.2, non-compliant households will be included in the ITT analysis with the last observation for drop outs or lost to follow up cases carried forward for analysis. Nevertheless, should any families drop out of the study, recruitment will continue until at least 84 families have completed the study.

References

1. Fry JS, Lee PN. Stratified rank tests. Appl Stat. 1988;37:264-6.
2. Fry JS, Lee PN. Test of statistics. London: P.N.Lee Statistics & Computing Ltd.; 1988. 60 p.

Analytical methods

Analyses will be conducted based on both the "intention-to-treat" and the "per-protocol" populations and will initially use conventional analytical methods employed in earlier studies. Differences between the groups in baseline characteristics, safety, acceptability, and efficacy will be tested using Fisher's Exact test for yes/no variables and the Mann-Whitney U test for ranked variables. Where analysis shows important differences in baseline characteristics between the groups, Chi-Square and rank tests stratified for these characteristics may also be conducted.

The primary endpoint, the rate of family members infested at the end of the trial, will be analysed by the stratified Kruskal-Wallis Test (Fry-Lee Test). This will be stratified on family size (<3 children in a household versus ≥3 children in a household) and overt infestations on Day 0 (=1 Index Case versus >1 Index Case). Significance will be declared at a level of 5% on a two-side test of the rate being lower in the treated group versus the placebo group.

3.5 Final Study Report

A clinical report, integrating the study design and the results will be prepared for the study and agreed by the Chief Investigator and the Study Managers. The Chief Investigator, the Clinical Research Manager, and representatives of Alliance Pharmaceuticals Ltd. will sign a copy of the final study report.

4 Administrative Procedures

4.1 Regulatory Documentation

Any required legislative procedures will be undertaken before the commencement of the study. The study will not proceed without granted written approval.

This study will be conducted according to the recommendations of ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice and ICH E6(R2) – Guideline for Good Clinical Practice.

4.2 Ethics Committee Approval

This formulation of Vamousse shampoo has not been approved for use in the European Union. Ethics approval will be required for the study (see http://www.hra-decisiontools.org.uk/ethics/).

4.3 Informed Consent

This study will be conducted in accordance with the principles laid down in the Declaration of the World Medical Assembly of Helsinki, and subsequent revisions (see Appendix 1).

Each participant or parent/guardian (where the participant is not legally competent) will be requested to provide written informed consent after receiving written information and a verbal explanation of what the study involves. A copy of the Consent Form will be returned to the participant and/or parent/guardian.

The Investigator will retain the original of the Consent Form and will also complete a Declaration of Receipt of Consent Form to confirm that written informed consent was obtained. The Investigator shall arrange for the retention of participant identification codes for at least 25 years after the completion or discontinuation of the study.

The Information and Consent documentation will include a GDPR statement regarding the security of personally identifiable data.

4.4 Insurance Policy

Alliance Pharmaceuticals Ltd. confirms that this specific clinical study is protected by insurance cover which provides an indemnity to the Investigators and their co-workers, subject to the Policy terms, conditions and limitations and provided always that the study is conducted and the data as reported agree to the standards fixed by the protocol. Indemnity, in the event of negligent acts by investigators in the field, must be covered by the professional liability insurance of the institution employing them.

4.5 Compensation

Alliance Pharmaceuticals Ltd. maintains in force a "no fault" compensation insurance indemnity in accordance with the current version of the ABPI Guidelines on Clinical Trials: "Compensation for Medicine Induced Injury". In the event that the compensation on a "no fault basis" is unacceptable to the claimant, the Policy will, subject to its terms, conditions and limitations, respond to an action for legal liability arising out of this clinical study.

4.6 Investigator's Responsibilities

Good Clinical Practice

It is the responsibility of the Investigators to ensure that this study is carried out in accordance with this protocol in respect of ethical, legal and technical aspects and

conforming to ISO 14155:2020, Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice and ICH E6(R2) – Good Clinical Practice. In this context, the Investigator shall arrange for the retention of participant identification codes for at least 25 years after completion or discontinuation of the study. Alliance Pharmaceuticals Ltd. will render all support necessary to assist the Investigator in discharging this responsibility.

Replacement of Principal Investigator

In the event of a Chief/Principal Investigator being unable to continue the study, another responsible person may be designated Investigator and documentation testifying to this will be submitted to the study monitor within 10 days. The new Investigator must be appropriately qualified and be approved by Alliance Pharmaceuticals Ltd. before the study can be continued.

Study Report

The Chief Investigator will submit a summary study report within approximately 4 weeks of completion of the study. This report will include:

1. Details of the investigative procedures involved.
2. The numbers of participants entered, completed, and withdrawn from the study.
3. Deviations from the study protocol on a general basis and for individual participants, with explanations.
4. Explanations for each participant withdrawn from the study.
5. Summary of the safety and tolerance data, including details of all Adverse Drug Events (ADE) including any follow-up. Case histories of all serious ADEs or ADEs leading to withdrawal should be provided.
6. Conclusions

4.7 Curriculum Vitae

In accordance with international standards, and Good Clinical Research Practice, a signed copy of the curriculum vitae of the Principal Investigators, Research Physician/Co-Investigator, and members of the MEC study team will be provided to Alliance Pharmaceuticals Ltd./Onorach Ltd. and kept in the Trial Master File.

4.8 Case Record Form

The Investigator is required to prepare and maintain adequate and accurate case records that have been approved by Alliance Pharmaceuticals Ltd. to record all observations and other data pertinent to the clinical study. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Black ballpoint pen should be used to ensure the clarity of reproduced copies. Any alterations or errors to the CRF should be crossed through once only and signed and dated by the person making the change, using black ballpoint pen.

The study monitor will examine the original CRFs at each monitoring visit and will approve them when the CRF is complete and any necessary amendments have been made. The Investigator will not sign the CRFs until the study monitor has approved them. The Investigator will retain the CRFs until completion of data collection when they will be given to the study monitor for transfer to Alliance Pharmaceuticals Ltd.

The Investigator will retain a copy together with other source data for his/her own files. The CPMP Guidelines on Good Clinical Practice for Trials in the European Community require that the Investigator shall arrange for the retention of the participant identification codes for at least 25 years after the completion or discontinuation of the study. Participant files and other source data shall also be kept for the maximum period permitted by the institution but not less than 25 years.

4.9 Monitoring of the Study

At regular intervals during the study, a representative of an independent monitoring company selected by Alliance Pharmaceuticals Ltd. (Onorach Limited) will visit the study centre. At each monitoring visit, the Investigator and the monitor will review study progress, compliance with the study protocol, CRF's, and any emergent problems.

4.10 Quality Assurance

In accordance with Good Clinical Practice Guidelines and recommendations, Alliance Pharmaceuticals Ltd. may undertake an independent quality assurance audit of the clinical study and related documentation during the course of this study. The purpose of the audit is to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, Alliance Pharmaceuticals Ltd.'s Standard Operating Procedures, Good Clinical Practice and the applicable regulatory requirements. At any stage during the

study, the Investigator has the responsibility to make all data available to Alliance Pharmaceuticals Ltd. and/or relevant authority (where required) for auditing purposes. Such audits will at all times be conducted in accordance with national, legal and ethical requirements.

4.11 Protocol Appendices

It is specified that the appendices attached to this protocol and referred to in the main text of this protocol form an integral part of the protocol.

4.12 Protocol Amendments

Neither Alliance Pharmaceuticals Ltd. nor the Investigators nor the Clinical Research Organisation may make any changes or amendments to this protocol, after the protocol has been agreed and signed by all parties, unless such change(s) or amendment(s) have been fully discussed and agreed by both the Investigator and Alliance Pharmaceuticals Ltd. Any change or amendment agreed will be recorded in writing, the written amendment will be signed by the Investigator and by Alliance Pharmaceuticals Ltd. and the signed amendment will be appended to this protocol.

4.13 Research Registration and Publication Policy

This study will be registered in a publicly accessible database before enrolment of the first research participant.

Submission of study results for publication will not take place without prior discussion with Alliance Pharmaceuticals Ltd., allowing the company sufficient time to analyse such results and provide written agreement to publication, which will not be unreasonably withheld. Alliance Pharmaceuticals Ltd. reserves the right to use the results and reports of this study for any purpose.

4.14 Early Termination of the Study

By agreement between Alliance Pharmaceuticals Ltd. and the Principal Investigators, the study may be terminated at any time if the recruitment rate is such that the required number of participants will not be recruited within the specified time, if the products being used are deemed to be failing unacceptably, or if any safety concerns arise.

Table 1: Schedule of Events

Day	Screening	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Provide Patient Information Booklet	x															
Eligibility	x															
Screen Index Case(s) for Active Lice Infestation (at Day 6 only if infested at Day 3)		x			x			x								
Inclusion/Exclusion Criteria Assessment		x														
Informed Consent		x														
Demographics		x														
Medical & Family History		x														
Treat Index Case(s) (only if infestation is still active after Day 0)		x			x			x								
Instruction in use of Shampoo & Patient Diary		x														
Supply Shampoo		x														
Participants Record use of Shampoo in Patient Diary		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Participants Screened for Active Lice Infestation																x
Record Safety Data																x
Collect User Acceptability Data																x
Collect Patient Diaries																x
Collect Excess Shampoo																x
Study Completion Form																x
VAM2301 Protocol: Version: 2.1, dated 3rd November 2021																

5. APPENDIX 1: DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that

participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other

relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee.

Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty

to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

6. APPENDIX 2: ISO 14155:2020 CLINICAL INVESTIGATION OF MEDICAL DEVICES FOR HUMAN USE – GOOD CLINICAL PRACTICE

EVS_EN_ISO_14155;
2020_RLV_en.pdf

7. APPENDIX 3: GENERAL DATA PROTECTION REGULATIONS (GDPR) STATEMENT

Privacy Notice – Clinical Trials

We will always respect your privacy and will only use your information for specified and lawful purposes as provided for under the General Data Protection Regulation (GDPR). We will use and handle your information responsibly and will take all appropriate organisational and technical measures to safeguard your information from accidental or unlawful destruction, loss, alteration, unauthorised disclosure or access.

Why do we collect personal information?

1. If you, or someone in your care, join a clinical trial we are required by national and international regulations to obtain certain personal information that can be used to identify you. This information is required for the following reasons:
    a. To ensure the correct person is being provided with the treatment undergoing study.
    b. To ensure that there are no underlying health issues that would place the person at risk or that would prevent the treatment from working properly.
    c. To enable assessment investigators to correctly identify the person they are dealing with.
    d. To ensure data integrity.
    e. To enable follow up contact in case new information about the treatment becomes available that may cause you to change your mind about taking part or that you should know as part of long-term safety monitoring.
2. The personal information and data collected by us will be the minimum needed to fulfil the requirements set out in 1) above.
3. All information will be recorded in your presence on the forms provided. You will be able to review those data at any time if you request it.

What information will we collect?

4. When you join a clinical trial, we provide you with an **Information booklet** that sets out a summary of the information we collect from you and how it is managed. If you have any questions about data management, the booklet states that you ask the investigator who visits you to explain this.
5. Before joining a clinical trial, you will be asked to read carefully and sign a **Consent form**. This form includes two paragraphs about data management and how we protect your personal data. This form includes an agreement to allow us to share or use non-identifiable information (i.e. those data only identified by anonymous numbers) even if you withdraw consent for taking part in the clinical trial or withdraw for some other reason.

How do we protect your information?

6. The information that can identify you personally, e.g. name, address, date of birth, telephone number(s), will be separated from all other study data and stored securely in a separate study file.
7. The majority of information from clinical trials will only be identified by a **Study Number** and **Participant Number**. Any transfer of data from Medical Entomology Centre at Insect Research & Development Limited (**MEC**) to other entities, e.g. study sponsors, regulatory authorities, or their associates in this or other countries, will only be identified by the Study and Participant numbers.
8. No personally identifiable information will be held in electronic media, computers, or other devices that can be hacked or otherwise accessed by unauthorised persons.
9. After you have signed a consent form, and agreed to provide us with personal information, it will be stored securely in our offices, in a locked room with restricted access. At any time after participation you may ask to see a copy of what data are held and to update the data if necessary.

How your information will be used

10. Your information will only be used to provide you with services involved in specific clinical studies that we are handling, and to engage in communications and correspond with you over the status, progress and progression of the study. If you authorise us, information may also be used to provide you with additional information or continuing services, for example, if you wish to be informed when we conduct different studies at a later date.

Who we might share your information with

11. Your information including your contact details, medical history, and other information related to taking part in our studies may be shared with relevant personnel within the Medical Entomology Centre who require access that information for ensuring your safety and the integrity of the trial information.
12. We may also share other anonymous relevant information with external parties including study sponsors, regulatory authorities, courts, and other third parties where necessary in connection with the provision of services and management of a clinical study.
13. When information collected in a research project is shown to other people, especially when data may be sent outside the European Union (EU) or European Economic Area (EEA) to countries with less strict Data Protection laws, the information will be identified only by an anonymous code number.

How long will we keep personal information?

14. There are statutory guidelines that control how long personal data from clinical trials may be stored. In the European Union, for children, this is normally long enough for them to become adults in case any medication has an effect on their development. Although our trials with head louse treatments do not have any risks of this type associated with them,

we comply with the regulatory guidance and in this respect personal data are currently stored for 25 years.

15. Because the personal data collected for clinical trial participants is retained for regulatory purposes, only limited information can be deleted before the end of the required storage period. At the end of this time all personal data will be securely destroyed.

Your rights

16. You may request access to the personal information which we hold about you under Article 15 of the GDPR, to do so requests must be made in writing (to the addresses specified below) and we may require you to provide valid forms of identification in order to process your request.

17. Additionally, if you wish to exercise any of your rights under GDPR, such as where you believe any information we hold about you is incorrect, inaccurate or incomplete, where you wish to restrict or object to processing or, if you are dissatisfied with the way in which MEC has used your information in any way you can report the matter to our Data Protection Officer using the following contact details:

Data Protection Officer

Medical Entomology Centre

Insect Research & Development Limited

6 Quy Court

Colliers Lane

Stow-cum-Quy

Cambridge

CB25 9AU

Email: admin@insectresearch.com

You also have the right to refer any concerns you may have regarding MEC's use of your information to the Information Commissioners Office (ICO) - more information can be found by visiting the ICO's website at: www.ico.org.uk