

A randomised, double-blind, cross-over, placebo controlled clinical trial to demonstrate the proof of concept for a product designed to protect against development of head louse infestation

CTMK15

Version: 1.1, dated 14th August 2012

A randomised, double-blind, cross-over, placebo controlled clinical trial to demonstrate the proof of concept for a product designed to protect against development of head louse infestation

VERSION NUMBER: Version: 1.1

PRODUCT NAME: Octanediol 1% Solution

COUNTRY: UK

CLINICAL STUDY NUMBER: CTMK15

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ESTIMATED START DATE: September 2012

ESTIMATED COMPLETION DATE: January 2013

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INVESTIGATOR'S AGREEMENT

We have read this Thornton & Ross Ltd approved protocol, number CTMK15, version 1.1, dated 14th August 2012, entitled "**A randomised, double-blind, cross-over, placebo controlled clinical trial to demonstrate the proof of concept for a product designed to protect against development of head louse infestation**", and have discussed it to our satisfaction with Thornton & Ross 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 Thornton & Ross 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.

Chief Investigator:

_____ Dated ___/___/___
 Ian Burgess

Clinical Trial Manager:

_____ Dated ___/___/___
 Elizabeth Brunton

Thornton & Ross Ltd

Clinical Research Manager:

_____ Dated ___/___/___
 Ashley Brierley

Should the decision be made by Thornton & Ross 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 Thornton & Ross Ltd.

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Appendices

- Appendix 1 Declaration of Helsinki.
- Appendix 2 European (CPMP) Guidelines on Good Clinical Practice for Trials on Medicinal Products.

1. INTRODUCTION

1.1 Summary of the Study

| | |
|--------------------------------|--|
| Title: | A randomised, double-blind, cross-over, placebo controlled clinical trial to demonstrate the proof of concept for a product designed to protect against development of head louse infestation |
| Chief Investigator: | Ian F Burgess |
| Estimated Study Start: | September 2012 |
| Estimated Study Finish: | January 2013 |
| Participants: | Sixty-eight (68) louse free participants will be recruited to the study, confirmed by treatment with Hedrin Once gel prior to entry. Thirty-four (34) participants will be treated with the Octanediol 1% Solution formulation and thirty-four (34) with a placebo. Participants who contract lice during the study will be treated using Hedrin Once gel. All participants will be randomly assigned to receive one treatment for six weeks, with a cross-over, including retreatment with Hedrin Once gel to ensure louse free status, followed by six weeks on the other treatment. |
| Type: | The youngest child attending school in each household |
| Products: | Octanediol 1% Solution and placebo leave in conditioner. |
| Methods of Application: | Both preparations will be applied after hair washing by the parent/carer. The preparations will be used as a leave in conditioner and hair detangler. Product will be applied by spraying the hair close to the scalp and then combed down the length of the hair to facilitate combing and spreading. The product will be left in place until the next hair wash, or if the hair is washed less frequently than twice each week, the preparation will be reapplied after approximately 3-4 days (i.e. the product is applied at least twice each week). |
| Study Design: | <p>Participants will be recruited into the study by household, and randomised to one of the two treatments described above.</p> <p>Participants will be assessed at Day 0 (recruitment) for presence of head lice. In order to ensure that all participants are louse free at the start of the study, all will be treated using a standard of care treatment (Hedrin Once liquid gel). A member of the Medical Entomology</p> |

Centre (MEC) study team will apply the treatment. They will be checked and treatment reapplied if appropriate on Day 7 and the hair combed while the treatment is still in place to confirm that no lice remain.

After the treatment has been washed out, the investigator will then demonstrate the use of the Octanediol 1% Solution conditioner or placebo conditioner. The parent/carer will be supplied with a supply of the appropriate, blinded, preparation.

Participants will be assessed for the presence of live head lice once each week by an investigator. If an infestation with lice is confirmed (see Section 2.3.3.3) the participant will be retreated using the standard of care treatment. They will then continue in the same group for the remainder of the 6 week period. Any lice from a confirmed infestation will be taped into the Case Record Form (CRF) for counting and size analysis. At the end of the 6 week period the participant will be retreated using Hedrin Once liquid gel, in the same manner as at the start of the study, to confirm that they are louse free or to eliminate any infestation overlooked during assessments (this will effectively create a “wash-out” period for each participant). They will then be crossed over to the other study preparation for a further 6 weeks.

Aims of the Study: To demonstrate the proof of concept that Octanediol 1% Solution is effective to limit the risk of development/growth of an infestation with head lice.

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 in the UK, partly because insecticidal products are still widely used and partly because most families act individually and there are no coordinated efforts to eliminate infestation in most communities.

The surface acting chemical 1,2-octanediol is effective to kill lice and their eggs and is currently marketed as a therapeutic product containing 5% of the active substance (Hedrin Treat & Go). (1) However, the active material in this product was shown during pre-clinical development studies to be active at concentrations as low as 1%, albeit with a slower rate of activity. (2)

There has long been a wish, amongst the parents of children likely to be affected by this condition, for a reliable preventive product that could stop an infestation from developing. Repellent formulations have only limited activity due to volatility and rely on daily reapplication. Using a “leave in” non-volatile formulation on the hair that reduces louse viability and inhibits louse egg production would fulfil the essential

requirements of a preventive product, and a preparation of 1% 1,2-octanediol fits that essential description.

This clinical study has been designed to evaluate the effectiveness of Octanediol 1% Solution, in the form of a leave in conditioner and combing aid, used at least twice each week (although application following each hair washing is desirable) in comparison with a placebo leave in conditioner and combing aid.

References

1. Burgess IF, Lee PN, Kay K, Jones R, Brunton ER. (2012) 1,2-Octanediol, a novel surfactant, for treating head louse infestation: identification of activity, formulation, and randomised, controlled trials. PLoS ONE 7(4): e35419. doi:10.1371/journal.pone.0035419.
2. Campbell J, Carver A. (2002) Pesticides based on vicinal diols. International Patent; WO 02/069707 A1.

1.3 Aims (Objectives)

1. To demonstrate effectiveness of Octanediol 1% Solution, applied at least twice each week, to prevent or limit establishment of head louse infestation.
2. To confirm the safety and acceptability profile of the product.

1.4 Design in Brief

This trial will be a randomised, controlled, double blind, cross-over study of a topical preventive treatment for head lice in comparison with a placebo preparation. Sixty-eight (68) participants will be recruited by household (see Section 3.4 for details), with the youngest member of the household who attends school participating.

At the first visit (Day 0), verbal consent will be obtained to check for the presence of live head lice using a fine-toothed plastic detection comb.

After the preliminary assessment, participants can be enrolled to the study, provided they 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. Consent will be sought for permission to inform the participant's GP that their patient is taking part in the study.

All prospective participants who fit the selection criteria (see section 2.1.2 and 2.1.3) will be confirmed louse free prior to commencement of treatment (see below). Any non-participating household members identified as having lice will be offered a standard of care treatment (Hedrin Once liquid gel).

The participants enrolled on to the study will be divided to receive one of the two study preparations with thirty-four (34) individuals allocated to each (see Section 3.4 for details). The Investigator will assign each participant a study number, this being the next available number from a randomised treatment allocation sequence. The treatment allocations will be held in sealed envelopes and will only be opened after consent has been received. Assignment will continue until there are at least thirty-four (34) individuals in each group.

Participants will be treated with Hedrin Once liquid gel at Day 0 and where appropriate also on Day 7 (+/- 1 day). A member of the MEC study team will apply the treatment and comb through the hair during the second treatment to confirm that all lice have been eliminated. This treatment is designed to eliminate infestation prior to commencement in the investigatory part of the study.

After the treatment has been washed out on Day 7 the investigator will demonstrate application of the blinded test preparation (either Octanediol 1% Solution or placebo) to the parent/care giver. After this demonstration the investigator will provide a sufficient quantity of test preparation for the parent/care giver to use over the following period.

Participants will be assessed weekly by a member of the MEC study team who is unaware of the treatment that was applied. One day before each visit is due; the parent/care giver will be sent an SMS (text) message to remind them of the appointment. If the parent/care giver does not have a mobile telephone, a landline telephone call will be made as an alternative.

If no lice are found at the regular weekly assessments, the investigator will replenish the supply of investigative product, and collect the used bottle(s) of investigative product during the routine visit.

It is possible that lice may be found at an assessment visit. However, due to the nature of the product and its mode of action this discovery does not necessarily confirm that an infestation has been established. Consequently, on the first discovery of a louse a note will be made in the CRF but no further action will be taken that day. At the next assessment visit if any lice are found, or if at any single visit ≥ 5 adult lice or any stage 1 or stage 2 nymphal lice are found, a sample will be collected and taped into the participant's CRF. The participant will then be treated using Hedrin Once liquid gel in a similar manner to the treatment on Days 0 and 7. After the second treatment the participant will continue in the same treatment arm until completion of the six week participation period for that treatment.

At the end of six weeks each participant will be treated again using Hedrin Once liquid gel to eliminate any lice present, or that have been missed by investigators during the combing assessments. Two applications of product will be made 7 days apart, with combing during the second application to ensure no lice are present. This will constitute a "wash-out" to ensure all participants start the second arm of the study louse free as at the beginning. Each Participant will then be crossed-over to the other treatment arm of the study, i.e. anyone who received Octanediol 1% Solution initially would receive placebo or anyone on placebo would receive Octanediol 1% Solution.

Participants will continue in the study until the completion of 12 weeks active participation (approximately one school term). During this time participants will be monitored throughout, as described above, and will be supplied with new bottles of the investigative product/placebo each week. Anyone who has a head louse infestation at the end of the study will be provided with the standard of care treatment, as will any infested family member who is a non-participant.

All adverse events will be monitored during the study (see sections 2.3.5 and 2.3.6) and all changes in concomitant illness and 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 thirty-four (34) participants. The duration of the study will be 12 weeks with one additional week allowed for the cross-over “wash-out” period (approximately one school term) with follow up visits at weekly intervals.

2.1.2 Inclusion Criteria

1. Participants attending school with no upper age limit, although they must be the youngest qualifying member of the household.
2. Participants who upon examination, are confirmed to be at risk of infestation with head lice.
3. Participants who give written informed consent, or if the participant is under 16 years of age whose parent/guardian gives written informed consent to participate in the study.
4. Participants who will be available for home visits by MEC study team members over the 12 weeks of the study.

2.1.3 Exclusion Criteria

1. Participants with a known sensitivity to any of the ingredients in Octanediol 1% Solution, Hedrin Once liquid gel or the placebo leave in conditioner preparation.
2. Participants 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. Pregnant or nursing mothers.
4. Participants who have participated in another clinical study within 1 month before entry to this study.

5. Participants who have already participated in this clinical study.

2.2 Clinical Supplies and Materials

2.2.1 Physical Forms of the Study Supplies

Octanediol 1% Solution:

Active: 1,2-octanediol 1%

Excipients: PEG 6 caprylic/capric glycerides 3.0%, carbomer 0.15%, PEG-12 dimethicone 1.0%, sodium hydroxide to pH 7.0, purified water to 100%.

Placebo:

Excipients: Glycerol <10%, imidazolidinyl urea 0.2%, purified water to 100%.

2.2.2 Packaging and Labelling

Packaging – both preparations

The product will be packed in plastic trigger spray bottles with each container holding 100mL of material. The bottles will be made from high-density polyethylene (HDPE) containers with a screw cap fitted with a trigger spray applicator.

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 and anonymized study arm (designated “A” or “B” in allocation documentation). A blank section will be provided for completion of participant number and initials. 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 Thornton & Ross Ltd.

2.2.4 Study Materials

Thornton & Ross Ltd will supply all the clinical study materials required for the duration of the study. In addition, numbered CRFs will be supplied for each participant.

2.2.5 Compliance

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

2.3 Procedures and Investigations

2.3.1 Treatment Regimen/Allocation

This is a randomised, controlled, double-blind, parallel group, cross-over study of Octanediol 1% Solution (Non-CE marked medical device) and placebo in the prevention of head louse infestation. Each participant who satisfies the inclusion/exclusion criteria will be randomised into one of two equal sized study arms. One arm will initially be treated with Octanediol 1% Solution and the second arm with placebo, with a cross-over after 6 weeks participation. Any participant who becomes infested during the course of the study will be treated using the standard of care product (Hedrin Once liquid gel).

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 7 balanced blocks of 10 treatments (one spare block will be randomised in case replacements are required) and the Seed number and date of randomisation will be recorded on the randomisation plan.

The treatment allocations will be prepared as sheets bearing the anonymous identification of the product to be used 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 numerical sequence will not follow chronologically.

Only after written informed consent has been obtained will the investigator allocate a study number and open the randomisation envelope for that number. 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

Participants will mostly be invited to join the study via letters or telephone calls to families who have expressed an interest in joining further clinical investigations and are listed on a database held at the Medical Entomology Centre. Some participants may be obtained via schools with whom MEC collaborates in screening for head louse infestation. In addition, advertising in public media: newspapers, magazines, or radio, may be performed as appropriate if the need arises. A detailed Participant Information Booklet (PIB) will be provided to explain the purpose of the study. This will include a children's section explaining what will happen if the person enters the study.

On first contact a member of the study team will conduct a brief interview to establish whether the person will be suitable for entry into the study. If the person wishes to enter the study, they will be conducted through a standardised consent procedure. Potential participants must have had access to the PIB for at least 24 hours before the recruitment takes place.

2.3.3.2 Recruitment (Day 0 and Day 7)

Screening:

Each potential participant 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. Other family members who give their verbal permission can also be assessed for the presence of living lice.

Details will be recorded of how many people share the place of residence with the participant. Details will also be recorded of the number of people assessed and found to have lice, the number assessed and found not to have lice and the number that were not assessed.

Consent/Assent:

Participants and/or parents/guardians will be asked if they understand the requirements of the study 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.

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.

The following information will be recorded in the CRF:

1. **Declaration of Receipt of Informed Consent:** Confirmation that informed consent and assent (where relevant) was obtained, that a copy of the consent has been given to the participant and/or parent guardian and that the original will be retained.
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, slight curl, tight curl
 - d) Type: dry, normal, greasy
4. **Head Lice Details:** If the participant is infested at the time of enrolment, the severity of the current louse infestation will be assessed using the following scale:
 - a) No lice
 - b) Light infestation: lice only found after 5-6 combs of the hair
 - c) Moderate infestation: single louse found on the first comb of the hair
 - d) 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.

Randomisation:

The Investigator will carry a block of sequential numbered envelopes, which correspond to the randomisation numbers that are allocated to the CRFs. Each envelope will contain a randomised, blinded, treatment allocation. After consent has been received, the next sequential numbered envelope will be opened and the specified treatment allocated to that participant.

Procedure:

All participants will first be treated using a product to eliminate any possible current infestation, so that all participants commence the investigation phase of the study "louse free". Treatment will be provided on Day 0 and, if appropriate, Day 7 (+/- 1 day) using Hedrin Once liquid gel. The product will be applied directly to dry hair. Sufficient product will be applied to saturate the hair and scalp. During the second application of treatment the investigator will comb through the hair to check that all lice

have been eliminated. The product will be left in place for 15 minutes and then washed off with non-medicated frequent wash shampoo. The hair will then be rinsed with water. Hair can be dried in the usual way following hair washing after treatment.

After washing the hair on Day 7 the investigator will demonstrate application of the anonymized preparation to be used in the investigative part of the study to the parent/care giver. The participant number and participant initials will be added to the label of the bottle used. The investigator will then provide sufficient of the preparation to the parent/care giver for regular application until the next visit 1 week later.

The investigator will also supply the parent/care giver with instructions to confirm the method of application of the product, which should be made at least twice each week or, if the participant washes their hair more frequently, to apply following each hair wash. The parent/care giver will also be instructed to inform the study team if at any time they find evidence of a new infestation with head lice so that appropriate action can be taken.

Any non-participating household members identified as having lice at any point in the study period will be offered a standard of care treatment (Hedrin Once liquid gel).

2.3.3.3 Follow up Assessments

At the next visit the investigator will check the participant for any sign of head louse infestation and collect any unused product, which will be retained so that the weight can be recorded and the amount of product used calculated. If the participant has not been infested a fresh supply of product will be given as appropriate.

If the participant is found to be infested (see 2.3.3.6 below) any lice discovered will be fixed in the CRF and treatment to eliminate the infestation initiated using Hedrin Once liquid gel, as described above when the participant was first enrolled. After completion of the rescue treatment, the participant will continue in that arm of the study until fulfilment of their 6 week participation period.

All adverse events and changes in concomitant medication will be recorded in the CRF.

2.3.3.4 Cross-over and Final Assessment

At the end of the first participation period of 6 weeks, each participant will be treated using Hedrin Once Liquid gel on two occasions a week apart to ensure they enter the second half of the study louse free. This treatment period will also constitute a “wash-out” period for whichever preparation was used during the first half of the study. Immediately after washing off the second application of treatment product participants will be crossed-over to the other arm of the study and the investigator will supply the parent/care giver with the alternative anonymized study preparation (i.e. if the person initially received Octanediol 1% Solution they will be allocated placebo, or vice versa). Participants will then continue in the study for a further 6 weeks.

At the end of the 12 weeks study plus one week for cross-over (approximately one school term), i.e. they have participated in both treatment arms of the study 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, the participant's hair will be combed with a 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 (Hedrin Once liquid gel).

All adverse events and changes in concomitant medication will be recorded in the CRF.

The Completion/Withdrawal Form will then be completed.

2.3.3.6 Assessment Analysis

Definition of "infested"

It is anticipated that during the course of the study a high proportion of participants will have encounters with head lice. It is also anticipated that the Octanediol 1% solution will have a sufficient inhibitory effect on the viability of the lice that they will not be able to establish an ongoing infestation. However, this effect is not immediate and may take effect over the course of several days. Therefore, it is quite conceivable that at some point a participant may be examined and one or more apparently viable lice may be discovered. Such an event should not be considered to be a failure of the treatment and at that stage no additional intervention should be undertaken. Instead the participant should continue with the routine and at the next examination if apparently viable lice are discovered again, especially if the numbers have increased, a therapeutic intervention using the standard of care treatment should be given.

At this point, or at any other stage of the study, if ≥ 5 adult lice are found or if any stage 1 or stage 2 nymphal lice are found, it will be considered that an infestation has established and the standard of care treatment (Hedrin Once liquid gel) will be given.

Evaluation of lice recovered

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 they will be adult or third stage nymphs that have newly migrated to the head. The presence of small lice (nymphs) will be evidence that lice had established before being found and had not been sufficiently affected by the treatment regimen that they were not inhibited from laying eggs, which in turn were not prevented from developing. 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 treatment while taking part in the study. If the use of such treatment occurs, the participant will be withdrawn from 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 Thornton & Ross Ltd by completing the Adverse Event form.

2.3.6 Serious Adverse Events

If the adverse event is serious, it shall be reported immediately, by e-mail and telephone and by facsimile to the Medical Contact and Thornton & Ross Ltd. A full written report will be forwarded to Thornton & Ross Ltd, by facsimile, 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:

Study Sponsor contact:

Dr Joanne Talbot
Pharmacovigilance and Medical Information Department
Thornton & Ross Ltd
Linthwaite
Huddersfield
HD7 5QH

Tel: +44 1484 848251 - Direct line with voicemail.
+44 1484 842217 - Main switchboard.

Fax: +44 1484 847301 - Address to "Pharmacovigilance and Medical Information Department" and mark as **Urgent**

E: phv@thorntonross.com or joannetalbot@thorntonross.com

Local Medical contact:

Dr Paul Silverston
The Mill Barn
Mill Lane
Exning
Suffolk
CB8 7JW

Tel: 01638 577729

E: 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 Thornton & Ross 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.

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 endpoint is the frequency of not contracting an infestation by head lice during the course of the study, indicated by no evidence of active head louse infestation.

The main secondary endpoint will be comparison of the frequency (number) of instances of reinfestation.

The other secondary endpoints are the safety and acceptability of the Octanediol 1% Solution preparation in regular use.

3.2 Definition of Populations to be analysed

The Per-protocol Population:

Includes all randomised participants who are treated according to the study protocol.

"Intention-to-treat" Population:

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

3.3 Proposed Primary and Secondary Analyses

1. To confirm that Octanediol 1% Solution can prevent the development of a head louse infestation either by killing lice that climb onto the head or so limit their viability that an infestation does not develop.
2. To compare the efficacy of Octanediol 1% Solution with that of a placebo in the prevention of head louse infestation.
3. To compare Octanediol 1% solution with placebo in the time to first infestation.
4. To compare the number of times each participant is infested while treated with Octanediol 1% Solution compared with the number of times they are infested while treated with placebo

5. To evaluate Octanediol 1% Solution in terms of safety and acceptability.

3.4 Statistical Methods

Sample Size Determination:

The study has been designed to detect superiority of the test product (Octanediol 1% Solution) over placebo in clinical use. It is known that octanediol 5% is effective to eliminate an established head louse infestation. However, it was also observed during the original in vitro studies of 1,2-octanediol that solutions containing 1% active material were able to kill lice, albeit more slowly, and inhibit them from laying eggs.

This suggests that regular use may prevent an infestation from developing in about 60%-70% of users over a period of a school term, whereas people at similarly high risk of infestation who take no action, or as in this study use placebo, might be expected to go through a school term without infestation in about 25%-35% of cases.

The structure and size of this study are based on parameters that are not normally considered in clinical investigations. Unlike most clinical investigations, the participants in this study do not already have a treatable condition. The aim is to prevent a treatable condition but is unlike other “preventive” studies, e.g. vaccine trials, in that those are normally long-term population studies engaging large numbers of participants with a quite small potential for detectable failure overall.

In order to address a number of unknown factors related to the risk of infestation, estimations for this risk have been made based on a calculated overall risk for the population as a whole. For this a number of estimations were based on public domain information and experience obtained in earlier clinical studies (there are no published independent data of incidence or prevalence for this infestation available). The estimation for incidence of risk of infestation is as follows:

The number of units of head louse treatments sold annually in the UK is approximately 2.5 million. Therefore, the number of units of head louse treatments sold weekly is approximately 49,145

It was estimated that approximately 50% of these are for new infestations in children, i.e. the remaining 50% of units are for adults or infants or either for retreatment after failure to cure or are additional purchases as part of a 2x application treatment regimen. Therefore, the number of new cases of head louse infestation is actually approximately 24,572 per week. And as there are approximately 5.4 million children in the highest “at risk” age group in the UK (4-13 years) this means that approximately 0.455% of children become infested each week.

In order to relate these data to this study it is known that the child population of Cambridgeshire in the “at risk” age group is about 51,000, which means that approximately 232 cases of head louse infestation occur in the whole of Cambridgeshire each week.

Two approaches to the study size estimation were considered, a straightforward

comparative study of two groups or a cross-over study using a survival analysis consideration, with each participant acting as his or her control. The arguments in favour of the cross-over model appear stronger in that smaller numbers of participants can be engaged, to minimise exposure to the new preparation, and it also offers internal controlling, with each participant acting as his or her control (with the assumption that the individual's risk remains more or less constant over the relatively short time of the study). The risk factors for each individual are sufficiently unknown that randomisation alone may not wholly address any disparity in infestation risk due to social and family circumstances, especially in a relatively small study cohort. Therefore, self-controlling for each individual is an attractive option to avoid any skew resulting from these unknown factors. By using a cross over study it would be possible to use a survival analysis approach in relation to time to first infestation (see **Analytical Methods**, below).

Calculations were made to investigate the possibility of using the cross-over estimations to limit participant numbers, for example to say 15 per group. However, when the "incidence" figures above were applied, it was found that it would be likely it would be impossible to make a reliable comparison between the product and placebo because of the possible low rate of infestation in the population as a whole.

In order to partially address the problems outlined above it is planned to mostly recruit from contacts, obtained from previous clinical studies, who have expressed an interest to take part in a study of this type. This group is known to be more at risk. Therefore, based on past study data relating to when people have contracted lice after study treatments, there is a reasonable expectation of an infestation rate of between 3 and 5 instances of reinfestation per year for each person in that group, i.e. a risk of about 3.6-4 possible reinfestation events per week for the whole study population. This doesn't mean that they will get lice but rather that they could come into contact with someone who does have them and lice could therefore be passed to them.

An estimation of sample size was made using conventional "survival analysis" calculations and the table below is taken from http://www.stattools.net/SSizSurvival_Pgm.php.

The table of sample size for 2 survival ratios is applicable to the common situation where the probability of Type I error $\alpha = 0.05$ (95% confidence) and power = 0.8 (80% power). In conventional survival analysis terms it assumes that the sample size in each of the two arms is the same, which in this case is certainly correct because each individual participates in both treatment arms sequentially.

The rows and columns represent the anticipated proportions of participants remaining louse free in each of the two treatment arms, and each cell is the total sample size (both treatment arms together) for that row/column combination. The shading covers the anticipated range of outcomes. These estimations of size that are proposed for this study appear to be at around the lower bound of population size required for the 30-35% difference in outcome between treatments necessary to detect superiority (range 62-90 participants) using a cross-over model, thus fulfilling the preferred aim of minimising the number of participants in the study.

For a randomise-by-individual approach, assuming a confidence level of 95% and a power of 80%, and anticipating the expected non-infestation rates to be 65% for Octanediol 1% Solution and 30% for the placebo, the required sample size is therefore estimated as 34 subjects per treatment. However, this study will operate a “hybrid” randomization in that only one person from each household will be randomized (index case) and all others in the house will be offered treatment when infestation arises but will continue to potentially act as a source of reinfestation. This approach reduces possible confounding issues of enrolling all members, in which some households will have all members on one intervention but others will have a mixture of active and placebo interventions. Therefore, for each participant on each arm of the cross-over the familial risk of reinfestation should be similar in this respect.

Sample size table for 2 hazard ratios in survival analysis

| | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 | 0.30 | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 | 0.60 | 0.65 | 0.70 | 0.75 |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 0.10 | 496 | | | | | | | | | | | | | | |
| 0.15 | 173 | 963 | | | | | | | | | | | | | |
| 0.20 | 99 | 295 | 1414 | | | | | | | | | | | | |
| 0.25 | 69 | 155 | 406 | 1826 | | | | | | | | | | | |
| 0.30 | 53 | 100 | 203 | 504 | 2186 | | | | | | | | | | |
| 0.35 | 43 | 73 | 127 | 245 | 588 | 2486 | | | | | | | | | |
| 0.40 | 36 | 57 | 90 | 149 | 280 | 656 | 2723 | | | | | | | | |
| 0.45 | 32 | 47 | 68 | 103 | 167 | 307 | 708 | 2894 | | | | | | | |
| 0.50 | 28 | 39 | 54 | 77 | 114 | 181 | 326 | 743 | 2997 | | | | | | |
| 0.55 | 26 | 34 | 45 | 60 | 83 | 121 | 190 | 338 | 761 | 3032 | | | | | |
| 0.60 | 24 | 30 | 38 | 49 | 65 | 88 | 126 | 195 | 343 | 761 | 2999 | | | | |
| 0.65 | 22 | 27 | 33 | 41 | 52 | 67 | 90 | 128 | 195 | 339 | 744 | 2897 | | | |
| 0.70 | 21 | 25 | 30 | 36 | 43 | 54 | 69 | 91 | 127 | 192 | 328 | 711 | 2727 | | |
| 0.75 | 20 | 23 | 27 | 31 | 37 | 44 | 54 | 68 | 89 | 123 | 183 | 310 | 660 | 2490 | |
| 0.80 | 19 | 22 | 24 | 28 | 32 | 37 | 44 | 54 | 66 | 86 | 116 | 171 | 284 | 592 | 2186 |
| 0.85 | 18 | 20 | 23 | 25 | 28 | 32 | 37 | 43 | 52 | 63 | 80 | 107 | 154 | 250 | 508 |
| 0.90 | 18 | 19 | 21 | 23 | 26 | 28 | 32 | 36 | 42 | 49 | 59 | 73 | 95 | 133 | 209 |
| 0.95 | 17 | 19 | 20 | 21 | 23 | 25 | 28 | 31 | 34 | 39 | 45 | 53 | 64 | 81 | 108 |

This estimate of the likely numbers in relation to application of the Octanediol 1% Solution active material for 6 weeks followed by placebo for 6 weeks assumes that the potential rate of contact and reinfestation is more or less linear so that, where it was estimated from past data that a likely reinfestation rate would be approximately 4 per week for the whole population, the possible number of new cases would be 24 over the 6 weeks of one half term, or 12 cases per treatment if neither had any effect. However, if the test preparation is effective this number of cases could be reduced by approximately 60% resulting in 5 cases. This difference offers essentially similar powering to that of a parallel group calculation, although the statistical significance would be reduced overall if the reinfestation rate were to be no greater than 4 per week.

Analytical Methods:

The primary endpoint analysis is the comparison between the Octanediol 1% Solution and placebo in the frequency of not developing an infestation, with the difference between the two study treatment arms tested using the "intention-to-treat" population. Secondary endpoint analyses will be the frequency (number) of instances of reinfestation and safety of the product and participant acceptance.

Analyses will be conducted based on both the "intention-to-treat" and the "per-protocol" populations.

As this is a cross-over study with equal numbers in each treatment arm it is appropriate to analyse efficacy using a Kaplan-Meier survival analysis. This analysis will compare the time to first infestation for each individual in each arm of the crossover, in which the time to first infestation is taken as the "survival" endpoint. This will essentially address the three first analytical tasks set out in section 3.3, although point 1. will also be addressed in other analyses.

It is not considered that censoring will present as a major issue during the first half term period and, if it does occur at all, right censoring from the second half term is the likely outcome. For these data it would be appropriate to use the log-rank test to analyse in relation to time to first infestation. Comparison of the "survival" curves would probably be more appropriate in this case using the Brand and Altman approach and hazard ratio curves rather than conventional Kaplan-Meier curves (Bland and Altman, *BMJ*, 2004, 328, 1073).

However, if no censoring occurs, it may be more appropriate, because the primary outcome measure is no evidence of active head louse infestation, that the primary analysis method could additionally use the McNemar's test on these binary outcome (evidence/no evidence of active head louse infection during the treatment period) data as a simple method to address point 1. of section 3.3, to answer the question as to whether the Octanediol 1% Solution is able to prevent establishment of a head louse infestation.

In addressing point 4. of section 3.3, which may potentially result in a ranked variable, from how many times each individual becomes infested over the course of each arm of the crossover, the Wilcoxon signed rank test will be used for the paired data derived from the time spent in each arm of the study by each participant.

Because this is a cross-over study there will be no conventional comparison of difference between groups in baseline characteristics. However, the two arms will be tested for comparability of some baseline characteristics, such as presence of infestation, and presence of infestation in other household members at the start of the study and at the commencement of the "wash-out" cross-over treatment. For these comparisons, and comparisons of safety, and acceptability data will be tested using Fisher's exact test for yes/no variables and the Wilcoxon signed rank test for paired data, or Mann-Whitney U test for unpaired, ranked variables.

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 Thornton & Ross 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 the European (CPMP) Guidelines on Good Clinical Practice for Trials on Medicinal Products and with the European Standard, and the EU Directive on Good Clinical Practice (2001/20/EU).

4.2 Ethics Committee Approval

The Chief Investigator will be required to obtain the written approval of the relevant Research Ethics Committee before commencing the study. In accordance with Good Clinical Research Practice, a copy of this approval together with the constitution of the ethics committee will be forwarded to Thornton & Ross Ltd before the release of trial supplies from Thornton & Ross Ltd.

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, but 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.

4.4 Insurance Policy

Thornton & Ross 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 appropriate institution employing them.

4.5 Compensation

Thornton & Ross 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 the European (CPMP) Guidelines on Good Clinical Practice for Trials on Medicinal Products. 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. Thornton & Ross 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 and the Research Ethics Committee within 10 days. The new Investigator must be appropriately qualified and be approved by Thornton & Ross Ltd and the Research Ethics Committee before the study can be continued.

Study Report

The Chief Investigator will submit a summary study report within approximately 2 months 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. Methodology and normal ranges for laboratory investigations (where appropriate)
6. 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.
7. If appropriate, details of any statistical analysis carried out by the Investigators, and a summary of efficacy data including clinical observations.
8. Conclusions

A copy of the report will be forwarded to the Research Ethics Committee.

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, Statistician and members of the MEC study team will be provided to Thornton & Ross Ltd.

4.8 Case Record Form

The Investigator is required to prepare and maintain adequate and accurate case records that have been designed by Thornton & Ross 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 Thornton & Ross 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 on Medicinal Products 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 Thornton & Ross Ltd 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, Thornton & Ross 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, Thornton & Ross 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 Thornton & Ross 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 Thornton & Ross Ltd nor the Investigators may make any changes or amendments to this protocol, after the protocol has been agreed and signed by both parties, unless such change(s) or amendment(s) have been fully discussed and agreed by both the Investigator and Thornton & Ross Ltd. Any change or amendment agreed will be recorded in writing, the written amendment will be signed by the Investigator and by Thornton & Ross Ltd and the signed amendment will be appended to this protocol.

Any substantive changes will be forwarded to the Research Ethics Committee and to the appropriate regulatory authority for approval before implementation of the amendments.

4.13 Publication Policy

Submission of results for publication will not take place without prior discussion with Thornton & Ross Ltd, allowing the company sufficient time to analyse such results and provide written agreement to publication, which will not be unreasonably withheld. Thornton & Ross 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 Thornton & Ross 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.

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

A. INTRODUCTION

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 not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

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

4. 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."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. 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 current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

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

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should 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.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. 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.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described 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, other potential conflicts of interest, incentives for subjects and provisions for

treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. 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 change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

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

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

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

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

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, 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, 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.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should 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 should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized 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 population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent 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 authorized representative. The potential subject's dissent should be respected.

29. 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 population. In such circumstances the physician should seek informed consent from the legally authorized 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 should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors 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. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research 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.

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

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the 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 interfere with the patient-physician relationship.

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

APPENDIX 2: ICH GUIDELINES ON GOOD CLINICAL PRACTICE

Responsibilities of the Investigator Investigator's Qualifications and Agreements

1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proposed conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).
2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.
3. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.
4. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Adequate Resources

1. The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects with the agreed recruitment period.
2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

Medical Care of Trial Subjects

1. A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

3. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.
4. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Communication with IRB/IEC

1. Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects.
2. As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.
3. During the trial, the investigator/institution should provide to the IRB/IEC all documents subject to review.

Compliance with Protocol

1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.
2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/ favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).
3. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.
4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/ favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
 - a) to the IRB/IEC for review and approval/favourable opinion,
 - b) to the sponsor for agreement and, if required,
 - c) to the regulatory authority(ies).

Investigational Product(s)

1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
2. Where allowed/required, the investigator/institution may/should assign some or all the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.
3. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.
4. The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).
5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.
6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

Randomisation Procedures and Unblinding

1. The investigator should follow the trial's randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

Informed Consent of Trial Subjects

1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Before the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.
2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if

new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

3. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.
4. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.
5. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favourable opinion by the IRB/IEC.
6. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.
7. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to enquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.
8. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.
9. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.
10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanation of the following:

- a) That the trial involves research.
 - b) The purpose of the trial.
 - c) The trial treatment(s) and the probability for random assignment to each treatment.
 - d) The trial procedures to be followed, including all invasive procedures.
 - e) The subject's responsibilities.
 - f) Those aspects of the trial that are experimental.
 - g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
 - h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
 - i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
 - j) The compensation and/or treatment available to the subject in the event of trial-related injury.
 - k) The anticipated prorated payment, if any, to the subject for participating in the trial.
 - l) The anticipated expenses, if any, to the subject for participating in the trial.
 - m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
 - n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.
 - o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
 - p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
 - q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
 - r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
 - s) The expected duration of the subject's participation in the trial.
 - t) The approximate number of subjects involved in the trial.
11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.
 12. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable

representative (e.g. minors, or participants with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

13. Except as described in 14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.
14. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
 - a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally.
 - b) The foreseeable risks to the subjects are low.
 - c) The negative impact on the subject's well being is minimised and low.
 - d) The trial is not prohibited by law.
 - e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in participants having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

15. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 10) should be requested.

Records and Reports

1. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
2. Data reported on the CRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.
3. Any change or correction to a CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigator's designated representatives on making such corrections.

Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.
5. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.
6. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.
7. Upon request of the monitor, auditor, IRB/IEC or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

Progress Reports

1. The investigator should submit written summaries of the trial status to IRB/IEC annually, or more frequently, if requested by the IRB/IEC.
2. The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

Safety Reporting

1. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate report. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.
3. For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal

medical reports).

Premature Termination or Suspension of a Trial

1. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition to:
 - a) If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.
 - b) If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
 - c) If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Final Report(s) by Investigator

1. Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.