Reviewer's report

Title: High efficacy of a dimeticone-based pediculicide following a brief application: in vitro assays and randomized controlled investigator-blinded clinical trial

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Reviewer: Ian Burgess

Reviewer's report:

This is a manuscript that describes the activity of a new/modified formulation of a marketed pediculicide product including clinical data that were presumably generated for both regulatory and marketing purposes. It also includes some preliminary testing data that were either generated at an earlier date in preparation for conducting the clinical study or else the tests were conducted quite separately with some other purpose (the reason for this last statement will become apparent below).

My overall impression of the manuscript is that different sections were written by different authors, as shown by style of writing, grammatical construction, etc. but none of the authors appears to have taken overall editorial control so that as a read it is somewhat disjointed, inconsistent, and in places contains duplicated or irrelevant material. Consequently, there are some logical inconsistencies throughout the text that require justification and clarification.

Introduction

Paragraph 1, lines 64-67: I think it would make this sentence clearer if it was turned about to state that in Germany the kdr-like mutations showed a minimal impact on the permethrin treatment described by references #16 and #17.

Paragraph 3: I do not see the relevance of this paragraph on hypothetical disease vector capacity of head lice to any of the aims of this study. It appears to have been "dumped" somewhat randomly in the middle of two paragraphs dealing with the need for effective products and the need to improve treatment compliance. It should be deleted.

Lines 92-93: As above the mention of "the emerging role of head lice as potential disease vectors" is similarly irrelevant to the main point of the study. The socio-economic burden of lice or compliance with treatment regimens in Germany and other developed countries where Nyda is sold is a more pressing argument.

Lines 99-107: These sentences are more appropriately incorporated into the Methods section, where much of this wording is duplicated anyway. It would be sufficient to state here that the manuscript describes "laboratory and clinical studies to investigate the efficacy and safety of the new Nyda formulation".
Line 103: It is something of a tautology to state that the permethrin-based pediculicide has a neurotoxic mode of action, given the information about resistance etc. provided earlier. Note this same statement also occurs at line 122.

Methods

Test and reference products

Lines 118-121: Why were two completely different dosage forms of permethrin used for the in vitro and clinical studies? Given that the bioavailability of an insecticide is affected to varying degrees by the formulation excipients, surely it would be logical to use the same comparator product for laboratory tests (0.5% permethrin in an alcohol vehicle) as was planned for the clinical study, especially as I suspect these laboratory data were used as corroborative evidence in the medical device submission to the German regulatory authorities.

Assessment of pediculicidal activity in vitro

This section is the most puzzling of the whole manuscript.

Based on the methodology employed, I have concluded that the test against adult body lice was possibly not conducted in Dr Clark's laboratory but at one of the laboratories in Germany that perform louse testing. Why was testing conducted against body lice rather than against the same BR-HL isolate of head lice that is maintained by Dr Clark as the louse egg tests? It appears totally illogical to run one set of tests versus a completely susceptible laboratory colony of body lice (adults) and the other set of tests versus pyrethroid resistant head lice (eggs in this case). If resistance was an issue under scrutiny, surely testing against adult resistant lice that could adequately express any resistant trait is the logical way to evaluate the likely clinical efficacy of a product, even if it was only the comparator product?

Line 142: Why was gerbil hair used as a substrate? Surely it would be more logical to either use human hair or, since these were body lice, to place them on a clean cloth substrate similar to the one they are reared on?

Lines 145-151: The determination of mortality is also a puzzle. It is true that two of the cited references #34 and #37 utilise a criterion in which categories M, G, and D could be considered non-viable. However, the lead author of this manuscript, Dr Heukelbach, has been a strong advocate in other publications of using more stringent criteria, notably:


Therefore, I would like to question why these more stringent criteria were not applied in this study.

Line 151, the citation of reference #36 is incorrect because this cited article does not mention assessment of mortality. The correct reference should be:


Assessment of ovicidal activity in vitro

Line 173: I believe this line should start "Besides immersion,..." not "Besides spraying,..."

Lines 173-181: I can understand spraying of the Nyda product and of the distilled water control but I find it hard to work out how the Nix 1% permethrin product could be sprayed because it is a relatively highly viscous cream formulation that would not be easily expelled from a regular atomiser pump head in the same way as the other two fluids. Please explain.

Lines 178-180 (also lines 138-139): Why was the Nix 1% permethrin product shampooed off rather than just rinsed off as required by the product instructions? This could impact on the bioavailability of the permethrin.

Clinical trial

Study design

Lines 195-196: This study was performed in line with reference #38 but a more recent international consensus was collected by Do-Pham, et al. Designing randomized-controlled trials to improve head-lice treatment: Systematic Review using a vignette-based method. Journal of Investigative Dermatology 2014; 134: 628-634, which could have provided a clearer endpoint by following that guideline for a 14 day follow up.

Eligibility criteria

Line 205: This section states "Patients >2 years of age." Does this mean that patients had passed their second birthday but that they had not yet reached their third birthday or does it mean that as they were "over" two years they had already reached their third birthday? This question is pertinent because the SPC for Infectopedicul states that the product is for children of three years and older.

How were patients recruited to the study?

Intervention
The wording of line 236 is potentially misleading. Where it states that "repeated treatments" were given it should be made clear that all participants received only two treatments. The term "repeated treatments" implies that multiple applications of product were given.

Line 244: The specification of the "nit-comb" should be given.

Line 252: Was this the same specification of nit-comb for both products?

Informed consent, outcome measures and assessments

Lines 265-267: I do not understand why or how an assessment of reinfestation could be made at day 1 (V2) but not at day 7 (V3) and does not match up exactly to the criteria used for assessment in the cited reference #40. This assessment is understandable at day 10 (V4).

Lines 268-276: This paragraph appears unnecessarily wordy. The categories of the response ratings and observations are adequately shown in the tables of these outcomes and so only the briefest mention is required here with a statement referring the reader to the tables in the text for the characteristic criteria.

Lines 293-296: If nit-combing was performed as part of the treatment and patients or their care givers were permitted to nit-comb at any time between study visits (irrespective of whether they did it or not), how could you possibly determine whether the efficacy outcome was due to the liquid treatments applied to the participants or whether the outcomes were confounded by the potentially multiple combing sessions (at least two during treatment but potentially as many as eight, if the people were really diligent)? Even if most carers failed to apply additional combing measures what is to say that the combing during treatment was not responsible for the majority of the efficacy of one or both products? This practice has made the whole study potentially meaningless from the point of view of claiming efficacy for Nyda express.

Results

Pediculicidal activity in vitro - Ovicidal activity in vitro

Why are no data shown for lice treated using the permethrin product?

Would it not be better to show numerical data for both lice and their eggs in tables rather than is these somewhat facile bar charts?

Clinical trial

Participants and baseline demographic data

There are inconsistencies of GCP and accounting in this section, lines 403-411. In line 406 the withdrawal was obviously a "Lost to Follow Up" and should be included in the final FAS
(Intention to Treat) analysis as a treatment failure. The patient suffering the SAE should have been automatically withdrawn from any further participation and also recorded in the FAS as a treatment failure. The two non-compliant participants in the comparison group should also be included in the FAS analysis as treatment failures. So Table 3 requires correction accordingly, as does the associated statistical analysis.

Was the SAE that was initially suspected as being possibly due to use of the treatment product reported to the appropriate ethics committee and the regulatory authority, or even reported as a SUSAR, in line with the requirements of GCP? If so, this should be recorded in the manuscript and if not a good explanation of why it was not done should be provided.

Lines 455-461: There is a considerable misunderstanding of louse biology in this paragraph. In lines 458-459 it states that the development of a N2-nymph from an egg between day1 (V2) and day 7 (V3) is not possible. However, if an egg were to be present on day 1 that was close to hatching the emergent nymph would have more than enough time to grow to stage 2 or even possibly stage 3 by day 7, depending upon its gender and nutritional uptake. In addition, stage 2 nymphs do not normally migrate from one host to another, this being mostly confined to stage 3 nymphs and adults because they are close to, or actually, reproductive. Young nymphs stay put and spend their time feeding and growing. Consequently, this nymph indicated lack of activity of the treatment irrespective of the status of the adult louse found at the same time.

Global tolerability

Please explain what "global tolerability" is. Does it mean the respondents were just happy to get rid of their lice so they would tolerate using it again? Given the number of AEIs it is surprising that so many thought either of the products was "good" or "very good" so the concept requires elucidation as the terminology is vague and "woolly".

Discussion

Line 536: The percentage cure rate requires clarification in line with any reanalyses resulting from addressing the points about lines 403-411.

Lines 569-571: What were the "available data" that suggested a lower efficacy for the permethrin comparator product? The studies reported in references #16 and #17 suggest a high level of efficacy for this particular permethrin product in Germany. However, as stated above, the possibility that nit-combing created/contributed to this high level of efficacy cannot be excluded from consideration, which also raises questions about nit-combing and the efficacy of the Nyda product.

Lines 576-577: Is there evidence for this suggestion that use of physically acting product like dimeticone in Germany has "diluted out" the level of resistance to pyrethroids? The fact that at least two pyrethroid-based products remain on the market under Section 18 of the German
Infection Protection Act suggests that use of pyrethroids has not been eliminated and so some continued selection pressure remains on the louse population.

Lines 589-598: There is repetition in this paragraph that needs editing out.

Line 603: The Strycharz publication is incorrectly cited and should be Strycharz et al. (2012) not (2002).

Line 645: The wording "..the only exclusion criterion that lead to non-inclusion was the absence of active infestation." is incorrect. It should read "..the only exclusion criterion that led to non-inclusion was the absence of active infestation."

References

There are several typographical errors and transcription errors in the reference list. These should be checked thoroughly and corrected.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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