Author’s response to reviews

Title: A Pilot Single Centre, Double Blind, Placebo Controlled, Randomized, Parallel Study of Calmagen® Dermaceutical Cream and Lotion for the Topical Treatment of Tinea and Onychomycosis

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The Editor, BMC Complementary and Alternative Medicine

Re: Response to Reviewers (BCAM-D-16-00792R1) – “A Single Center Double Blind, Placebo Controlled, Randomized, Parallel Study of Calmagen® Dermaceutical Cream and Lotion for the Topical Treatment of Tinea and Onychomycosis”

Dear Editor:

On behalf of the co-authors of the aforementioned manuscript, we would like to thank the reviewers for their constructive comments. Please find below our reply to their comments and suggestions.

1. Shari Lipner (Reviewer 1): The authors have responded to most of the suggestions in the manuscript.

I think lack of photos is a major concern, I would be interested in seeing the photos and seeing whether any are suitable for publication.
Reply: Please refer to the file “Calmagen Trial onycho photos” showing the best before and after photos we have on file from a subject treated with the Calmagen lotion from the actual study. Although it has been disappointing to us that the recorded photos were of low quality, we would also like the reviewers to peruse a poster on a different clinical study on the same product presented during the 44th Scientific Meeting of the Australasian College of Dermatologists in 2011 (Freeman AM and Freeman MG. Nailkalm (Arthrospira maxima) for the treatment of dermatophyte nail infections. Australasian Journal of Dermatology 2011;52 Suppl 1: 25; please refer to file “Poster - Australasian College of Dermatology’s Scientific Conference May 2011”).

Furthermore, we would like to share photos from two recent examples of actual subjects (males, Caucasians) who have used the Calmagen lotion after the study was conducted. Both cases include photos after a washout or ceasing treatment for more than two months (please refer to files Calmagen Case 1; Calmagen Case 2). These 2 subjects have tried using current available drugs recommended for onychomycosis for several years without success before using Calmagen. Although these latter photos cannot be included in the publication, we hope these provide evidence of the product’s efficacy. Nevertheless, we believe that the current study warrants further clinical studies in larger trials and we are currently preparing for a few.

The other major problem is the design of the study. To my understanding, in the onychomycosis part of the study, the subjects were applying the cream for all 24 weeks and then mycological analysis was performed. This will likely confound the results. It is now standard practice to have a washout period so that the subject is not using any medication when mycological analysis is performed.

Reply: We agree with the reviewer. However, the study was conducted in 2010, prior to the recent efinaconazole and tavaborole trials and represents a limitation of the study. We have addressed the reviewer’s concern by adding a statement in the manuscript describing this limitation and that it will be considered in future clinical trials. The change is reflected as a sentence “Furthermore, there was no washout period or a period of complete cessation of treatment to ensure that fungal infections did not recur.” is inserted in page 15, 2nd paragraph, 3rd sentence.

Nevertheless, it is worth noting that from the aforementioned recent 2 anecdotal examples (Calmagen Case 1 and Calmagen Case 2), there was no recurrence observed of onychomycosis after 2 months to more than a year from complete cessation of treatment.

2. Ignacio García-Doval (Reviewer 3): This paper describes a RCT of topical Calmagen™ for fungal skin infections.
My main concerns are:

* Given the sample size and mixed patients, the title should call it Pilot RCT

Reply: We have changed the title accordingly. Please refer to title on the title page and below.

“A Pilot Single Centre, Double Blind, Placebo Controlled, Randomized, Parallel Study of Calmagen® Dermaceutical Cream and Lotion for the Topical Treatment of Tinea and Onychomycosis”

* Patient selection was too restrictive: Positive KOH and fungal culture: Given that these methods have low sensitivity, many patients have been excluded, and regression to the mean can justify a large part of the improvement in the primary outcome (mycological cure).

Reply: We respectfully disagree with the reviewer. The same criteria (KOH and fungal culture) have been used in previous studies such as the recent clinical trials on efinaconazole and tavaborole as referenced below:


* Causes of exclusion of nearly 50% of screened patients should be described

Reply: Exclusion of the patients was based on failure to meet the inclusion requirements described in Figure 1. We have included this now in the text (page 10, paragraph 1, lines 2-4).

* References to previous therapy as toxic (page 4, line 51 and others) should be avoided.

Reply: We have deleted accordingly as well as in page 14, line 12-13
Efficacy analysis should be ITT: that means that all randomized patients should be analysed, and this is not what authors did ("patients who received the study treatment and had at least one efficacy measurement"): This is a per protocol analysis, not "modified ITT".

Reply: Efficacy analysis was based on modified ITT, which is a subset of the ITT population and considered a standard method for efficacy analysis in clinical trials of anti-infectives (Gupta SK (2011) Perspect Clin Res 2(3):109-112). Noncompliance and missing outcomes are frequently seen in randomized controlled trials. ITT analyses every subject who is randomized and ignores noncompliance/deviations/withdrawal etc. CONSORT requires ITT analysis. To counter against the argument that ITT subject may not have gotten any treatment and may have no efficacy data, mITT may be used, which excludes patients who never started treatment. For this study all randomized patients who received study medication and had at least one efficacy measurements were included under mITT. Furthermore, in the clinical protocol, the plan was to also analyse the PP population and if there were any differences between the ITT and PP populations, these will be reported.

It should be noted that in the study, we have used all 28 randomised subjects in the analysis, which satisfies an ITT population. For clarification, due to limited space, we did not explicitly describe the clinical protocol submitted to the ethics committee. We have now included the detailed planned statistical analysis with the text below inserted in paragraph 2, page 8.

“The primary efficacy endpoint was also analyzed for the Per-protocol (PP) population which includes all randomized patients who complete both the baseline visit and end of treatment visit and who have no major protocol violations. Since all subjects completed the study without protocol violations, the PP and mITT populations were essentially the same. All secondary efficacy endpoints were analyzed for the mITT and PP populations. Safety data were analyzed for Safety Population, which included all patients who have received at least one application of study drug.”

We respectfully differ with the reviewer regarding the definition of Per Protocol population, which is rather defined “as a subset of the ITT population who completed the study without any major protocol violations” (Gupta SK (2011) Perspect Clin Res 2(3):109-112).

However, it should be noted that all 28 enrolled subjects completed the study without protocol violations making the PP (per protocol) population the same as the ITT and mITT populations. We have included a statement that all 28 subjects enrolled were part of the same respective populations (page 10, lines 7-8 of Results section).
Regarding safety, the most conservative analysis is per protocol (and authors used ITT this time)

Reply: The study design called for ITT for safety analysis given the small sample size. If, we instead set the PP for safety analysis before the study started and in the event that some subjects do not follow the protocol, there may not be enough subjects for safety analysis. We have pointed above that the plan was to analyse the PP population and if there were any differences, these will be reported. However, since all 28 subjects enrolled in the study followed the protocol, the PP (per protocol) population is essentially the same as the ITT and mITT populations in this case. We have included a statement that all 28 subjects enrolled were part of the same respective populations (page 10, line 7-8 of Results section).

Given the unexpected results and obvious conflict of interest, pictures are mandatory.

Reply: See response #1 to Reviewer #1

* Taking into account the low sample size, all results should include 95% CI (not included in primary outcome or abstract), and these should be stratified by disease (onychomycosis and tinea)

Reply: The primary outcome of the trial was for the combined tinea and onychomycosis subjects therefore we did not separate the 95% CI for onychomycosis and tinea. We have clarified this on page 10 under the Efficacy analysis, Primary endpoint section.

The 95% CI information is already included in Figure 1 and has been revised per previous reviewer’s recommendation to present the data in a graphical form instead of a tabular one. We have now included the 95% CI values in the abstract, page 2, bottom 3 lines). Stratification between onychomycosis and tinea was done during the secondary analysis and the 95% CI for all samples are already included in Secondary endpoints section (pages 11-12).

* Safety cannot be concluded form such a small trial. Please avoid strong claims of safety.

Reply: We have re-worded accordingly by adding the word “potentially” in the last sentence of the Conclusion section in the abstract and text (pages 3 and 15, respectively).

Please check that you comply with all CONSORT checklist.
Reply: Re-checked CONSORT checklist – refer to CONSORT checklist

I hope that we have addressed the reviewers’ comments and look forward to having our manuscript accepted for publication at BMC Complementary and Alternative Medicine.

Sincerely,

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