**Author's response to reviews**

**Title:** A randomized, double blind, crossover, placebo-controlled clinical trial to assess the effects of a mouthwash containing chlorine dioxide on oral malodor

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**Author's response to reviews:** see over
Dear the Trials Editorial Team

Thank you for your kind consideration of our manuscript.

Please find attached the re-revised manuscript. The re-revised points (responses to the reviewer’s comments) are described and we made the same required changes to the format of our paper. All authors have approved this re-revised submission.

Sincerely yours,

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Response to the Reviewer

The authors are grateful for the kind advice of the Reviewer.
We have re-revised our manuscript accordingly.
Please see the revisions described below.

1. Review English grammar and vocabulary.

# We had our manuscript reviewed by a native English speaker.

This part has been successfully corrected.
→ Thank you for your acceptance.

2. Introduction: the introduction should be improved: scarce information is cited, especially about other products/mouthwashes for the treatment of oral halitosis. It gives the impression that the active product that has been evaluated in the paper is the only treatment available for oral halitosis.

# We included a statement about other products/mouthwashes for the treatment of oral halitosis in the Introduction (p3, lines 10-16).

In this reviewer’s opinion, the statement included in the Introduction still lacks some relevant information about other products that have shown statistically significant reductions in halitosis-related outcome variables. Without this information is difficult for the readers to put the results of this paper in perspective.

→ Moreover we included a statement of some relevant information about other products that have shown statistically significant reductions in halitosis-related outcome...
variables in the Background (p3, lines 15-24).

3. A clear description of hypothesis and justification is lack in the paper.
   # We described the hypothesis and its justification on page 4, line 12-14.
   **This part is now acceptable.**
   → Thank you for your acceptance.

4. Material and methods:
   1) The study included only male volunteers, is there any rationale for that?
   # We excluded females subjects because their menstrual cycle might affect oral malodor
   **This reviewer does not understand the possible influence of the menstrual cycle on the results of a study with a follow up of 4 hours, it could influence the baseline levels of malodor but not the effect of a tested product on these levels. In other words, the exclusion of female volunteers introduces an important bias in the results of the study and should be clearly stated in the paper.**
   → We described the reason why we excluded female volunteers and it might be an important limitation in the results of this study. We covered this point on page 5, line 6-8 in Materials & Methods and page10, line 2-3 and page 12, line 10-12 in the Discussion.

   2) Was the wash-out period calculated based on the carry-over effect? In other words, the authors should statistically analyze their results taking into account the order of
use of the products.

# There were no significant differences in any malodor measures between the two groups at either the first and second baseline measurements before mouth rinsing. Similarly, there were no significant differences between the first and second baseline measurements after the washout period. Hence, we think the oral condition returned to baseline during the one week wash-out period and that one week is long enough for a trial like this study.

**The authors should clearly remark this on the paper.**

→ We described that the one week wash-out period was long enough for this trial on page 5, line 20-24 in Materials & Methods.

3) The inclusion of a positive control would have been desirable in a crossover study.

# While it would be desirable to include a positive control such as 0.2% or 0.12% CHX based on former research, this is impossible because the known side-effects in Japan prevent Institutional Review Board (IRB) approval.

**In this reviewer opinion there is no rationale for the non acceptance of the inclusion of chlorhexidine or any other positive control in the design of this crossover study and especially when it is only used as a single rinse. It is well known that the possible side-effects appear after prolonged use of these products.**

**In any case you should clear this on the paper.**

→ We described the limitation about a lack of a positive control on page 4, line 24-26 in Background and page 10, line 2-3 and page 12, line 10-12 in Discussion.

4) The authors should clearly state that this is not a real clinical trial, but it is more a
study model, similar to the model used to assess antiseptics and the reduction in salivary bacterial counts. In addition, the limitation of the follow-up should be pointed out, since oral halitosis is a chronic condition.

# As you suggested, our research design is more like a study model than a real clinical trial and is limited by the short follow-up of only 4 hours because halitosis is a chronic condition. We need to examine the long-term effect as well as the effect on periodontal disease and plaque accumulation of the mouthwash in a future research. We added related sentences to the manuscript on page 11, line 13-19.

This part is not clear when reading the paper and still can give an equivocal impression of the results to the readers. So the authors should remark this on the paper and not only in the discussion.

→ We described the limitation about the short duration of the outcome measurement and the exclusion of halitosis patients and the lack of bacterial consideration on page 4, line 24-26 in Background and page 10, line 2-3 and page 12, line 10-12 in Discussion.

5. Conclusion: they are not supported by the results: the impact on morning breath was not truly assessed. Again, limitation of the study model should be acknowledged at this point.

# Current results show that the mouthwash effectively reduces morning breath of healthy subjects, but whether the same results would be obtained from halitosis patients is unknown. We added related sentences to the manuscript on page 12, line 1-2.

This part is now correct.

→ Thank you for your acceptance. Moreover, we added sentences to the manuscript on page 12, line 19-20.