Author's response to reviews

Title: Clinical trial: Probiotic treatment of acute distal ulcerative colitis with rectally administered Escheria coli Nissle 1917 (EcN)

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Author's response to reviews:

Dear Editor,

Thank you for your commitment in the reviewing process of our manuscript "PROBIOTIC TREATMENT OF ACUTE DISTAL ULCERATIVE COLITIS WITH RECTALLY ADMINISTERED ESCHERICHIA COLI NISSLE 1917".

We think the manuscript definitely improved a lot by giving it to reviewers who were able to closely judge also on the statistics. Their calculations and subsequent comments revealed great scrutiny.

Please find below our reply to the reviewers comments. Hopefully, we were able to address even the last criticism fully and sufficiently. We also hope our reply is clear and understandable to you and all experts involved. Of course we are willing to give more explanations at any time.

Wishing all the very best to you and your team we kindly await your decision.

Kind regards on behalf of all authors,

Dr. H. Matthes

Answers to Reviewer's report

Reviewer's report:
The revised manuscript has been improved, but my main objections remain unchanged. I comment only on the major and important points.

• Intention to treat (ITT) analyses should always be the primary results when presenting the results of RCTs. The response rates in the groups treated with 40, 20, 10 ml and placebo were 10/23, 11/23, 8/22 and 7/20 respectively, and statistics with Jonckheere-Terpstra Test gives a p-value of 0.44 (asymptotic, 2-sided). There is no effect of the treatment, and these results (with the numbers
and statistics given above) should be given in the abstract as well as in the conclusion on the last page. But, they could then report the results of the PP-analyses and give the results with Jonckheere-Terpstra Test which gives a p-value of 0.0446 (asymptotic, 2-sided) or 0.0464 (exact, 2-sided).

Reply:
We have changed the abstract and the conclusion accordingly.

• I do not accept the use of 1-sided tests. Use 2-sided tests all over, in the text as well as on the figures. In the present version of the paper it seems as if the result of a 2-sided test is given on figure 2.

Reply:
We have now supplied 2-sided test results in the whole manuscript instead of 1-sided.

• The authors have clarified the randomization procedure. The patients got different volumes of the enema, which means that this is not a double blind study (because everyone knew the volume) but a randomized and in part open study.

Reply:
We disagree with this point. Because placebo was used in every volume group neither the investigator nor the patients could be aware that they received the active substance. This is a double-blind design.

• I disagree with the conclusion that the treatment was well tolerated. 4 out of 88 (4.5%) had to stop treatment because of intolerable adverse events, which is a rather high prevalence of intolerable adverse events to a probiotic drug.

Reply:
Here, we cannot follow the reviewer’s opinion completely. Four of 88 patients, 1 of these under placebo treatment, dropped out of the study due to a suspected causal relationship of an AE to the study medication, although none of these AEs were assessed as serious. We still think this safety record is acceptable. However, the sentence “As is expected for a probiotic, EcN treatment was also safe and well tolerated.” has been removed from the conclusion.

• The presentation could still be improved, the language as well as the figures. Leave out figure 2 (the numbers are given in the text and appear from figure 3a. Does figure 4 give any meaning with a lot of missing data (e.g. 55% not available after treatment in the placebo group)?

Reply:
We dropped Figure 2 from the manuscript. Also, we omitted all references.
pointing to Figure 2 in the manuscript’s text.

Ardyepharm GmbH financed the study and employees in Ardyepharm GmbH are authors who have taken part in the analyses, discussions, writing and presentation. Has the sponsor had a high influence on the presentation?

Reply:
Ardyepharm GmbH’s personnel was involved in coordinating the study and subsequent correspondence. All analyses were performed by an independent biometrician. All authors agreed on the interpretation and presentation of the results.