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Reply:

Refers to: Paul Enck. Not more, but less studies are warranted – if you take your meta-analysis seriously

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Abbreviated abstract:

This submission is in reply to a letter by Dr. Paul Enck regarding our recent conclusions regarding the clinical efficacy of patented probiotic, VSL#3, in Irritable Bowel Syndrome.

We thank Dr. Enck for his interest in our paper. We appreciate his thoughtful comments and his modeling exercise to demonstrate the predicted impact of adding a fictive sixth study to our current meta-analysis. Dr. Enck raises the important question of the utility of adding two additional studies when a previous meta-analysis covering three studies showed no significant benefit over placebo. One important distinction to make is that in the previous meta-analysis, authors examined the effect on global IBS or abdominal pain scores and found that the direction of benefit, although not statistically significant, favored VSL#3. Of the two studies added to this previous meta-analysis, one newly published study included more subjects than all three previous trials combined and reported benefit with VSL#3 over placebo for the endpoint of “adequate symptom relief.” Therefore, it seemed reasonable to update the previous analysis to assess and include the two new trials and to examine individual IBS-specific endpoints.

Through his modeling exercise, Dr. Enck proposes the addition of a fictive sixth study and replicates the analysis for the primary endpoint of abdominal pain, failing to show a shift towards a positive overall outcome. Upon repeating this exercise, we find his conclusions to be accurate. However, we note that adding a fictive sixth study using the means and standard deviation of the best available study of 78 patients in each treatment arm resulted in a statistically significant benefit (SMD 0.20, 95% C.I. 0.01–0.40) in abdominal pain for VSL#3 over placebo. Although one could debate the addition of a larger trial that represents the best of the included studies, we would like to point out that only two studies, focused solely on patients with diarrhea-predominant IBS (IBS-D). Of these two studies, only the study by Kim et al. was at low risk of bias for the outcome of abdominal pain. If we were to repeat the modeling exercise using only those trials of IBS-D patients, the addition of a fictive third trial with 30 patients in the VSL#3 arm and 33 patients in the placebo arm using

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Disclosures: None

mean and SD values identical to the best study would result in a pooled effect (SMD 0.40, 95% 0.02–0.78) showing a statistically significant benefit of VSL#3.

We agree with Dr. Enck's comments that the results of our meta-analysis do not support efficacy of VSL#3 in IBS with respect to individual endpoints for abdominal pain and stool consistency. However, our conclusion that further studies are required stems from our observation that the published trials have studied different IBS phenotypes. It cannot be assumed that probiotic effects on IBS symptoms will be adequately studied without careful patient selection and consideration of underlying pathophysiology. Further, although it may be true that quality criteria are often better for more recent studies than for older studies, we did not find this to be true in our evaluation for our meta-analysis. As described in our paper, three studies[,] , including the two "older" trials, were considered to have low risk for bias according to GRADE criteria.

Overall, we believe it is reasonable to conclude that VSL#3 is not universally effective for a heterogeneous group of IBS patients. However, we suggest that our findings emphasize the need for rigorously-designed trials based on mechanistic pathways to further clarify the role of strain-specific probiotic therapy in IBS.

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