Response to Mullie and Vankrunkelsven.

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We thank Dr. Mullie and Vankrunkelsven for their interest in our study.[1]

A concern was raised that the additional 50mg of maltodextrin in the placebo formulation may have confounded our results. Besides the studies mentioned in their letter, we also note the paper commented by Burns *et al*.,[2] which showed significant differences in terms of fecal macronutrient excretion and microbiota for resistant maltodextrin at a dose of 50g compared to equal amounts of maltodextrin.[3] Besides the absence of important adverse events for 50g of (resistant) maltodextrin,[3] this was also not expected for the 1000-fold smaller difference in maltodextrin between the placebo and verum in our study. Indeed, gastrointestinal (GI) adverse events were similar (3% vs. 15%, p=0.12) and no immunological or microbial changes from baseline were found for 350mg of maltodextrin,[1] which is similar to a previous probiotic trial in irritable bowel syndrome (IBS) using 1g of maltodextrin as placebo.[4] Even if previous studies suggested a relation between maltodextrin and bowel disorders, presence of IBS was never predominant in our study and overlap was comparable to epidemiological data. Also, reported IBS-prevalence at baseline was similar between groups (44% vs. 55%, p=0.33). Altogether, we do not believe that the inclusion of maltodextrin in placebo and verum had any contribution to clinical efficacy or adverse events.

We confirm the lack of quantitative dietary intake, as already acknowledged in the limitations,[1] and would like to point out the common inclusion of maltodextrin as placebo for dietary interventions in the referred meta-analysis.[5]

We would also like to clarify the inclusion of subjects with at least mild (≥ 1) baseline postprandial distress syndrome (PDS) scores, as predefined in the statistical analysis plan before database lock. Although arbitrary, the higher cut-off for clinical response (0.7) compared to the minimum clinically important difference (0.5) of the daily diary was chosen to maximize the potential gain over placebo. Even if inclusion of subjects with low baseline PDS-scores indeed reduced the gain over placebo, positive probiotic effects on symptom scores from baseline were confirmed in all subjects.

Immunological and microbial changes were also assessed in all subjects and associated with clinical efficacy.[1]

Despite the exploratory nature of this study, as repeatedly acknowledged in the methods and discussion, the results are of major interest for further trials and a first step to establish the position of these probiotics especially considering their safety and beneficial immune and microbial effects.

References.

1. Wauters L, Slaets H, De Paepe K, et al. Efficacy and safety of spore-forming probiotics in the treatment of functional dyspepsia: a pilot randomised, double-blind, placebo-controlled trial. *Lancet Gastroenterol Hepatol*; 6(10): 784-792.

2. Burns GL, Hoedt EC, Keely S. Spore-forming probiotics for functional dyspepsia. *Lancet Gastroenterol Hepatol* 2021; 6: 772–773.

3. Baer DJ, Stote KS, Henderson T, et al. The Metabolizable Energy of Dietary Resistant Maltodextrin Is Variable and Alters Fecal Microbiota Composition in Adult Men. *J Nutr* 2014; 144: 1023–1029.

4. Pinto-Sanchez MI, Hall GB, Ghajar K, et al. Probiotic Bifidobacterium longum NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome. *Gastroenterology* 2017; 153: 448-459.e8.

5. So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr* 2018; 107: 965–983.