73521-Answering Reviewers

The authors would like to thank the reviewers of our manuscript for their comments. Please find hereunder a point-by-point response to each of the issues raised in the peer review report and within editorial's office comments.

Reviewer's comments	Answer/Changes
However, two revisions needed regarding their conclusions. Authors used ITT analysis, but the % of responders are not correct. They reported %Responders in probiotic (n=101, 45.1%) and placebo (n=74, 33.9%) with p=0.017, fisher's test (which is not appropriate, should use Chi). No denominators for these calculations were given in the text. If ITT denominators are used (Fig 1), these results differ: % responders in probiotic (n=101/230, 43.9%) and placebo (n=74/226, 33.2%, with p=0.02 from chi squared).	The test used was a Chi2, the error has been corrected across the manuscript; methods (2.7); results (3.3); figure 3; supplementary figure 1. The authors confirm the percentage of responders are correct, the denominators are the number of subjects with available data. The denominators are now given in results section 3.3.
The primary outcome (AUC for pain score) is reported as "A more important but nonsignificant difference in AUC for..." How can this result be MORE important, when it is NOT significant (p=0.10). Authors should revise this as a non-significant difference finding.	Revisions have been made across the manuscript: abstract; results (3.2)
Another significant finding was the improvement in overall quality of life score (Fig 4), but it would be helpful to provide the raw data in the sentence in the text, not just giving a p-value and showing it in a Figure. Provide overall means in text please.	Estimated differences have been included in the text.
Safety data. This is an important outcome of any RCT and you need to provide the actual number of patients developing at least one AE by group in the text, not just a p value. It would be helpful to also provide a table with the description of the types of AEs that developed in Supplementary data.	Table 2 has been added to provide the number of subjects with at least one adverse event for each term of severity and for adverse events whose relationship with the study product or with the research was "not excluded". Supplementary table 3 has been added to provide description of the adverse events by body system.
Delete Figure 5. Not informative.	Figure 5 provides IBS-QoL scores in abdominal pain responders in comparison with nonresponders. This analysis was performed to provide a more accurate understanding of the overall impact of diet supplementation with this probiotic on daily function of responders. The authors believe this Figure is important to illustrate results presented in paragraph 3.4.
Also, please remove findings from your headings.	Findings have been removed from the headings.
Consider revising your title (last word should be	Title has been revised accordingly.

trial not study).	
In INtroduction section (paragraph 3), you cite four references when describing 3 RCTs done for I-3856 & IBS. Remove #21 as Cayzeele-Deh. is a meta-analysis and NOT a RCT. You will need to renumber your references.	For more clarity, the 3 references of RCTs and the reference of the meta-analysis are now cited separately.
Why did you not include the RCT by Al Helo 2019?	This RCT has not been published in a peer-reviewed scientific article and we therefore have decided not to consider this study which does not provide additional information to the literature on *S. cerevisiae* CNCM I-3856.

Editorial Office's comments	Answer/Changes
Science editor	
However, there are concerns regarding the statistical methods used and the correct interpretation of the results (please see comments from reviewer 1) as also inconsistencies with prior clinical trials findings on the beneficial effect of probiotics on the gastrointestinal symptoms (such as bowel movements, bloating) that can be addressed in the discussion paragraph. The explanation based on high placebo rates in previous studies may not be the best one. Rather, patient population characteristics (more severe abdominal pain at the baseline) may be entertained.	Comments from reviewer 1 have been answered (please see above). Inconsistencies with prior clinical trials findings have been addressed in the discussion paragraph (*The effect of S. cerevisiae CNCM I-3856 on gastrointestinal symptoms*). The explanation based on high placebo rates is related with the patient population characteristics (and particularly the more severe abdominal pain at baseline), the corresponding part of the discussion has been further refined to provide clearer explanation: "*In contrast with previous findings, no significant between-group differences were observed in the AUC for gastrointestinal symptoms. Although the clinical studies conducted on S. cerevisiae CNCM I-3856 in IBS present consistent designs, a significant change here is the use of Rome IV criteria to select the participants. A worldwide comparison of IBS prevalence by Rome IV and Rome III diagnostic criteria demonstrated that individuals diagnosed by Rome IV criteria exhibit higher IBS severity. Consistently, a higher level of abdominal pain was reported at baseline in this study than in previous clinical trials conducted on S. cerevisiae CNCM I-3856. Among factors associated with response to placebo in IBS-C, higher baseline symptom severity was reported as an important predictor of placebo response.*[40] *Differences in the studied population could therefore have contributed to the lower between-group size effect reported in this study."*
Additional information on adverse events	Additional information on adverse events have

related to the use of S cerevisiae CNCM I-3856 are important to decide their utilization in clinical practice.	been included.
Company editor-in-chief	
Patient population: It is important to well define the study population . The conclusions of the clinical trial can be influence by the patient population, inclusion and exclusion criteria and/or randomization. For example, I would like to know how the clinical settings were decided (if any criteria) and which ones are they. This is important when changes to clinical practice are implemented, as these findings may only fit a specific population.	The characteristics of the study population are defined in paragraph *2.1 Study population*. The authors do not identify which additional information could be expected in this paragraph.
With regards to the statistical analysis, there are many questions on statistical methods used. For example, why Fisher test (usually used for small sample size) and not chi square ?. As pointed by the reviewer 1	Comments from reviewer 1 have been answered (please see above).
Results: As the authors mentioned there is a high placebo response in this clinical trial, that is indeed seen with functional disorder, but also associated with a certain anxiety related to interpretation of these results. It is important therefore, to include more details about the patient population including a possible explanation of the higher level of abdominal pain tat the baseline than patients included in other studies.	Possible explanation of the higher level of abdominal pain at baseline in comparison with patients included in previous studies is given in the discussion: "*although the clinical studies conducted on S. cerevisiae CNCM I-3856 in IBS present consistent designs, a significant change here is the use of Rome IV criteria to select the participants. A worldwide comparison of IBS prevalence by Rome IV and Rome III diagnostic criteria demonstrated that individuals diagnosed by Rome IV criteria exhibit higher IBS severity.*"
Furthermore, in the discussion paragraph, the authors invokes the high placebo effect noted on prior clinical trials using probiotics as an explanation of the positive effect on gastrointestinal symptoms and lack of effect in the current trial. In fact, if that will be the case, we will see contrary results.	This is not the hypothesis raised by the authors. Higher baseline symptom severity was reported as an important predictor of placebo response. Therefore, the higher level of abdominal pain observed at baseline in the present study may lead to a higher placebo effect which could have contributed to the lower size effect reported in our study.
Safety: needs a detailed table with side effects.	Additional information on adverse events have been included.

73521-Answering Reviewers_Round 2

The authors would like to thank the reviewers of our manuscript for their comments. Please find hereunder a point-by-point response to each of the issues raised in the peer review report.

Reviewer's comments	Answer/Changes
1. In section 3.4 on Quality of Life (and throughout text). Please define the risk measure (not just giving the p value and CI), because the readers need to know of this is SMD, OR, etc.	The manuscript has been revised accordingly. Standardized Mean Deviation have been added to section 3.4, supplementary table 1 and supplementary table 2.
2. Please provide the QoL score FOR EACH GROUP by week 8 in the text and not just in Figure. Probiotic QoL score by week 8 (~78 +/- std dev) vs placebo (~76 =/- std dev) with p=0.047.	The QoL score for each group by week 8 has been added.
3. For safety data, your numbers in two table not match. For example, Supple Table 3 provides "any AE" for probiotic (109/230, 47%) vs. placebo (87/226, 38.5%), but from Table 2 adding AE (mild to severe) gives us a total of 138/230, 60%) for probiotic and 108/226, 47.8% in placebo. These two totals should match, but they do not. Explain or correct.	Table 2 provides the number of subjects with at least one adverse event for each term of severity. A subject may have experienced several adverse events and it is therefore normal that the sum of the number of subjects with at least one adverse event for each severity does not match the number of subjects presenting at least one adverse event given in Supplementary table 3.
4. In Table 2 the first two rows are not clear "...relationship not excluded..." What does this mean? please add clarification to Methods (section 2.7) and in Table 2 footnote.	A causality assessment has been performed for each adverse events in compliance with the ICH Guideline for Clinical Safety Data Management. There is currently no standard international nomenclature to describe the degree of causality (attributability) between an investigational product and an event. The causality of all cases judged by the investigator as having a possible relationship with the study product or the research procedure (act, method, etc.) were evaluated as "not excluded". The term "relationship" has been used as synonym of "causality". The term "relationship" has been replaced by "causality" in table 2 and in Methods (section 2.7 Safety analyses).
Please re-provide the original figure documents. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes; For line drawings that were automatically	The original figures with editable text and with coordinate of each points has been provided using Powerpoint.

generated with software, please provide the labels/values of the ordinate and abscissa in text boxes; Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.	
2. Please reprovide the copyright license agreement that autographed by all the authors themselves.	Each authors have given their agreement and signed the copyright license either electronically or by hand. The copyright license agreement has already been shared.
3. Please reprovide the CONSORT 2010 statement and Clinical trial registration statement refer to the template.	The consort 2010 statement and the clinical trial registration statement have been filled and shared.