

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73521

Title: *Saccharomyces cerevisiae* CNCM I-3856 in IBS with predominant constipation: a randomized, placebo-controlled clinical trial

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05329903

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: France

Manuscript submission date: 2021-12-22

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-22 16:34

Reviewer performed review: 2021-12-23 23:08

Review time: 1 Day and 6 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

1. Overall, an interesting article on a RCT of a probiotic (well described) *S. cerevisiae* CNCM I-3856 for IBS. This trial focuses on one subtype of IBS (IBS-C) only, which the prior 3 RCT of I-3856 enrolled mixed types of IBS and only one reported IBS-C subgroup efficacy. This RCT also looked at quality of life and other outcomes of IBS. Hypotheses confirmed. 2. Quality and importance. This study used a specific strain of probiotic that is well studied and has good mechanism studies. 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 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. The data shows the change in abdominal pain scores do NOT significantly differ for the probiotic vs placebo. However, there is still a significant finding for their other outcome measure (% responders). 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. 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. Delete Figure 5. Not informative. Also, please remove findings from your headings. Give the results in the text, not in the subheadings! Consider revising your title (last word should be 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. Why did you not include the RCT by Al Helo 2019? Otherwise, good figures and tables.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 01488602

Position: Editorial Board

Academic degree: AGAF, MD, PhD

Professional title: Full Professor, Professor

Reviewer's Country/Territory: Romania

Author's Country/Territory: France

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Reviewer chosen by: AI Technique

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Reviewer performed review: 2021-12-26 09:11

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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**Peer-reviewer
statements**

Peer-Review: [☒] Anonymous [☐] Onymous

Conflicts-of-Interest: [☐] Yes [☒] No

SPECIFIC COMMENTS TO AUTHORS

This is a correct study on the effect of supplementation with *S cerevisiae* vs placebo in IBS-C. Methodology is correct. However this ms. is not able to solve the problem of IBS-C pain, as control group is on placebo and not on other probiotics; we cannot exclude the possibility that subjects in trial may use including functional food

RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Peer-review model: Single blind

Reviewer's code: 05329903

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: France

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Reviewer chosen by: Han Zhang (Online Science Editor)

Reviewer accepted review: 2022-03-01 02:02

Reviewer performed review: 2022-03-01 20:43

Review time: 18 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Peer-reviewer	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you for revising your manuscript. There are still a few outstanding issues. 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. 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. 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. 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. Otherwise, ok.