Round 1

Dear WJGPT,

It is our privilege to accept the EIC's invitation to transfer our manuscript (No.88566) from WJG to WJGPT for publication consideration. We revised our initial submission to the best of our ability. Criticisms around a study placebo arm, study duration, and lack of objective biological assay measures cannot be reconciled retrospectively, but we do address them as study limitations in our Discussion. We also used the *Reference Citation Analysis* tool to help us review additional possible articles of relevance. We look forward to future correspondence.

Best Regards,

Samantha Niles

Responses to Reviewers

Reviewer #1:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade A (Priority publishing)

Conclusion: Rejection

Specific Comments to Authors: By means of the logic, methodology and use of indices this is a well-designed study. The title is compatible with the manuscript. However the duration, lack of placebo and different interfernce of IBS support and drugs (ie. rifaximin) make the approach debatable. Since the product)Enterade-trademark) is in a commercial status, the study had to be placebo controlled. In such a commercial product study such an observational, real-life data pattern may be questionable. Thus study had to include Calprotectin, anti tissue transglutaminase IgAi Total-IgA, anti-CdtB and anti-vinculin antibodies, differential diagnosis supported by upper and lower endoscopies and biopsies. Also, 2 weeks is not sufficient to conclude a beneficial effect. The follow-up period shouldn't be less than 12 weeks and preferably it may be 6 months. Drawing a result without a placebo controlled double blind randomised trial in such a study may not give a reliable conclusion. Despite those caveates, thank you for this high-level well-written manuscript.

Response: *We thank the reviewer for their input on our paper. We agree that our study conclusions would be stronger and more definitive had we conducted a randomized, placebo-controlled study that included blood and fecal measurements associated with IBS-D. However, this was an initial study to primarily investigate the tolerability of a novel medical food as adjunct therapy for people suffering from*

IBS-D without relief using the standard of care. We acknowledge and address all the reviewer's concerns in the Discussion of our paper so that readers can interpret our findings with appropriate caution.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Major revision

Specific Comments to Authors: 1.The components of the amino acid based medical food beverage in this study included should be described more specific.The paper should not just list the names of ingredients. And should specify whether the medical food beverage is self-made or purchased separately. 2.Both observation and control groups are necessary. The authors designed only one group during the conduct of this study. Further explanation is required. 3.This paper does not explain adequately that the amino acid based medical food beverage has a good efficacy on IBSD. Patients with IBSD are often associated with anxiety, depression, and other adverse emotions due to abnormal expression of inflammatory factors and VIP Levels. A key issue is the lack of above pharmacodynamic indicators. 4.The author may need additional experiments.Only IBS-SSS method is not enough, IBS-QOL and HAMD The can also be used to evaluate the function of the amino acid based medical food beverage. 5.Did the subject take any other medications in addition to the beverage? If so can it be clarified whether the beverage had a therapeutic effect or whether the other medication had a therapeutic effect, the author need to explain.

Response: *We thank the reviewer for their time and recommendations for improving our paper. 1 & 3. We now provide more details about the medical food studied. 2. We agree that our study conclusions would be stronger and more definitive had we conducted a randomized, placebo-controlled study that included blood and fecal measurements associated with IBS-D. However, this was an initial study to primarily investigate the tolerability of a novel medical food as adjunct therapy for people suffering from IBS-D without relief using the standard of care. We acknowledge and address the reviewer's concerns in this regard in the Discussion of our paper so that readers can interpret our findings with appropriate caution. 3 (only). We respectfully feel that our data 'do' demonstrate efficacy using nearly every PRO available and the benchmark of 'responders' by FDA drug-standards. It is our study design that limits the interpretations, which we acknowledge (#2). 4. We now address future experiments since we cannot do*

so retrospectively. 5. Yes, this is mentioned throughout as 'standard of care' and that our product is adjunct dietary therapy.

Reviewer #3:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The two principle concerns raised seem to be: 1. The intervention period is only two weeks, which is too short a time, and 2. Whether the beverage has been approved for human use and whether its safety has been verified. 3. Please provide the batch number of the beverage. 4. The observational measures are too simple, too subjective (questionnaires on patients' self-perception may bias the results), and have no objective or quantitative basis. It would be fine if we had analytical data on the gut flora.

Response: *We thank the reviewer for their time and expert opinions on our manuscript. 1. We agree that our study was shorter than most nutritional intervention studies on IBS-D. We discuss both the limits and merits of our 4-week (2-week run-in and 2-week intervention period). 2. We provide and have added details concerning the regulatory status and safety of our medical food product, which is sold commercially in the U.S.A. 3. We have provided the batch number in the manuscript. 4. We agree that our study had limited observational measures of biological nature; however, all outcome measures utilized are validated and used as industry standards for evaluating IBS-D symptomology. We discuss both the limits and merits of the endpoints and outcome measures in the manuscript.*

Reviewer #3: The article deals with a interesting issue which concerns a lot of patients with irritable bowel syndrome. The stud is well organized. The number of patients is relatively high. The parameters are well set up. The results support the primary hyypothesis. I believe the conclusion of the study provides a benefit for patients and doctors who are dealing with diarrhea issues due tto irritable bowel syndrome.

We thank the reviewer for their insights and positive feedback.

Round 2

Dear WJGPT,

We are grateful for the opportunity to respond to additional reviewer comments (reviewers 1-3) and to revise and improve our manuscript further. For responses and inline edits to our original review (reviewers 4-6), please see the response letter that accompanied our transfer submission. We look forward to future correspondence.

Best Regards,

Samantha Niles

Responses to Reviewers

Reviewer #1: This is a study on a commercial multi-ingredient amino acid based oral rehydration solution in IBS-D patients who were taken diagnosis by a wide range of multicenter sources. This manuscript may increase the awareness and importance of supportive diets besides classical treatment of IBS-D. Despite to caveates mentioned previously, a sentence expressing the inability to decide the main ingredient primarily responsible from the beneficial effect have to be added. Since this is somewhat a shotgun therapy, besides AAs , electrolytes and vitamines may ameliorate the QoL. Among ingredients, there are contradictory results of Zinc on IBS, beneficial or irritating which may ne the cause of side effects. Some omitted literature evaluating Enterade should also be discussed.

Response: *We thank the reviewer for recommending improvements for clarifying our manuscript. We have added language to describe why we believe that our amino acids are principally responsible for the benefits observed. We also reference five enterade studies (references 18-22).*

Reviewer #2: This article summarises the central studies conducted in IBD settings using non-PEG preparations by discussing their results.It is very meaningful.

We thank the reviewer for their time in reviewing and remarking positively on our manuscript.