

Andrzej S Tarnawski

**Editor-in-Chief**

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Dear Editor,

We would like to thank you and the reviewers for the time and effort invested in reviewing our manuscript titled "Beyond the Gluten-Free Diet: Innovations in Celiac Disease Therapeutics" (Manuscript ID: 96898). We have carefully considered the constructive feedback provided and have made the necessary revisions to improve the quality of our manuscript.

Below is a point-by-point response to the reviewer's comments:

**Reviewer Comment 1:**

**"Chapter 1. Current Challenges in Celiac Disease Management: 'Secondly, gluten-free products, to be more tasty, are often high in fat and sugar content and low in fibers, vitamins, and minerals increasing, on one hand, the risk of obesity and metabolic syndrome and on the other the risk of deficiencies (16, 17)' Please consider adding to this part also a theoretical risk for mycotoxins from corn and arsenic from rice exposure in those who have a diet restricted only to few carbohydrate sources. Please consider these references for these issues PMID: 24694905 and PMID: 28223206."**

**Response:** We appreciate this suggestion and have incorporated the theoretical risk of mycotoxins from corn and arsenic from rice exposure in individuals with limited carbohydrate sources into the manuscript. The relevant references (PMID: 24694905 and PMID: 28223206) have also been cited in this context.

**Reviewer Comment 2:**

**"Different preparations of this enzyme are already available over the counter, but their ability to digest gluten peptides can be different and, in some cases, inferior to the pure enzyme (40). Few words of caveat should be written about the risk of CeD patients taking these over-the-counter medications at the time being."**

**Response:** We have added a cautionary note in the manuscript regarding the potential risks for CeD patients using over-the-counter enzyme preparations, highlighting that their effectiveness may not be sufficient to prevent gluten-related damage.

**Reviewer Comment 3:**

**“When summarizing data on the modulators of the tight junctions, a few words about a zonulin-independent constitutional alteration of the permeability in celiac patients and first-degree relatives of CD patients (PMID: 31921880 and PMID: 26535478) and an alteration of zonulin in the very early phases of celiac disease (PMID: 38062791) might be noteworthy to mention.”**

**Response:** We have included a discussion on the zonulin-independent constitutional alteration of permeability in celiac disease patients and their first-degree relatives, as well as the alteration of zonulin in the early phases of celiac disease. The relevant references (PMID: 31921880, PMID: 26535478, and PMID: 38062791) have been cited accordingly.

**Reviewer Comment 4:**

**“Please rephrase: 'This study aims to evaluate the efficacy of TAK-101 in reducing gluten-related symptoms and immune activation in adult CD patients following a GFD undergoing gluten challenge and WAS expected to be completed by May 2024.'”**

**Response:** The sentence has been rephrased for clarity and now reads: “This study aims to evaluate the efficacy of TAK-101 in reducing gluten-related symptoms and immune activation in adult CD patients following a GFD and undergoing a gluten challenge, and it was expected to be completed by May 2024.”

**Reviewer Comment 5:**

**“Please rephrase: ... 'its primary completion date was expected in May 2024 (Table 2).’”**

**Response:** The sentence has been revised as requested and now reads: “...its primary completion date was expected in May 2024 (Table 2).”

We believe that the revisions have addressed all the reviewer’s comments and have improved the manuscript's clarity and content. We are grateful for the valuable insights provided by the reviewer and look forward to your feedback on the revised manuscript.

Thank you for considering our revised submission.

Sincerely,

Sara Massironi, MD, PhD

On behalf of all authors