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# PEER-REVIEW REPORT

**Name of journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 79880

**Title:** Glucagon-like peptide-2 analogues for Crohn's disease patients with short bowel syndrome and intestinal failure

**Provenance and peer review**: Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02941507
**Position:** Editorial Board
**Academic degree:** FACG, FEBG, MD, PhD
**Professional title:** Associate Professor, Staff Physician
**Reviewer's Country/Territory:** Greece
**Author's Country/Territory:** Italy

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**Reviewer chosen by:** AI Technique
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**Reviewer performed review:** 2022-09-11 11:27
**Review time:** 20 Hours

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| **Scientific quality** | [ ] Grade A: Excellent [ Y] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ Y] Yes [ ] No |

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| **Peer-reviewer statements** | Peer-Review: [ ] Anonymous [ Y] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

This is an interesting review of the data concerning the treatment of patients with Crohn's disease who developed short bowel syndrome with intestinal failure due to surgical resection of the intestine, using Teduglutide and apraglutide. My suggestions are the following: • Is there literature information regarding the effect of the activity of the underlying Crohn's disease on the therapeutic effect resulting from the administration of the drugs? • What is the effect of the use of biological agents, either as induction or as a maintenance treatment, on the therapeutic effect resulting from the administration of the drugs? • What is the evolution of the patients after stopping the treatment? For how long can they be administered? • A more complete description of the pathophysiological actions of these drugs would probably be useful. • Finally, I wish for the sake of the readers that the authors would express more clearly their opinion as to the utility of these drugs in clinical practice. • A table listing details of existing clinical studies, e.g. drug dosage, clinical outcomes, laboratory data, and major side effects, would be helpful to readers. • Regarding the cause(s) of the reduction in the surgical rates of patients with Crohn's disease (Conclusion part of the paper), I would suggest the authors mention the following (Dittrich et al Inflamm Bowel Dis 2020;19:1909-16): "…Although anti-TNF therapy seems to play a role, the decrease in surgical trends is likely multifactorial, owing to a decline in smoking trends, earlier diagnosis, earlier treatment, improved patient education, and changes in clinical practice…"

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**Provenance and peer review**: Invited manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 05122223
**Position:** Peer Reviewer
**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Germany

**Author's Country/Territory:** Italy

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| **Scientific quality** | [ Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ Y] Yes [ ] No |

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| **Peer-reviewer statements** | Peer-Review: [ ] Anonymous [ Y] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

This is an excellent review on SBS, SBS-IF and GLP-2 pharmacotherapy, technically sound, and very well written. Definitely fun to read and very informative. The introduction and the positioning of the special, but common situation of CD-patients with SBS-IF, is well achieved, thoroughly reviewing the literature. The paragraph on the special focus is technically clear and well referenced, citing the current literature and describing the most recent and most important findings. One little suggestion could be a paragraph or a statement on what further research is needed for this certain population. Effectiveness of GLP-2-analogues is mentioned, but would be expected. Maybe one could ask, if GLP-2 analogues are safe in CD-patients with clinically controlled, but subclinically active disease – some clinicians are worried of "potentiating" the inflammation, but maybe this is not the case, who knows…. Some Minor suggestions: Minor: - Introduction: reference should be made that this review is focused on adult SBS – not pediatric SBS. - CD22.4 % - brackets are missing - The cited numbers in the last paragraph on the first page of the introduction -although from a very large cohort - may not necessarily reflect all IF-populations – compare with the intestinal transplant registry report from 2015 – the largest fraction in the US-cohort were ischemia-SBS, this should be discussed or the numbers attenuated. - Ref [5] is not appropriate – a basic research study from mice is cited, but human SBS is referred to – Warner 2016 CMGH may be a better reference. - Ref [6] is not appropriate – relates to GLP-2-action, but endogenous adaptation is described – also Warner 2016 CMGH may be a better reference. - "possible severe dehydration" – this statement is not needed – the opposite may be the case in many situations due to ample volume resuscitation. - "Approximately 90% of the

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intestinal adaptation described above occurs in this phase." This is not referenced and not covered by data (90% of what?). - "oral nutrition alone" – can already be introduced as "oral autonomy", because this term is an important technical term in the field and also used later. - "The most frequent and invalidating symptom is diarrhea due to…" – in most SBS-IF-patients, diarrhea is a problem, but not necessarily the "invalidating symptom". - Ref. [7] cites IBS-diarrhea, which is not applicable in the SBS-situation. Ref. [10] should be removed, because it is not applicable to the SBS-situation. A better citation for the bile acid problem could be "Hvistendahl et al. 2022 JPEN - Bile acid-farnesoid X receptor-fibroblast growth factor 19 axis in patients with SBS…". For the transit problem, another reference could be "Kunkel et al. 2011 Neurogastroenterol Motil. - Ref. [11] is cited at the statement that particularly patients with PN have high prevalence of gall stones – while it may true, it is not related to PN, this should be stated more clearly. - The mechanism for oxalate stone formation is not completely deciphered, and it is not clear if increased passive diffusion is the only mechanism involved, this should be phrased a little more cautiously. One reference for this could be "Saunders et al. 1975 Gut - Regional differences in oxalate absorption by rat intestine…" One important study has recently re-evaluated the prevalence and incidence of nephrolithiasis – "Yang et al. 2019 Ann Nutr Metab - Risk Factors for Nephrolithiasis in…", this study should be cited in this context. - "refractoriness" is not preferred terminology - "Patients with perianal disease have more bowel resections" cannot be maintained – it is probably a subgroup effect as described in the paragraph before – the p-phenotype is associated with higher risk of resection, because the disease phenotype is more severe. But p-phenotype also may exist independent of resections – In our IBD practice, we do have a very large cohort of perianal disease, but not many - if at all - bowel resections. - "greater age" – age is great, but should be termed "higher age" - "multidisciplinary team" – careful with the terminology here. If strictly only medical disciplines are meant, this would rather be

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termed “interdisciplinary”, but then technically not involve a “nutritionist”. If indeed “multidisciplinary” is meant, this would also involve special pharmacy, home care (infusion) nurse, stoma nurse, rehabilitation … - “dietary manipulation” – not really manipulation, but maybe rather intervention? - Ref. [29] pediatric study is linked – maybe rather an adult study? - CRBSIs “the most feared complications” – I would fear IFALD/PNALD much more, although of course it is not as common as CRBSIs. - “CRSBI”

“CRBSI” - “Up to 32% of patients receiving HPN can develop microcytic or ….” This number is very much context-specific and should either be put in context of the cited ref. [52] or the statement on anemia should be phrased more broadly - “Intestinal absorption may also be increased by hormonal manipulation[56]–[58]. Refs [56] and [57] do not show this, ref. 56 shows the effect of IGF-1 on mucosal morphology – it could be cited with a statement on mucosal hypertrophy/proliferation. Ref. [57] discusses the anatomy of SBS-types, this could be cited in the introductory paragraph. A possible referencesfor improved absorption due to GLP-2-therapy could be “Reiner et al. 2020 Dig Dis Sci - Teduglutide Promotes Epithelial Tight Junction Pore…”. - “GLP2” -> “GLP-2”, should be always used. - “One of the first open-label trials on teduglutide was carried out and published in 2005.” Why not “The first open-label trial on teduglutide was published in 2005”. - “Sixty-three percent” -> 63%, or do not use at the beginning of the sentence. - 20% -> missing ) - “Recently, new GLP2 analog molecules have been studied”, references should be given, and references could cite elsiglutide and dapiglutide as well, although mostly preclinical data are available on these novel GLP-2 analogues. - “apraglutide have also been studied in piglets. In this case, the two molecules showed similar results: the intestinal growth appeared to be a lasting outcome of treatment with long-acting GLP-2, persisting at least 7 days after the discontinuation; in contrast, mucosal hypertrophy appeared to regress 7 days after the end of treatment with both agents[77].” This finding must be interpreted with caution – I suggest not to spell this finding out so

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clearly here, because the experimental setup in the paper [77] is not 100% clear as to when the last dose before treatment discontinuation was given. Also, the discrepancy between longitudinal and horizontal growth is not entirely clear. - Phase 2 should be spelled Phase II. - Language/style issue as above: eighteen patients -> 18 - “before the beginning of therapy” -> “before the beginning of teduglutide therapy” - “438.825 and 584.825 μm” -> avoid too many post decimals, maybe avoid the original numbers, the 33% may suffice. - Ref [89] is an important and probably the most sophisticated study on the topic to date. It should also be discussed if the Crohn remission/response rates were due to reduced diarrhea as an item on the CDAI, which was used for the assessment clinical response/remission. - Glepaglutide should also be mentioned under keywords.

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**Provenance and peer review**: Invited manuscript; Externally peer reviewed

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**Reviewer's code:** 00503405
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**Academic degree:** MD, PhD

**Professional title:** Senior Lecturer, Senior Scientist

**Reviewer's Country/Territory:** Hungary

**Author's Country/Territory:** Italy

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| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[Y] Minor revision [ ] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [Y] No |

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| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

In the review article by Pizzoferrato et al. the authors the current clinical and pathophysiological knowledge about short bowel syndrome, focusing on Crohn's disease, moreover, they summarize the experiences from clinical studies about GLP2 analogues in SBS. The topic is of great clinical importance. The review is well structured, all the crucial data are mentioned and discussed. Several recent articles about the topic is not referred (e.g.,J Invest Surg. 2018 Jun;31(3):243-252. doi: 10.1080/08941939.2017.1294217. or J Invest Surg. 2018 Jun;31(3):253-255. doi: 10.1080/08941939.2017.1300715.). I suggest to discuss the relation of GLP2 analogues to intestinal epithelial stem cell functions together with their possible future side effects. After minor revision I suggest accepting the manuscript for publication.

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**Title:** Glucagon-like peptide-2 analogues for Crohn's disease patients with short bowel syndrome and intestinal failure

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| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
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| **Re-review** | [Y] Yes [ ] No |

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| **Peer-reviewer statements** | Peer-Review: [ Y] Anonymous [ ] Onymous<br>Conflicts-of-Interest: [ ] Yes [ Y] No |

**SPECIFIC COMMENTS TO AUTHORS**

Change the tittle: it is not "new therapies" but GLP2 analogs A table with all, the short (often only clinical case) and indirect, results of GLP2 analogs in Crohn's disease will be very useful for this article ref 81: is daily and not weekly for glepaglutide?