Response to Reviewers for Manuscript:

'OUTCOMES OF A NATIONWIDE DRUG SHORTAGE OF BALSALAZIDE REQUIRING SWITCHING TO OTHER AMINOSALICYLATES IN PATIENTS WITH ULCERATIVE COLITIS'

Reviewer 1:

General comments Dr. Daniel R van Langenberg, et al. investigated. The article is informative. The reviewer has some comments.

Comments 1) The authors described clinical or endoscopic disease activities were no significant difference between two groups, there was a higher rate of hospitalization in 5-ASA group compared to balsalazide group for 5 years. Please explain how these differences in rates of hospitalization would be shown in two kinds of 5-ASA in spite of same 5-ASA.

Authors' response*:* We agree that at first glance this might appear a discrepancy, but the fact is that the clinical and endoscopic activity measures were done at specific timepoints ie at 3 and 5 years, whereas the rate of hospitalisations (and other variables presented in Table 2) in each group were cumulative across the five years of follow-up. Hence it is likely that individuals could have had a flare of colitis in between the disease assessment timepoints resulting in hospitalisation but then regained remission prior the next timepoint.

As for the difference in hospitalisation rates, we surmise that this reflects disease stability over the long term in those on balsalazide, who clearly responded and remained in stable remission on the drug, compared to those who switched to alternative 5-ASA and were more prone to flares resulting in hospitalisation from time to time. At least anecdotally we believe that not all 5-ASA agents are equal for a given patient and based on their various formulations that an individual may achieve better outcomes/ less side effects on one versus another 5-ASA.

2) The authors describe side effects after switched to 5-ASA, the reviewer thinks abdominal pain would be one of the recurrent symptoms in UC patients. Nausea was shown one of two patients, the authors showed the rate was 50 %. The authors should show the rate of one of 31 patients.

Authors' response: We agree that abdominal pain could well be UC related, but it also is a reported side effect of 5-ASA agents and there was a preponderance especially in Mezavant recipients. With relation to the nausea and other side effect percentages in Figure 2, we have corrected these with percentages to reflect the denominator of the total 31 patients – thanks for pointing this out.

3) The definition that the authors switched back to balsalazide was uncertain.

Authors' response: To clarify this, a statement has been added to the first paragraph of the Methods section: "After supply of balsalazide resumed, the occurrence of switching back to balsalazide was solely at the discretion and agreement of the patient and treating clinician." It was beyond the scope of the study to exactly determine why patients and their clinician decided to return back to balsalazide versus continue with the alternative 5-ASA they had

been switched to in the shortage. However as depicted in the Results in the paragraph under "Adverse events with substitution of balsalazide to alternative 5-ASA agent during shortage", 8 of the 12 patients who immediately returned to balsalazide after the shortage ended had experienced adverse effects from the alternative 5-ASA, so obviously this was a major factor in the reason.

Reviewer 2:

In my view, it is interesting to see how the authors made huge efforts to override the acknowledged several limitations of this study, including the observational design and small sample size which limit the ability to make definitive conclusions given potential bias, or ascribe causality. However, providing the obvious need for the studies related to this important problem, which may have also practical implication, this reviewer is ready to accept the background of the study.

Authors' response: We thank the reviewer for recognising that despite the limitations such as the observational design and relatively small sample size, the authors have addressed these and tried to minimise biases wherever possible, thus the study remains valid and of importance.

Consequently, assuming that the worsening can be indeed ascribed to the other medication used, and not to the spontaneous negative course of disease, the authors should provide a real hypothesis about "way", providing some clue for the worsening in a particular drug mechanism(s).

Authors' response: Given the limitations of an observational study and sample size, it was beyond the scope of this study to make strong conclusions about why there was higher rates of disease worsening and/or adverse effects resulting from switching from balsalazide to an alternative 5-ASA. Nevertheless in response to the Reviewer's comments, we have now included an extra sentence in the Discussion (see Page 17) to provide an hypothesis as to why switching to an alternative 5-ASA might result in disease worsening: "*One may therefore hypothesise that for a given individual, not all oral aminosalicylate preparations are equal and due to reasons including disparate tablet/ granule composition, delivery system, pharmacodynamics and phenotypic differences, switching between agents within class may result in improved/worsened disease control and/or adverse effects."*

Then, if possible, more comparison should be done for the similar situation in other countries. If so, this study can be a real basis for the further larger studies.

Authors' response: We believe this study provides a novel basis for further larger scale studies on the effect of drug shortages in IBD and other diseases. The role of this study was to raise awareness of the potential impact of drug shortage in chronic diseases like IBD.

Reviewer 3:

This is an interesting and innovative study. However, there are several short comings which have been acknowledged by the authors. Since this has been an island wide situation the authors should have done a multi centre study to get the required numbers. Also it is obvious that a continuous supply of drugs are necessary to treat patients.

Authors' response: We agree that a nationwide, multicentre study would be optimal to explore the effects of drug shortage further. However we disagree that a larger study just for the sake of larger numbers would necessarily change or dramatically enhance the outcomes of this study. Our numbers in this study were sufficient to demonstrate the potential impact and effects on individual patients of a sudden drug shortage and raise awareness of the readership to this growing problem.

Of course it is obvious and well known that continuous supply of drugs are necessary to treat patients, yet based on the lack of published data it is certainly not well known how drug shortages do occur frequently and can have major impacts in both clinical and commercial ways, which may be long lasting (ie years) as we have demonstrated in this study for the first time in IBD. Since we submitted this manuscript the authors have encountered shortages in H2 antagonists, pancreatic enzymes and cholestyramine in at least our country, which cause patients significant stress and can have significant health and quality of life impacts. Clearly we need to promote more awareness and more research into drug shortages and this study is one of the first few clinical studies worldwide in a chronic disease.