Name of Journal: *World Journal of Gastrointestinal Pharmacology and Therapeutics*

ESPS Manuscript NO: 32821

Manuscript Type: Frontier

Title: 5-ASA to maintain remission in Crohn's disease: Interpreting conflicting systematic review evidence

Response to reviewer comments:

Editor comments – With regards the comments on references, DOI and PMID / PMCID have been added, as have all authors. This is with the exception of appropriate references to none articles, including NICE guidance. There is one exception and that is the first reference. This is the key first report 70 years ago of 5-ASA drugs and whilst I have seen it as a print article I don't have it to forward. There are no DOI. It has been cited on other wjgnet journals. I hope this is acceptabe.

This is an interesting paper trying to identify the reasons for the differences seen in the use of 5-ASA as a way to maintain remission in Crohn's disease, depending on whether that remission was medically or surgically induced.

We thank the reviewer for these comments

Could the authors please respond to the following questions/comments? 1) In an effort to explain the differences between the medically and surgically induced remission cases and the use of 5-ASA to maintain those, the authors mention "It is therefore possible that in the post-surgical setting, the patient has been reverted to a more disease na?ve state within the remaining bowel, which due to pre-surgical medical management, is most commonly in a remission state. This issue of clinical heterogeneity between the patient groups may explain why post-surgery evidence demonstrates efficacy of 5-ASA agents." As reasonable as this sounds, one could counter argue that the patients that had to undergo surgery had a more advanced state of the disease (thus having complications necessitating surgery) and as such it would be less responsive to 5-ASA post-surgically.

This is a fair point and we have updated the text to mention, but also state that despite this opposing perspective, remission is the key and once a patient is in remission that advanced disease has been removed. Within medical studies defining remission with clinical criteria, the possibility of histological disease remaining exists. The following has been added:-

'In many of the medical remission studies, this has been defined using clinical criteria and so at an endoscopic or histological level, there may well be disease activity. A counter view may suggest that because surgical patients had more severe disease, they do not have more mild disease. However, the author maintains that given the combination of surgical resection of these diseased areas and pre-surgical medical management, it is still likely that they represent a group with a different level of disease activity to the medical induce remission cohort of patients. This issue of clinical heterogeneity between the patient groups may explain why post-surgery evidence demonstrates efficacy of 5-ASA agents.'

2) The authors mention that one way to deal with the differences in the length of remission between the different types of patients (in terms of how that remission was achieved) it may be useful to establish the severity of the disease with endoscopic or histologic scoring. Could the authors elaborate on the different types of disease severity based on these types of scoring, maybe with a table.

This is an interesting point, but I feel similar to the comments from the reviewer below, this would be moving outside of the remit of this paper as a frontier piece. As such scoring systems are established within the guidance cited and ubiquitous in the field, I think such a table would detract from the message of the paper.

3) The authors raise several methodological issues, even with Cochrane database papers, and it may be useful to elaborate a bit more on those, as this is an important point in this paper.

This is a very valid comment and highlights this section was not clear. Rather than suggesting limitations of Cochrane methodology, it proposes limitations of the per protocol analysis used in primary studies and the strength of the Cochrane approach. This is key and I have rewritten the section below to address this:

'For those who have considered the individual study data within the Cochrane review[16] it will be apparent that there is clearly a contrast between primary study conclusions of purine analogue efficacy and the meta-analysis performed. This is due to the intention to treat analysis performed in the review. A per protocol analysis would suggest superiority of purine analogues, in line with the individual studies. This is not the method used in the review for several Cochrane methodological reasons related to risk of bias from incomplete outcome data. Given the clearly pervasive problem with over a quarter of patients on purine analogues not able to continue due to side effects[16] this clearly demonstrates the limitations of per protocol analysis and supports this approach from Cochrane. This was worth comment as readers may have found this discrepancy concerning. The wider relevance of this intention to treat finding is to once again suggest that 5-ASAs are not necessarily the most efficacious therapy in Crohn's disease for either induction or maintenance of remission, but there is universal agreement on their good safety profile[7,8,11,14,15,16].'

General comments Dr. Gordon reported 5-ASA to maintain remission in Crohn's disease: Intepreting conflicting systematic review evidence. The article is informative and well-presented.

We thank the reviewer for these comments and support

The reviewer has some comments. 1. The author should show any tables or figures, then the reviewer can understand what the author would like to say most.

We recognise the comment, but as the article is a digest of the evidence, we don't feel specific tables or forest plots would add, rather they would detract from the readability of the article. These are all available open access within the Cochrane reviews. Instead, our goal was to clearly and concisely summarise in the text the broad findings and so we feel this would not be helped by tables.