Reviewer's report

Title: Lubiprostone ameliorates the cystic fibrosis mouse intestinal phenotype

Version: 2 Date: 17 July 2010

Reviewer: Hugo De Jonge

Reviewer's report:

The authors have responded adequately to most of the points of criticism raised by the reviewers and have modified their manuscript accordingly. Importantly, they have updated the list of literature references and adapted the Introduction and Discussion section resulting in a more balanced discussion of the many controversies in the lubiprostone research field. However a few points still need further attention:

1. p. 5 para. 3 (revised text): “However, at high concentrations, lubiprostone can also activate the CFTR Cl- channel”. The same statement based on incorrect quotation or untidily reading of the 2009 Gastroenterology paper by Bijvelds et al (ref. 23) can be found at several places in the recent review by Dr. Woods (ref. 19). In reality, the EC50 for lubiprostone activation of CFTR in T84 cells and in non-CF mouse and human ileal epithelium reported in the Gastro paper (e.g. see p. 982) is appr. 50 nM, i.e. not so different from the “less than 100 nM concentrations required to activate ClC-2-like channels” in ref. 39, the EC50 reported by Cuppoletti et al. in T84 cells (appr. 20 nM), and the EC50 of 43.5 and 31.7 nM in guinea pig small intestine and colon (ref. 24). The EC50 of 50 nM reported in ref. 23 is certainly far below a “potency in the micromolar range”, as erroneously stated in ref. 19. Therefore, CFTR activation by lubiprostone in the intestine is not an artefact of suprapharmacological dosages, but is likely to occur in patients undergoing oral treatment with this drug. In conclusion, the term “at high concentrations” is misleading and should be omitted from the text.

2. p. 5 para 3 (revised text): ref. 23 is also quoted for the suggestion that “lubiprostone-induced transport is completely CFTR-dependent”. This is only true for the Cl- secretory component of intestinal ion transport in the crypts, but certainly not for the NaCl and fluid absorptive component of transport in the intestinal villi. In fact, on p. 984 of ref. 23 it is suggested that lubiprostone, through its ability to trigger EP4-cAMP-PKA signalling, might inhibit electroneutral absorption of NaCl at the level of NHE3 and could therefore act anti-absorptive rather than pro-secretory in CF patients. Such a model might also help to explain the beneficial effects of lubiprostone reported in a recent case study (ref. 18). Therefore, the quotation that lubiprostone-induced transport is completely CFTR-dependent should be modified.

3. Author’s responses to referee 3, comment 1: It is still highly regrettable that the authors did not persue their original plans to study possible beneficial effects of in vivo lubiprostone treatment on survival of Ctrf/- mice from intestinal obstruction “for ethical reasons”. Even negative results would be very important for the field,
considering the controversies around lubiprostone action. But there is a fair chance that lubiprostone, either though CIC-2 activation (if Cuppoletti et al are correct) or though inhibition of salt and water absorption (ref. 23; see above) might increase the fluidity of the intestinal lumen and lower mortality by intestinal obstruction. The effect of lubiprostone treatment might be similar to the effect of crossing Cfr-/- mice with NHE3+/- mice (having lost ~50% of their salt absorptive capacity), resulting in a dramatic improvement of the CF phenotype (see Bradford EM et al 2009 Am J Physiol 296: G886-G898).

The authors have provided satisfactory answers to major points 2-4 and minor points 1-2.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.