Reviewer’s report

Title: Efficacy and Safety of a Novel Naltrexone Treatment for Dry Eye in Type 1 Diabetes

Version: 1 Date: 17 Sep 2018

Reviewer: Sarah Atkinson

Reviewer's report:

This is very interesting paper, highlighting the use of naltrexone with an alternative delivery system than that previously used. There are some minor comments which may need to be addressed before publication, these are as follows:

1. The prevalence of Dry Eye Disease (DED) is higher in females than in males, does this have ramifications for the sex of the animal used within the study?

2. Within the Background, Lifitegrast is mentioned as a primary prescription treatment for DED, it might be worth including the efficacy of this treatment (if possible) to provide more evidence for the need for a new drug.

3. A sentence needs to be included on why it was necessary to replace the antibiotic-containing carrier Vigamox, within the Background section

4. Within the methodology section, the age of the animals used has not been included, this would be helpful to confirm that the age between different experimental animals is consistent.

5. Within the treatment section of the methodology, it would be helpful to provide a comparison of doses between NTX-001 and NTX dissolved in Vigamox, eg. NTX-001 is in ug/ml and NTX dissolved in Vigamox is in M. This could be provided elsewhere in the manuscript if more appropriate.

6. On page 7 of the manuscript, within the methodology, it states 'Following cessation of treatment, tear volumes were measured daily in a subset go rats to assess when the dry eye returned', it would be useful to have this subset defined, for example numbers and which experimental groups?

7. Was Intraocular pressure only measured at the termination of the study? It may have been useful to measure it earlier to define a baseline.

8. Is 3 a sufficient sample size for the group of T1D rats which received buffer?
9. Figure 3 and 4 need to be re-formatted as the labels are unclear.

10. Within the figures, considering using alternative patterns or legends within the graphs that make it easier to differentiate between groups.

11. Within the results section, it is not clear where the 'Normal' measurements have come from, particularly as the 'Normal' measurements are so much higher than those of the untreated T1D eye.

12. How is 'appeared to have normal vision defined' for the rabbit experiments? It may be useful to include this within the manuscript.

13. Would it be useful, to include come images from the H&E staining? Particularly where features described in the text are demonstrated.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

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