Reviewer’s report

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

Version: 1 Date: 09 Sep 2018

Reviewer: Alvin Munsamy

Reviewer's report:

Title: Consider adding "...treatment for dry eye in diabetes."

Full title: Consider revising "...Diabetic Dry eye" to "...Dry Eye in Type 1 Diabetes"

Abstract:

pg 2; line 22: specify Schrimers1 or 2?

Background:

p4; line 7: "Dry eye disease(DED)" specify if its correct to say "Tear Defecient Dry Eye (TDDE)" as opposed to "evaporative dry eye(EVE)"

p4;line 14: "If left untreated DED may cause pain, corneal ulceration and potential loss of vision"- consider adding the word "severe DED" as not all dry eg mild directly translates to this.

p4; line 9: "5-34%"; I see this was referenced but can you alert this reader where in general ; like "North America" which is what I can grossly infer from the author and publication names??

p4; line 22-24: ".....(in particular diabetes)" consider "...(including type 1 diabetes)"

p4 ; line 34: consider changing "[3.5-9] to [3, 5-9]

p4; line 41: "...primary prescription....clinical dry eye...Restasis...." : I humbly beg to differ that restasis is the primary prescription treatments; "primary" implies the first line line??; secondly "clinical dry eye" in the context of restastis consider ....” clinical TDDE dry with inflammatory etiology" which sounds more accurate.

p4; line 51: " ....lengthy period of application..." please specify what is "lengthy" so it may imply when reading the results of Naltrexone the reader will straight away know in comparison.

p4; line 58: "..through punctal plugs or surgical treatment through occlusion...for chronic dry eye syndrome"...that statement is far reaching and includes dry eye with an inflammatory etiology where punctal occlusion is contraindicated to increase tear retention as it keeps the inflammatory mediators on the ocular surface longer. If you disagree please support with a citation.
p5; line 22: "...diabetic animals [16-18]"; these citations only refer to rats so the use of the word animal is again far reaching, maybe add other citations to other animals or mammals? It is concerning as these are self citations and it should be clearer to say mammals/rats.

p5; line 49: .."1000-fold" may be seen as a sensational number but its not comparing directly topical concentrations to systemic and in some light an unfair comparison . I stand to be corrected but it appears the author is answering the safety hypothesis of this paper before presenting the results and suggests its very safe already because the concentration is lower! Consider re-phrasing by simply recording the concentration and not prescribe to the reader, in the interest of impartiality.

p6; line 22-26: Did these bridging studies that proved the safety; convey any behavioral changes considering Naltrexone is primarily used to treat alcohol and opioid dependence.

Methodology:

p6; line 39: The use of male Sprague-Dawley rats- was the gender bias premeditated?; if so please substantiate. This questions the background (p4; line 22) where the female gender is reported to have an increased risk. With respect, was the choice of male rats used to ensure a performance bias?

p7; line 5 "5 weeks"; line 12 "70%". I am sure these were not an arbitrary choice- please provide a brief reason or insert a citation.

p7; line 34: "1mm widex17mm long": This is not a standard Schirmer width. How was this validated. Can you elaborate how this augmentation differs from standard use and if done in one minute what is regarded as normal. What informed this approach and if a pilot was done using this augmented approach. THIS IS VERY IMPORTANT AS IT IS THE MAIN INDICATOR OF THE SUCCESS OF THE INTERVENTION.

p8; line 19: was the IOP measured at the beginning of the study?

p11; line 49: how was IOP measured? the asymmetry in the treatment group to the untreated group was significantly higher even after 10 days of treatment- if its implied why I apologise for missing it- please explain why? I am concerned especially since on pg13; line 17 where it is mentioned the optic nerve was not adequately examined? I am concerned about the neural impact of the drop over time.
RESULTS:

For Figures 1-3; considering there is more than one test for tear secretion and to contextualise better can the author replace the label of y-axis from "tear secretion" to "Schirmers 1" or even "Modified Schirmers 1"

Fig 4: no p-values as show in fig 2? only mention on p11; line 38- are all other observer insignificant?

The corneal sensitivity results on pg 11; lines 19-46 is not explored in the discussion as a palliative cure for diabetics living with dry eye? any reason?

ALL THE RESULTS SHOW AN IMPROVEMENT BUT ITS NOT CLEAR IF THE DRY IS CURED? THE SCHRIMERS VALUES ARE NOT DEFINED IN THE METHODS FOR VALUES THAT REPRESENT DRY VS NO DRY EYE.

DISCUSSION:

p14; line 7: which pre-clinical studies?

p14; line 19: "..longer than previously reported and spanned 10 days" ; what exactly are you comparing it to? how much longer? over how many days in other drops? I am not convinceD this drop is better as I am convinced its an alternative using an alternative M.O. and that's perfectly fine and advocating its more efficient judging from the results is far reaching in my humble opinion.

p14; line 27: insert citation or say what it is.

p14; line 34: "...reversed dry eye": The use of reverse implies cured- was it reversed to normal- this goes back to methods and what is regarded as cured with the augmented Schirmer's used.

p14; line 41: "..normal tear fluid".. I want to challenge the accuracy of this statement- please justify from your methods and results what is normal tear fluid levels?

p14; line 46-51: from a time perspective for how long?

p14; line 58: " It is.. previous published..." insert citation.

p15; line 14: I am not convinced about the IOP unless it was high to start of with which was not shown anywhere.

p15; line 29: "...most likely" this appear very vague and almost arbitrary; sure the mechanism of action must be more concrete if not state why.
p15; line 39: "...restore both tear production and corneal sensitivity.": Is it tear retention or tear production? as previous work by the author evidenced in the reference 13-21 - is the restoration of wound healing allow for the tearfilm to attach better to the cornea and thus improve sensitivity and is this co-dependant on tear retention or tear production? I say this because there NO mention of the lacrimal gland (responsible for tear production) anywhere. Can I request the authors clarify this concern? Or is the premise that the use of Schirmer's is enough to infer tear production and improvement in sensitivity disregarding the previous work of corneal wound healing? Is the improvement in Schirmer's an observation noted in previous studies and this is an "off label" exploration for main stream consumption of dry eye vs niche treatment of corneal wound healing? All this is questionable in the absence of a direct pharmacological mechanism of action on the eye. It is worth the authors attention.

REFERENCES:

p17; line 49: date accessed?

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

No

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 am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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