Author’s response to reviews

Title: Treatment with PBI-4050 in patients with Alström syndrome: study protocol for a Phase 2, single-centre, single-arm, open-label trial

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Author’s response to reviews:

Dr S. Baig,
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15.10.2018
Dear Dr James Mockridge

We would like to thank you for your considering our manuscript and hope that we have now addressed the additional requirements laid out for submission to BMC Endocrinology. We outline the responses below:

1. Technical comments

Please provide email address details for all authors on the title page of the manuscript.

We have now done this

2. Reviewer 1 comments:

a) Page 14 line 1, specify ELF test acronimous

We have changed the sentence to “An Enhanced Liver Fibrosis (ELF) test will be performed”.

b) *Page 18 line 36, probably "if" not "is".

We have changed this now

3. Reviewer 2 comments:

a) Please adhere to the most recent consensus definitions of hypoglycemia as given by the International Hypoglycaemia Study Group, Diabetes Care 2017;40:155-7.

Patients with Alstrom syndrome were a vulnerable group with visual and hearing impairment. Hence for safety reasons we had increased the threshold for hypoglycaemia for data collection and ongoing regular Data Safety Monitoring Board review. We will endeavour to report hypoglycaemia events separately during publications for Glucose Concentrations of less than 3.0 mmol/L as per International Hypoglycaemia Study Group recommendations.

b) Please specify which HOMA you will use (HOMA-B?).
We plan to use the HOMA 2 model and report on HOMA2-IR for insulin resistance and HOMA2-β for beta-cell function. We have amended the sentence as below

“Homeostasis Model Assessment (HOMA2) for steady state beta cell function (HOMA2- β) and for insulin resistance (HOMA2-IR) will be calculated.”

c) The use of Bonferroni seems too strict to me given the small sample size which is limited by the rareness of the disease, making a proper power calculation a futile exercise. Significance might sometimes be hard to achieve despite clear apparent differences. And in the end the 95% CI around the point estimate tells the reader all there is to know.

We agree with above comments and do not plan to use Bonferroni correction anymore. We have amended the sentence as follows “For comparing results of repeated samples, for example adipose tissue microdialysis where there are multiple time points during the same test, repeated measures analysis of variance will be used.”

d) I would recommend that clamp quality is reported, according to Benesch J Diabetes Sci Technol 2015;9:792-800.

We plan to follow above recommendation. We have added a sentence to effect “Samples taken at time points 0, 90, 105, 120, 210, 225 & 240 will also be analysed with another reference laboratory method and clamp quality for these paired samples reported according to Benesch et al., 2015.”

e) Typo: Background line 19. patients not patient's.

We have corrected these.

We hope that these changes meet the approval of the Editor,

Yours Sincerely,

Dr Shanat Baig