**Reviewer's report**

**Title:** Nasal administration of the neuroprotective candidate NeuroEPO to healthy volunteers: A randomized, parallel, open-label safety study

**Version:** 0  **Date:** 20 Apr 2017

**Reviewer:** Miguel Tábuas-Pereira

**Reviewer's report:**

The article describes a trial with the aim to evaluate the safety of recombinant human erythropoietin.

I think that, although a valid hypothesis and apparent strong methodology, the paper needs a major revision.

Some points:

1. a major revision of language is recommended,

2. In the methods (Statistical analysis section), comparison methods are described, but those results are not mentioned throughout the text or in the tables. How can anyone infer that there are no differences if the values were not rigorously compared?

3. Why have you chosen not to include a placebo-only group?

4. The fact that 93 patients were screened and the exact desired amount of 30 patients fulfilled the criteria is suspicious, especially when 5 patients did not start the study (one could admit that screening went on until 30 includable patients were found, but if 5 of them were later excluded before the trial, what is the reason not to find more volunteers?).

5. Is the final sample big enough to study the hypothesis?
Page 3

Results: "No severe adverse events were reported; thus the hypothesis was complied." - not the right place to say this and the data does not completely support this statement.

Some references are needed in introduction

Page 6

Methods

I would suggest a revision of the English language.

Line 14: "had to have been Cuban citizens" please improve phrasing

"both sexes" - although that it is understandable that you wanted to include patients of the tow genders, this is dubious

Line 19: "interrogation" - I would suggest rephrasing

Line 21: "including no presence of HIV and hepatitis B and C virus infection markers in serum." - rephrasing for clarity

Line 24: "or are breastfeeding" remove are

Line 33: "or during the trial" - I would suggest to separate criteria that would imply the termination of the trial for that patient in a different paragraph

Lines 34-36: "and"..."and"..."and" I would suggest rephrasing

Please define severe adverse events

Would patients with neurological disorders be able to participate?
Lines 49-51: "(Certain)"?

"product was lesser to 10%" please improve the English

"CIMAB S.A, Havana, Cuba," please insert in brackets

Page 7

Line 10 "kindly agitated in form of eight, with the aim to guarantee homogenization before volume extraction with a graduated type-insulin syringe." - please improve English

Line 21 "Because practical reasons" please improve English

Line 45: "Group B:" remove ":"

Page 8

Lines 15-17: "The subjects were put to bed in decubitus supine position, with the head dorsally bowed 45 degrees from the axis of the body'' please rephrase

lines 32-35: "None of them could affect the results because interactions neither direct effects on the tested safety variables." Please improve phrasing

page 9

lines 53-55: "y were considered as adverse events except for transient very close variations." Please redefine

page 10

lines 3-8: "The presence of signs of toxicity in the nasal mucous (local tolerance) was evaluated thorough medical examination of the nasal cavity by Otorhinolaryngology Specialists." Thorough is it through medical examination or through thorough examination? Which were the
signs that would be interpreted as toxic? Would inflammation be considered? Were all the patients evaluated by the same ENT doctor?

Page 11

Line 26: "Definitely" please rephrase

How much time went by between pre-screening and the actual trial?

Line 36: "Subjects were slightly more women (>50%)," please improve English

Page 13

Lines 36-42: "The findings obtained confirm the hypothesis that the frequency of severe adverse events following intranasal administration of NeuroEPO would be less than 10% since no severe event occurred. This are in agreement with the literature" remove obtained; rephrase confirm; major revision of both language and structure needed; change "this are" to "this is"

Lines 52-57: "This result is expected due to this EPO possess a low content of sialic acid, which plays a key role in the preservation of EPO structure avoiding its destruction by the live" rephrasing needed

Please add the compound's half-life
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.

No

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

No

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

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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