Author's response to reviews

**Title:** Pharmacokinetic and pharmacodynamic characterization of a new formulation containing synergistic proportions of interferons alpha-2b and gamma (HeberPAG) in patients with mycosis fungoides: an open-label trial

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**Version:** 3  **Date:** 29 October 2012

**Author’s response to reviews:** see over
All the words/phrases/sentences added in the current revised version of the manuscript appear highlighted (in yellow). The eliminated text is showed strikethrough. In addition to the requested minor changes, other words or small phrases were now added to improve grammar as well as comprehension for readers.

Referee 1

Reviewer: Hidefumi Wada

Comments to the Author

I have read your article with great interest. I have a minor point of concern: This manuscript reported that an exploratory, prospective, open-label clinical trial was conducted in 12 patients with mycosis fungoides. This paper gives us the quite important information of a novel synergic IFN mixture (HeberPAG®) for pharmacokinetic and pharmacodynamic studies. To publish this manuscript, I want to know some additional data of the enrolled patients.

Thank you very much

Minor revision

1) A limited number of patients were enrolled in this study. However, the author should describe the data of each patients in more details, such as the prior systemic treatments (PUVA, radiation, IFN-g, CHOP therapy etc), laboratory data (WBC, LDH, sIL-2R, etc). This information will be more helpful for the readers.

    Two sentences that describe prior patients’ systemic treatments were added at the beginning of the Results section, followed by LDH values (mean and range). Routine laboratory parameters including WBC were within or near to normal ranges in order to fulfill with inclusion criteria. sIL-2R or any other previous immunologic evaluations were not achieved at entry.

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'

**Referee 2**

**Reviewer:** Mirte Malingre

**No major compulsory revisions.**

**Minor essential revisions:**

1. What can be the reason for the high pre-dose endogenous IFN concentrations? Please add possible explanation(s)

   We don’t have at moment a reliable explanation about the high baseline endogenous IFN alpha-2b concentration in patient No. 12. Maybe a virus-incubation status at the moment of the IFN mixture injection?, but many other non-viral IFN production-inducer conditions could be responsible, taking into account that a group of oncologic patients, not healthy individuals, were included in this trial.

2. Discussion: this last result could lead to space the dosage interval for the IFN mixture formulation. The study design was twice a week, is this the best frequency for further studies? Please add some discussion about the probably best frequency for this formulation.

   The end of the corresponding paragraph was extended to clarify more that point. Indeed, twice a week could be a reasonable best frequency for the IFN mixture formulation according to pharmacodynamics. Efficacy data from this study at twice a week dosage interval will be further published.

3. Discussion pg 14: This is the first PK/PD study in humans with this variety of IFN formulation. Is this correct, see reference no.5?

   Reference no.5 correspond to a clinical trial designed to evaluate efficacy/safety of this formulation, it was not a PK/PD study. Therefore, the current study is certainly the first PK/PD study in humans with this variety of IFN formulation.
4. Discussion pg 16: adverse events: were qualitatively similar to those previously reported

- qualitatively? correct word choice? were they similar in severity or / and in percentage? Please clarify.

The word “qualitatively” was incorrectly used. We prefer to say that “Flu-like symptoms and other clinical and laboratory adverse events associated with HeberPAG® have been previously reported for recombinant IFN treatment” as was modified. Severity and percentages largely differ between studies since different dosage and schedules are used in the vast clinical experience with recombinant IFN treatment. Nevertheless, in our study none severe adverse reaction was recorded after the PK/PD dose.

5. Improve words/sentences:

pg 7: study design: pharmacodinamyc -> pharmacodynamics

In this context, the correct expression is “pharmacodynamic parameters”

pg 11 results: twelve patients, 7 females -> add and 5 males

Done

pg 11: results: no.8 who serum samples were no available -> no.8 whose serum samples were not available

Correct, “who” was replaced by “whose”, and “no available” by “not available”.

6. Correct word choices?:

- synergic? -> synergistic? please check

Synergistic is the correct word. Corrections were only necessary in the Abstract section.

- pharmacodinamy? -> pharmacodynamics? please check

The correction was done (see 2nd paragraph in Background section, and Conclusion)
- pg 12 pharmacodynamic analysis: until 0,9 pg/ml regarding pre-dose values -> compared to? please check

The phrase “until 9.6 pg/ml regarding pre-dose values” was substituted by “until 9.6 pg/mL compared to pre-dose values”. Please, see that value is 9.6, not 0.9.

**Level of interest:** An article of importance in its field

**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

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**Editorial Requirements:**

**--Ethics statement:**

Research involving human subjects (including human material or human data) that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html). A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

The statements “The trial was in compliance with the Helsinki Declaration” and “The protocol was approved by the Ethics Committee of this hospital” were already present in the first paragraph of the Methods section. We now add “and its amendments” for Helsinki Declaration. In the same paragraph, the name of the body which gave approval together with the corresponding reference number for our study was included.

**--Kindly confirm if the Trial Registration number is valid and registered.**

Trial Registration number: **RPCEC00000130**

We notice that you are reporting a clinical trial but have not cited a trial registration number. This must be obtained before we can begin peer review of your manuscript.
We would like you to confirm that your clinical trial is in a publicly accessible registry before we begin peer review. The trial registration number should be included as the last line of the abstract of the manuscript.

Yes, we confirm that the Trial Registration number is valid and registered (see above). An email with that confirmation was send by June 09 to 'BMC Editorial' (Christopher Morrey, PhD). The specific Trial Registration Number for our article is “Registro Público Cubano de Ensayos Clínicos RPCEC00000130”. Details about the protocol of this clinical trial could be obtained from the URL: http://registroclinico.sld.cu/trials/RPCEC00000130-En

At that time, a new version of the manuscript containing this Trial Registration Number at the end of the Abstract Section was submitted into “My BioMed Central”. Additionally, the “Manuscript details” were updated with the trial registry, the unique identifying number and the corresponding URL. The current revised version contains the same Trial Registration number.