Author’s response to reviews

Title: Active Post-Marketing Surveillance of the Intraleisonal Administration of Human Recombinant Epidermal Growth Factor in Diabetic Foot Ulcers

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Author’s response to reviews: see over
Reviewer No. 1:

The authors evaluate the effectiveness and safety of the intralesional administration of human recombinant epidermal growth factor (hrEGF) for treatment of diabetic foot ulcers in a post-marketing surveillance.

Some concerns arise from the manuscript:

First of all it should be clearly expressed that all the references come from the same group and that the approved regulatory come from the same country.

R/ We do not understand what the reviewer means. The authors of each clinical trial from the reference are clearly expressed in each paper. Some authors coincide among the trials; others do not, depending on the participating institutions. In this work, authors from 60 institutions took part, and are listed in the paper (see Appendix). The same was done for each of the previous clinical trial. Of course this one is the wider investigations since it deals with a nation-wide use of the product. It is evident that for the use of the product in Cuba, the approval of the Cuban authority is enough and other authority approval is not needed. We guess that this is the same for all countries. The product is approved in 15 other countries but those approvals are not needed for the work presented in this paper. Eventually, other articles could come from other countries and then the corresponding approvals should be declared.

Nevertheless we added final sentence after the conclusions: “Further clinical research and post-marketing information from other countries should enrich the evidence shown in this paper”.

The authors report the outcomes: complete granulation, amputations, adverse effects, complete healing and relapses of the whole group analyzing the influence of single factors as characteristics of the ulcers (simple, complex, calcaneal) or grading according to Wagner classification (from 1 to 5) or presence or not of peripheral arterial disease. In addition they pool together patients treated by 25 or 75 ug.

R/The outcomes are reported both for bivariate (single factors) and multivariate analyses, according to the different variables taken into account. The text in the Results section is clear on this respect. The only variable presented more specifically (in Table 2) is the ischemia since it is known to be the most important factor with influence in the outcome of these lesions.

This way to present the data is confusing and the reader does not get the real advantage of using EGF in the different ulcers. Probably all the results should be much more clear if it could possible re-classify the ulcers according the university of Texas wound classification and evaluate the outcomes according to the different classes and grades, deviding also the groups of patients according to the dosage use.

R/ The Wagner classification is commonly used in DFU trials and accepted in many papers. This was used in all clinical trials with this product so the protocol for the nation-wide introduction used the same criteria. So that was the one reported. It is known that this classification takes into account only the depth of the lesion and the presence of infection and gangrene, but not ischemia, which is taken into account by the
Texas classification. Since the presence or not of ischemia in the patients was recorded, and in fact is shown as the main factor with influence in the outcome, to reclassify each patient by Texas at this point would not provide additional or different information. The dose was included among the factors analyzed. It was not a purpose of the work to compare doses since the indications are not exactly the same for both doses and the patients were not randomized between them.

A final consideration is related to the major outcome. 'complete healing' is a subjective parameter and in the absence of a control group it could be debated whether can be used to establish the efficacy of a therapeutic approach. On the contrary complete healing, amputation and death are objective outcomes and therefore my suggestion is to use these outcomes to highlight the therapeutic potentiality of hrEGF.

R/ The purpose of the investigation was to evaluate the use of the product in common clinical practice. Therefore there is no control group in this case. The effectiveness refers to the behavior of the product in clinical practice, and in this case a control group is not ethically feasible since the procedure is approved by the health authorities. The efficacy of the procedure was established in the phase III placebo-controlled clinical trial (see ref. 7), before the approval. The idea was to see if the results in common clinical practice confirm those of the clinical trials, which is discussed in the paper.

We suppose that the reviewer meant “complete granulation” in his first sentence. It is not a subjective parameter since granulation tissue is very well defined and distinguished by specialists (see Methods section of the paper). We agree that “complete healing” would be a better outcome. However in this work, as explained, patients were hospitalized during treatment up to 8 weeks. In this period of time complete granulation can be evaluated in all patients. Then complete healing was evaluated as a secondary outcome during follow-up and some patients could be lost in this period. Nevertheless the information on complete healing, amputations and deaths is already included in the article (Results section) and discussed.

Additionally, it was found that complete granulation is a good predictor of complete healing in this kind of patients, and this was validated with this particular series, but this aspect corresponded to another article that is cited in the discussion (ref. 17).

**Reviewer No. 2:**
There is nothing to answer. He recommends to accept the paper, as it is: a post-marketing surveillance.