Title: Bioequivalence of two recombinant erythropoietin formulations in patients with anemia due to end-stage renal disease on hemodialysis: A parallel, randomized, double blind study

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Author's response to reviews: see over
Response to reviewer’s comments

Title: Comparison of two recombinant erythropoietin formulations in patients with anemia due to end-stage renal disease on hemodialysis: A parallel, randomized, double blind study

Date: February 25, 2005. (Comments received on February 4, 2005; replied to the Editor on February 7 and received request to response on February 15)

General

We appreciate the thorough revision done by Dr. Schellekens. We made profound changes in the article, including the title, in order to follow his observation on the bioequivalence concept. Therefore, this term has been almost completely removed from the text and changed to more flexible statements.

We also appreciate his kind words relative to biotechnology research and development in our country, and regarding the setup, performance and analysis of the study.

Considering his opinion that the article is of limited interest, we can argue that it was sent to a Nephrology journal because we think that it is within this specialty that the article should be of interest, more than for pharmacologists or biotechnologists. The data show how a home-made EPO can contribute to improve CRF patients conditions in places of the world were current treatments are unaffordable for extension programs.

Major Compulsory Revisions

1. There are other, more optimistic points of view on the subject (see. Ref. 41 in the new version of the article), even considering the same EMEA guidelines, derived from ICH Q5 document. Nevertheless we modified the article so that it doesn’t claim bioequivalence or therapeutic interchangeability any more. Just the comparison of the pharmacological properties between the two molecules and formulations studied. Additionally we included data on the further follow-up of the patients,
which give an idea of efficacy information, and an initial, limited, immunogenicity evaluation.

Several paragraphs were added, including the last one of the discussion that states on the need for the introduction of EPO treatment for hemodialysis patients in a developing country. This would be unaffordable with “proprietary EPO’s” at current prices. At the same time, to repeat all phase III trials at this time, when EPO has been used for more than 15 years, would be unethical and unfeasible. Therefore we have followed a strategy of demonstrating molecular and pharmacological similarity, and then to introduce the product and pursue a suitable monitoring of efficacy, safety, and immunogenicity, which is a particular issue in the case of EPO.

2. The reviewer is right and we appreciate his observation. There was a mistake in the article, due to old data “copy-paste”. In fact it was the albumin-free EPREX which was used. This was corrected in the Methods section.

3. A paragraph on immunogenicity was added in the discussion referring to the most recent article on the subject were the frequency of anti-EPO neutralizing antibodies with EPREX have decreased after they took some packaging and storing precautions. We also added the result of the anti-EPO screening done in the study patients after 3 months of treatment, although it is still limited and this work continues.

**Minor Essential Revisions**

Language and spelling were revised and minor changes were done.