ANSWERING REVIEWERS

Havana, August 21, 2013

Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 3869-edited revised).

Title: Recombinant Streptokinase versus Phenylephrine-based Suppositories in Acute Hemorrhoids. Randomized, Controlled Trial (THERESA-3)

Author: Francisco Hernández-Bernal, Georgina Castellanos-Sierra, Carmen M. Valenzuela-Silva, Karem M. Catasús-Álvarez, Roselin Valle-Cabrera, Ana Aguilera-Barreto, Pedro A. López-Saura

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3869

The manuscript has been improved according to the suggestions:

From the editors:

1. Format of Headings 1 was corrected as requested

2. All reference numbers were reformatted as requested.

3. Four references were added to reach 26, as requested.

4. Ref. No. 16 was completed, since the Epub appeared in June 2013.

5. English was reviewed and few grammatical corrections were done. We do not think that an English certificate is needed in this case since the reviewers understood well and praised the article. On the other hand our group has experience in writing to English journals (US or British). This can be checked, for example, looking at the senior author´s (Lopez-Saura P) PubMed profile. Therefore we can take liability of the English writing.

From the reviewers:

Reviewer No. 00042289

"I would appreciate if the cost of the therapy with streptokinase would be addressed."

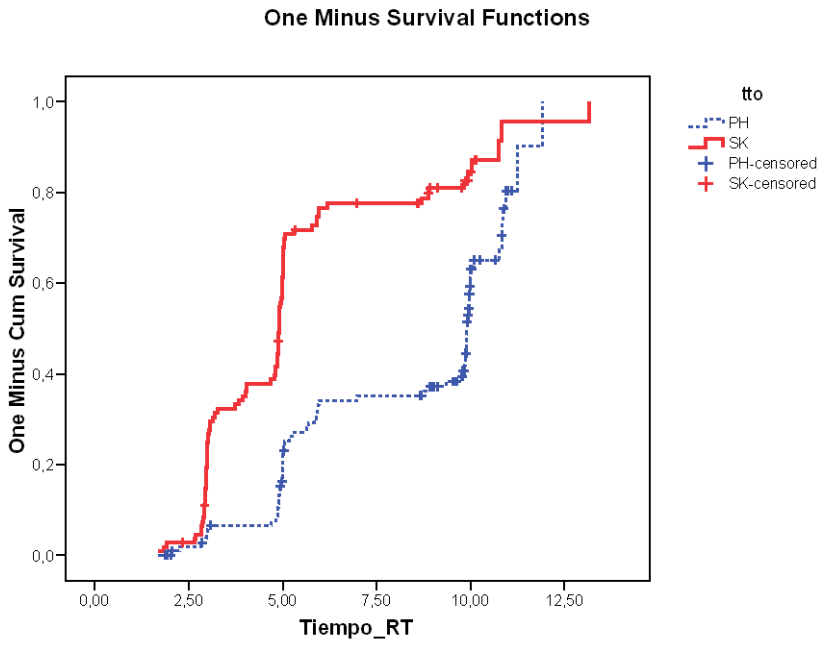
The authors have dealt only with the clinical development of the product, so we have no precise answer to that issue. However, after the report of this trial was submitted to the Cuban Regulatory Authority, the product approval was granted, but it is not yet commercially available since this kind of product has to pass through a one-year active pharmacovigilance before any commercial activity is launched. At present it is distributed free in Cuba. A far as we know, the commercial estimates indicate that the treatment will be certainly cheaper than a thrombectomy approach, and most

probably also cheaper than other non-invasive procedures, given its high efficacy. The final cost-benefit analysis will define the prices. It would be very risky to include this item in this paper. Probably when the result of a wider pharmacovigilance is published this aspect will be clarified.

"Table 2 should be converted to a Kaplan-Meier curve."

We think that the Kaplan-Meier plots will not improve the comprehension of the result. The main variable of the trial was the rate of complete response at 5 days after the onset of treatment. This cannot be shown in a KM plot, as well as most lines of the table, which are proportions with their corresponding 95% confidence intervals. The only possible item to show in a KM plot is the last line of the table (time to complete response).

Time to complete response was a secondary variable. Its main feature is shown in the table, which summarizes all the results. An additional graph would make the paper longer and add little to the understanding of the difference between the times to response that are shown in the table. In any case, see the KM plot below, only for that variable.



Reviewer No. 02489549

"*the P values for between group comparisons of the demographic data should be included in table 1 in order to demonstrate the significance or insignificance of the differences.*"

As a matter of fact, we have followed the CONSORT recommendations, which say not to do so. It is not necessary because if the patients were randomly distributed, any difference is due to chance, so it is not necessary to test this. We transcribe the corresponding part of the CONSORT statement (BMJ 2010; 340: c869 doi: 10.1136/bmj.c869; item 15):

"**Randomised trials aim to compare groups of participants that differ only with respect to the intervention**

(treatment). ……..... **Any differences in baseline characteristics are, however, the result of chance rather than bias.** ……...……. **Such significance tests assess the probability that observed baseline differences could have occurred by chance; however, we already know that any differences are caused by chance. Tests of baseline differences are not necessarily wrong, just illogical. Such hypothesis testing is superfluous and can mislead investigators and their readers. Rather, comparisons at baseline should be based on consideration of the prognostic strength of the variables measured and the size of any chance imbalances that have occurred."**

By the same manner, the p values for the between group comparison of the adverse drug reactions should be provided in table 4 to allow better assessment of the results.

We prefer to present the adverse events just in a descriptive nature. The number of events is too small to do any statistical analysis. Besides, the analysis would be a multiple comparison (8 events in this case). Then the Bonferroni correction for such analyses would have to be introduced and the p for significance would be 0.05/8 = 0.006, which is very difficult to achieve with so few events and false negative conclusions could be drawn. In any case, most of the events presented are less frequent in the experimental group and all of them related to the underlying disease.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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