Author's response to reviews

Title: Dose and aging effect on patients reported treatment benefit switching from the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study

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Version: 2 Date: 4 May 2012

Author's response to reviews: see over
May, 2012

Dear Jigisha Patel,

Series Editor (Medicine) of BMC Urology,

I am enclosing the revision of the manuscript entitled: “Dose and aging effect on patients reported treatment benefit switching the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study” to be reviewed and considered for publication as an original article in the journal “BMC Urology”. ID: 1540717393677686.

The authors of this manuscript are David Castro-Diaz, Pilar Miranda, Francisco Sanchez-Ballester, Isabel Lizarraga, Daniel Arumí and Javier Rejas.

In this paper, we have assessed the effect of aging and dose escalation on patient-reported treatment benefit after changing their first Overactive Bladder (OAB) therapy with tolterodine ER to fesoterodine in daily practice. Taking into account the age and the different doses it is a new approach that could give further information about the patients for a better treatment. So, therefore, we have decided to send this manuscript to your journal because we consider it very suitable for this sort of publication.

The authors of this manuscript state that:

- All of the authors have seen and approved the submitted version of the manuscript.
- The material is original and unpublished previously.
- All authors have contributed substantially in the manuscript preparation, interpretation of results or study design.
- All authors confirm that no material submitted as part of this manuscript infringes existing copyrights, or the rights of a third party.

This study was funded by Pfizer, S.L.U. Isabel Lizarraga and Javier Rejas are employees of Pfizer, S.L.U. and Daniel Arumí is employee of Pfizer Inc, Europe. David Castro-Diaz, Pilar Miranda and Francisco Sánchez-Ballester have not received any financial support from Pfizer for writing or interpreting the present research, and declare
that they do not have conflict of interests as a consequence of this paper. A funding paid by Pfizer was received by Esther Tapia for drafting the manuscript.

We have answered to the reviewer independently as follows:

Dear Dr. Alayne Markland:

In reply to your letter, please find enclosed the new version of our manuscript: 1540717393677686 “Dose and aging effect on patients reported treatment benefit switching from the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study” which has been carefully revised in response to your comments as detailed on the attached sheets.

We wish to thank you sincerely for all your helpful comments, and we trust that this revised version will now be judged ready for publication.

Look forward to hearing from you.

Sincerely,

Dr. Castro
Reviewer's report

Title: Dose and aging effect on patients reported treatment benefit switching the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study

Version: 1 Date: 30 March 2012

Reviewer: Alayne Markland

Reviewer's report:

This is a well-written manuscript supported by Pfizer, Inc. Europe that adds supportive data showing that age was not a factor in treatment benefit from switching from Tolteradine ER to Fesoterodine. Dosage (4 mg or 8 mg) did appear to be a factor in patient and physician treatment benefit statistically, although this benefit is questionable for any clinical benefit with possible ceiling effects seen (improvement from 91% to 96% on the CGI-I, p=0.004).

No possible ceiling effect in the CGI-I scale has been described yet. However, as the TBS is a one-item scale with four possible categories of response (greatly improved, improved, no change and worsened during the treatment), a ceiling effect could not be completely ruled out.

A few minor comments below by section may need to be addressed prior to publication.

Comments by section:

Abstract: Please include methods section in abstract. Revise statement in results and conclusion sections, “improvements were mostly not affected by age.” The improvements were not affected by age.
We have included the Methods section and changed the sentence “improvements were mostly not affected by age” for “The improvements were not affected by age” as reviewer commented.

Upon including a Methods section, we have been forced to make some additional minor changes in the abstract so as not to go over the limit in the final word count.

**Introduction:** No further comments.

**Methods:** Please include methodology section after the introduction.

We have added it.

Revise what is meant by “HTA” and “ictus.”

There was a mistake in translation and now we have included “high blood pressure” instead of “HTA” and “cerebrovascular accident” instead of “ictus”

**Results:**

Table 1 – please clarify what is meant by “OAB evolution time,” “HTA”, and “ictus.”

As stated above, there was a mistake in translation and now in the Results section and Table 1 we have now included, “high blood pressure” instead of “HTA” and “cerebrovascular accident” instead of “ictus”. “OAB evolution time” has also been substituted in Table 1 with “time since OAB diagnosis”

Tables 3 and 4 – values are not represented by mean values and 95% CI. For tables 3 and 4, Mean values and standard deviation or 95% CI are needed. For the reader, including p values comparing the two groups in the table would be helpful. Reporting
the F statistic and the correlation coefficient is not helpful. Please report this for both Tables 3 and 4.

We have reported it

Discussion:

Please comment on the ceiling effects seen in the different subgroup analyses – age and dose.…

We have added in the Discussion section at the end of the fourth paragraph: “No possible ceiling effect in the CGI-I scale has been described yet. However, as the TBS is a one-item scale with four possible categories of response (greatly improved, improved, no change and worsened during the treatment), a ceiling effect could not be completely ruled out”

Acknowledgements:

Should Esther Tapia be an author for drafting the manuscript?

The authorship of this manuscript is based on the recommendations and criteria for authorship of the ICMJE (International Committee of Medical Journal Editors): “Authorship credit should be based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

We have revised and corrected it throughout manuscript.
The second reviewer comments are done bellow, as well:

Dear Dr. Christopher Chermansky:

In reply to your letter, please find enclosed the new version of our manuscript 1540717393677686 “Dose and aging effect on patients reported treatment benefit switching from the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study” which has been carefully revised in response to your comments as detailed on the attached sheets.

We wish to thank you sincerely for all your helpful comments, and we trust that this revised version will now be judged ready for publication.

Look forward to hearing from you.

Sincerely,

Dr. Castro
Reviewer's report

Title: Dose and aging effect on patients reported treatment benefit switching the first
Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis
from an observational and retrospective study.

Version: 1 Date: 27 March 2012

Reviewer: Christopher Chermansky

Reviewer's report:

BMC Urology Manuscript ID# 1540717393677686

Major Compulsory Revision:

1. The authors present a study detailing a subgroup of patients from the IMPACTA
study who switched from tolterodine to fesoterodine. They present their study as a "real
world" study. What does that mean? I don't know an accepted definition of a real world
study.

The present study is a post-hoc analysis of data from an observational study. The term
“real world“ was used in order to underline not only the non-interventional nature of the
study but also the usual clinical practice setting in which it was carried out.

We have substituted the term “real world” for such others as “usual”, “normal” or
“routine” throughout of the manuscript.

Either strike out that language throughout the entire manuscript or respond to how this
study differs from the 3 already published clinical trials mentioned in the Background
section (references 18, 19, and 21) showing superiority of fesoterodine over tolterodine.
The reader would appreciate better clarification in the Discussion section of how this
study compares to the other 3 published studies.
We have a different point of view on the matter. It was never our intention to compare our results with those of the randomized studies of references 18, 19, and 21. We only wanted to point out that if previous randomized studies have already demonstrated the superior efficacy of fesoterodine over tolterodine, it should be no surprise to see replication of such results in routine medical practice.

To clarify this, in the Discussion section we have deleted the 4th sentence of the second paragraph: “These findings from real clinical practice were as expected, considering the results of previous randomized studies [18, 19, 21] that demonstrated the superior efficacy of fesoterodine 8 mg over tolterodine ER 4 mg.”

Instead, in the Discussion section we have added the following paragraph: “Additional explanations for these findings, particularly the high figures of effectiveness as perceived by both clinicians and patients, could go in two ways. In one way, previous randomized studies have demonstrated the superior efficacy of fesoterodine over tolterodine [18, 19, 21]. Therefore, it should be no surprise to see replication of such results in routine medical practice. On the other hand, these findings should also be interpreted in the light of the fact that the cohort of patients included in this analysis needed a change in the previous tolterodine ER-based therapy of their OAB symptoms. Then, moderate improvements, as shown in the urinary questions (see table 3 and 4), could be perceived as important benefits from the patient’s or clinician’s perspective, particularly because such moderate improvements were observed in the urinary symptoms that best define the OAB condition.”

On the other hand, in the Discussion section, at the end of the third paragraph, we have added: “Moreover, there is substantial interindividual variability in CYP2D6 metabolic activity, while, the esterases that convert fesoterodine to 5-HMT do not exhibit
genotypic variations [8,38,39]. Thus, the pharmacokinetic variability among individuals treated with fesoterodine is lower [8].

**Minor Essential Revisions:**

2. In the Background section in the 2nd paragraph and in the Discussion section in the 2nd paragraph the authors state that dose escalation has not become routine in clinical practice. I don't believe that is correct. Contemporary studies support dose escalating solifenacin and fesoterodine. Please respond and provide additional references.

   In the Background section, we have eliminated the first sentence of the third paragraph: “...however, dose escalation has not become routine in clinical practice [22-23] ” and we have added “The literature supports that the efficacy of anticholinergics is enhanced by dose escalation [22-24]. Moreover, flexible dosing reflects clinical practice better than fixed dosing [23].”

   We have also eliminated, in the Discussion section, the second sentence of the fourth paragraph: “…but using higher dosages has not become routine in clinical practice [23]”.

   On the other hand, in the Background section, at the end of the third paragraph, we have also substituted the sentence “Studies with different antimuscarinic agents failed to demonstrate a clear dose-response efficacy [4,24,25]” for “This dose response has not been demonstrated with all of the other antimuscarinic agents that offer multiple doses [4]”.

3. The authors need to describe the OAB-V8 score mentioned in the Abstract and Methods sections, and they need to reference the article that best describes that score.
The OAB-V8 score has been described in the Measurements and Instruments section as “The OAB-V8 [33] is a reliable 8-item questionnaire used to identify patients with OAB symptoms. Each item is scored on a 6-point Likert scale ranging from 0 (not at all) to 5 (a very great deal). Total score is obtained by adding up the score of each item. Patients were considered to have OAB if their OAB-V8 score was ≥ 8.”


4. In the Results section in the paragraph titled "Switching Characteristics" the authors report differences in treatment length. What was the exact p value when comparing dose and age? p<0.05 isn't specific enough.

We have added it

Also the authors further mention in their Discussion that this difference in treatment length is a study limitation. Yet, they refute that statement with the very next sentence by stating that is was not a cofounding factor. Thus, is it or is it not a study limitation? If not, remove that confusing language.

Observational studies have limitations inherent in its design. Thus, it could happen that the groups of patients were not well-balanced and that, as is the case of treatment length, if it varies from one group to another, it may be considered to be a confounding factor.

In order to clarify this in the Discussion section, we have eliminated the sentence: ” ….the treatment length was therefore different between groups. This actually was not a confounding factor as significant fesoterodine improvements had been reported as
early as two weeks after initiation of treatment [22] and the mean time of treatment length was more than two months in all our groups” and we have added: “. So, in this study, the groups of patients were not well-balanced. Most of the patient characteristics assessed were different between groups. One of them is the treatment length. This, could be a confounding factor, but it is not, so because the mean time of treatment length was more than two months in all our groups, and significant fesoterodine improvements had been reported as early as two weeks after initiation of treatment [22].”

5. In the Results section the authors summarize their findings in Tables 3 and 4. They states that nocturia was slightly higher in the older group (p=0.051). This wasn’t statistically significant and should be removed from discussion.

We have removed it in the Results and Discussion sections.

6. With respect to Figure 1 legend, choose better words than “patient disposition” to describe the diagram.

We have changed the Figure 1 legend “Patient disposition “for “Summary of study populations”

7. Throughout the text the English grammar is borderline poor. I see fragments separated by semicolons throughout. Please revise the manuscript to include only complete sentences that are clear and concise.

We have revised and corrected it throughout manuscript.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I serve on advisory boards for both Astellas and Allergan, and I also serve on Speakers Bureaus for both Astellas and Allergan.

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.

If you require any further information, please do not hesitate to contact me:
Sincerely,

David Castro-Díaz

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