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

Authors:

David Castro-Diaz (davidcastro@teide.net)
pilar Miranda (pmirandas@sego.es)
Francisco Sanchez-Ballester (sanchezballester@gmail.com)
Isabel Lizarraga (isabel.lizarraga@pfizer.com)
Daniel Arumi (daniel.arumi@pfizer.com)
Javier Rejas (javier.rejas@pfizer.com)

Version: 3 Date: 6 July 2012

Author's response to reviews: see over
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 from the first Overactive Bladder therapy with Tolterodine ER to Fesoterodine: Post-hoc analysis from an observational and retrospective study

Version: 2 Date: 5 June 2012

Reviewer: Christopher Chermansky

Reviewer's report:
Dear Authors,

The first revision represents an improvement in the original manuscript. Thank you for addressing my comments and revising. However, I do have the following comments and I believe the manuscript must be edited again before final acceptance.

Comment 1: Thank you for addressing and striking the words "real world".
Regarding the additional paragraph (now paragraph #4) added in the Discussion, the last 2 sentences of that 4th paragraph in the Discussion should be combined into 1 sentence as follows and the word "then" should be moved as follows: "Moderate improvements, as shown in the urinary questions (see tables 3 and 4), could then be perceived as important benefits from the patient's or clinician's perspective because such moderate improvements were observed in the urinary symptoms that best define the OAB condition.

We have changed “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” for “Moderate improvements, as shown in the urinary questions (see table 3 and 4), could then be perceived
as important benefits from the patient’s or clinician’s perspective, because such moderate improvements were observed in the urinary symptoms that best define the OAB condition.”

Comment 2: You revised the 3rd paragraph of the Background Section such that the last added sentence reads "This dose response has not been demonstrated with all of the other antimuscarinic agents that offer multiple doses." This is incorrect and must be deleted. In my original comment I specifically stated that there were contemporary studies that did support dose escalation of solifenacin. Delete the Ellsworth reference and review the paper by Haab et al entitled "Long-term open-label solifenacin treatment associated with persistence with therapy in patients with overactive bladder syndrome” in European Urology (2005) volume 47: pages 376-384. You should incorporate language to support the fact that the dose response has been demonstrated with solifenacin and add that reference in support.

We have a different point of view on this matter. We regret not being able to include the sentence "dose response has been demonstrated with solifenacin” because we have not found evidences of this in the different articles that we have looked through.

Following up on your recommendation we have reviewed the paper Haab et al European Urology (2005) volume 47: pages 376-384. Haab et al reported that during the open-label extension study period, the dosage for 51% of the patients was increased and remained on solifenacin 10 mg, however, efficacy outcomes were reported based on all patients participating in the extension study treated with solifenacin (5mg and 10 mg). Authors did not show a comparative efficacy analysis between patients who only received solifenacin 5mg and those treated with solifenacin 10 mg. In fact, these authors indicated that “A detail description of efficacy outcomes based on the extension study dosage groups (5mg solifenacin, 10 mg solifenacin and placebo) will be published separately” but we have not found it.

We also reviewed the two original 12-week placebo-controlled, double-blind studies (Cardozo et al J Urol 2004;172 (5 pt 1):1919-24 and Chapple et al BJU Int 2004;93:303-10), whose patients subsequently participated in the 40-week open-label extension study described by Haab et al 2005. These studies were designed to examine the efficacy of solifenacin 5 mg and 10 mg, however, authors did not compare 5mg
solifenacin efficacy outcomes vs. 10 mg, even though they had the opportunity to do it. They only reported that *treatment with solifenacin 5 mg and 10 mg once daily significantly improved all the major symptoms of OAB*. We observed slight numerical differences on some efficacy data between 5mg and 10 mg groups. Authors showed that, compared with placebo outcomes, the dose of solifenacin 10 mg provided a slighter improvement in some symptoms (e.g. nocturia episodes) than 5 mg. However, dose-response has not been demonstrated.

Further, Cardozo et al. BJU Int 2008;102(9):1120-1127 published a rising dose, randomized, placebo-controlled, double blind, efficacy trial in which a comparative analysis of efficacy between solifenacin 5mg and 10 mg was not carried out either. Authors only showed pooled efficacy data from solifenacin 5 and 10 mg.

Not only Ellsworth et al. Ther. Clin Risk Manag. 2009;5: 869-876 reported "This dose response has not been demonstrated with all of the other antimuscarinic agents that offer multiple doses" but also Khullar et al Urology; 2008:71(5): 839-843 indicated "....previous fixed-dose studies with the antimuscarinic agents darifenacin and solifenacin (Cardozo et al 2004 and Chapple et al 2004) have failed to demonstrate a clear efficacy dose-response in parallel dosing studies".

For all these reasons we cannot include the sentence “dose response has been demonstrated with solifenacin”. In plain view of the given data we would wish you to share our opinion.

Comment 3: Thank you for adding language to describe OAB-V8, and thanks for adding the reference.

Comment 4: Thanks for adding the p value. Also, thanks for the clarification in language on treatment length.

Comment 5: Thanks for deleting the discussion on nocturia since it wasn't statistically significant.

Comment 6: Thanks for the change in language to "Summary of Study Populations".
Comment 7: This revision reads better in English. Yet, there is still some grammatical editing that must performed.

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. We have revised and corrected it throughout manuscript.

Statistical review: No, the manuscript does not need to be seen by a statistician.

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.