Reviewer's report

Title: Modeling Dose-Response Relationships of the Effects of Fesoterodine in Patients With Overactive Bladder

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Reviewer: werner schaefer

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One key problem seems to be properly described by the authors themselves:

“Methods: A population analysis was conducted using pooled data from several studies.” I don’t think the term “several” is appropriate in a publication claiming to be scientific, particularly when it is very difficult to find out from the rest of the text what this “several” may stand for. There are 2 phase III trial with 2 doses only, and 2 phase II trials with 3 doses of which only 1 is published, the other just an abstract. In addition we learn: “… a dose-response relationship in the strictest(?) sense cannot be established with fewer than 3 dose levels. Therefore(?), mathematical models were developed to describe quantitative and predictive dose-response relationships of the effects of fesoterodine using a rich(?), subject-level longitudinal data set from the phase II and III(?) studies. This model-based dose-response characterization is more comprehensive(?) because all available subject-level data obtained at each study visit after administration of 3 different dose levels (4 mg, 8 mg, or 12 mg) in the phase II and III trials were combined and analyzed.” Further the authors state: “Data from 2514 subjects given placebo or fesoterodine 4 mg, 8 mg, or 12 mg in 2 phase II …and 2 phase III …. double-blind 8- or 12-week trials were used to develop the dose-response models”? This language is more obscuring than explaining. How many complete data sets are there? What does that mean when there are only complete 3 dose data published from a total of 186 or 225 pts? Or has a less than “strictest sense” been used? What does it mean that a model is "anchored" on less than 10% of the subjects' data?

Similarly obscure, it is stated for PVR that only 0.5% exceeded a threshold of 200 ml. From the trends shown in Fig 4 it would be most appropriate to additionally clarify this percentage dosage dependent for men over 70 yrs, i.e. those where such changes seem to occur.

Overall, when modeling any changes of inter-dependent parameters, here number of voids and leaks and MVV, one would expect some plausibility checks for these changes. If the number of voids decreases for placebo by -1.1, approximately -10%, then the MVV should increase by +10%, with diuresis being constant (in first approximation ignoring leakage), but the increase is only 9.7 ml, and a MVV of 100 ml is unlikely(?). Similarly non-plausible are the changes for verum. Thus, any comprehensive discussion of changes in number of voids, in leakage, and MVV, has to be tested/modelled against a plausible volume
balance, particularly when most changes are so small.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

no COI