Author’s response to reviews

Title: Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer’s disease

Authors:

Martin Farlow (mfarlow@iupui.edu)
Felix Veloso (drfveloso@sasktel.net)
Margaret Moline (margaret_moline@eisai.com)
Jane Yardley (Jane_Yardley@eisai.net)
Elimor Brand-Schieber (Elimor_Brand-Schieber@eisai.com)
Francesco Bibbiani (Francesco_Bibbiani@eisai.com)
Heng Zou (Heng_Zou@Eisai.com)
Timothy Hsu (Timothy_Hsu@eisai.com)
Andrew Satlin (Andrew_Satlin@eisai.com)

Version: 2 Date: 2 April 2011

Author’s response to reviews: see over
Response to Reviewers’ Comments

Manuscript: Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease (MS# 6810780955035856)

Authors: Martin Farlow, Felix Veloso, Margaret Moline, Jane Yardley, Elimor Brand-Schieber, Francesco Bibbiani, Heng Zou, Timothy Hsu and Andrew Satlin

Due Date: April 2, 2011

Dear BMC,

Please find below the responses of the authors to the reviewers’ comments.

We appreciate this opportunity to work with you to improve the quality and value of this manuscript submission.

Sincerely,
Martin Farlow, MD and coauthors

Editorial request:

Experimental research that is reported in the manuscript must have been performed with the approval of an appropriate ethics committee. Research carried out on humans must be in compliance with the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/index.html), and any experimental research on animals must follow internationally recognized guidelines. A statement to this effect must appear in the Methods section of the manuscript, including the name of the body which gave approval, with a reference number where appropriate.

Response: The following text has been added to the manuscript (Page 5; paragraph 2):

“The protocol and informed-consent form were approved by the independent ethics committee/institutional review board at each independent research site and conformed to the principles of the World Medical Association’s Declaration of Helsinki and all local regulations.
The study design was reviewed and deemed appropriate by the US Food and Drug Administration (FDA) and other global regulatory agencies.”

Reviewer I (Ben Seltzer)

Summary: This is a comprehensive review of the safety and tolerability of the recently Approved 23 mg/day formulation of donepezil with some additional analysis of data from 2 previous clinical trials where the temporal relationship between dose initiation and AEs could also be studied. This is important and useful information which deserves to be published. The data are presented in clear and appropriate fashion.

1. Minor Essential Revisions
The authors should simply make clear that
1) this study greatly expands the safety assessment of the 23 mg/day study and is not just repeating information that has already been presented,

Response: As suggested by the reviewer, a clarifying statement was added to the manuscript. Please see the following revised text on page 4, middle of paragraph 3:

“These analyses substantively extend the presentation of safety and tolerability findings previously published.”

and 2) this paper includes an analysis of 2 previous trials because of the more fundamental question it raises, viz., what is the relationship between dose transitions and AEs. They have to distinguish, at various points in the text, between “this paper,” which has two methodologies and two data sets, and what they frequently term “this study,” which is actually reference 3. So, for example, the first sentence of the Discussion should read “Both the 23 mg/d …. used in the study of Farlow et al…..” Similarly, under Patient Disposition, “Of 1467 patients in the 10 mg/day vs 23 mg/day study who were randomized…..” And, under Objectives, “the primary objective of the study of Farlow et al…..” In other words, make it clear that this paper is an analysis of three different trials, not just an appendix to reference 3.
Response: As suggested by the reviewer, the manuscript has been revised to better distinguish the sources of the various analyses. In addition to making the specific changes recommended in the reviewer’s comment, we revised text in the following sections:

Page 6, paragraph 2:

“Analysis of pooled data from prior studies

To further compare the impact of an abrupt transition from a lower to a higher donepezil dose, a pooled analysis was performed on previously published data from studies of mild-moderate AD.”

Page 12:

Added subheadings above the 1st and 2nd paragraphs under Timing of AEs and discontinuations:

Higher dose study

Analysis of pooled data from prior studies

2. Discretionary revisions

A few other minor points:

2.1 The paragraph under Methods that describes the analysis of references 8 and 9 needs to be a little clearer. I think the first sentence is missing a verb.

Response: The text has been revised to clarify the statement and now reads as follows:

Page 6, paragraph 2:

“To further compare the impact of an abrupt transition from a lower to a higher donepezil dose, a pooled analysis was performed on previously published data from studies of mild-moderate AD patients newly receiving donepezil.”

2.2 Last sentence, second paragraph of Discussion, say “previous studies did not specifically examine the temporal relationship....”
Response: The text has been revised as suggested and now reads as follows:

Page 13, paragraph 3:

“However, previous studies did not specifically examine the temporal relationship between dose initiation and AEs.”

2.3 Patients receiving memantine scored lower than those on donepezil alone, but was the difference statistically significant?

Response: Since subjects were not randomized to treatment with or without memantine, but were just permitted to continue memantine if they were taking it at baseline, a statistical comparison of these 2 subgroups would not be valid. Memantine is approved for use in moderate-severe AD and it is therefore expected that its use might be associated with more severe disease at baseline. This supposition was supported by a lower mean MMSE score among these patients, and we feel this information is important because the adverse events that were more common in the subjects taking memantine were those associated with more advanced AD. However, our key point is that these events were not associated with dose and were no more associated with dose in the memantine-treated subjects than the subjects not taking memantine.

2.4 At the very end, do the authors want to speculate on what might be an appropriate titration from 10 mg to 23 mg to cut down initial AEs?

Response: We appreciate the reviewer’s request. However, the study did not generate data to provide dose titration information, nor was it designed to do so. The results support the lack of a need for an additional titration step, given the good safety and tolerability observed and the comparability of the initially increased AE’s to those seen with dose escalation from 5 to 10 mg/d. In response to the reviewer’s comment, a sentence was added to the relevant paragraph on p. 14, paragraph 2:

“No data are currently available to support an interim dose titration when increasing from donepezil 10 mg/d to 23 mg/d.”

Reviewer 2 (Gregory Jicha)
Summary: The authors present detailed safety data from the recently published trial of high-dose donepezil (23mg) and further expand the safety evaluation to include two additional 5 & 10 mg trials safety data. While less than the most exciting breakthrough in therapeutics for AD, the manuscript expands on the data published in the original trial report (Farlow et al, 2010) and so serves a useful purpose as an addition to the present literature. The manuscript is well written and I have few comments as outlined below that I consider “minor essential revisions” according to BMC reviewer policy:

1. References begin at #3? What happened to #1 & 2? References should be renumbered.

   Response: The references have been renumbered.

2. The ‘Treatment-emergent laboratory abnormalities, ECG, or vital signs’ section in Results states that there were no differences between groups, and yet clinically significant differences in bradycardia are noted above? This needs to be clarified, as bradycardia is an ECG finding. I assume the authors meant “ECG findings other than bradycardia”? This should be clarified.

   Response: The text has been revised as suggested. Please see page 10, paragraph 2.

3. The analysis of Age-effects is confusing. The groups represent different time spans 20 years, 10 years, 10 years, and 15 years? How were the cutoffs for these groups determined? How was the analysis performed? Why wasn’t age simply used as a continuous variable? What are the relative frequencies in these age groups?

   Response: The age categories comply with regulatory reporting guidelines and are limited at the low and high end by the study entry criteria. The following sentence was added to the Methods section, page 6, paragraph 1:

   “Age categories were selected to comply with regulatory reporting guidelines and are limited at the low and high end by study entry criteria.”
Also, the number of subjects in each subgroup has been added to the Results section, page 10, paragraph 3:

“45-64 years (n=235), 65-74 years (n=440), 75-84 years (n=643), and 85-90 (n=116) years.”

4. Likewise for the weight group analysis, essentially no details were shared on the grouping or the analysis? This limits the usefulness of this data for clinicians evaluating individual subject risks. I recommend providing more detail and establishing some sort of clinically relevant framework for the analysis.

Response: We agree with the reviewer that additional information is warranted. Weight groupings were selected to provide consistent ranges on one hand and comparable number of subjects on the other. The following sentence was added to the Methods section, page 6, paragraph 1:

“Weight groupings were selected to provide both consistent ranges and comparable number of subjects.”

Also, The number of subjects in each subgroup has been added to the Results section, page 11, paragraph 3:

“(55 to <65, n = 245; 65 to <75, n = 240; ≥75, n = 259).”

5. The first paragraph of the discussion states that ‘Overall, age and gender had a minor effect on a small number of AEs’ which is not supported by the data presented that demonstrate significant effects on diarrhea, urinary tract infection, fatigue, somnolence and urinary incontinence, anorexia, and weight decrease. Either delete this sentence which is misleading or expand on why the age and gender effects should be so casually dismissed.

Response: The point by the reviewer is well taken; the sentence was deleted as requested. In addition, we added information about gender effects on page 10, last sentence:

“Overall, however, the incidence of common AEs was slightly higher in males for each treatment.”
We also added information about age effects on page 10, paragraph 3:

“Interestingly, the rate of nausea and vomiting generally decreased in successively higher age groups among those receiving 23 mg/d, from 15.6% and 10.5%, respectively, in the youngest age group to 6.5% and 2.6% in the highest.”