Author's response to reviews

Title: Exenatide Once Weekly Treatment Maintained Improvements in Glycemic Control and Weight Loss Over 2 Years

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Author's response to reviews: see over
25 March, 2011

Re: MS 1343862011464658

Dear Dr. Shipley,

The manuscript “Exenatide Once Weekly Treatment Maintained Improvements in Glycemic Control and Weight Loss Over 2 Years” has been revised according to the reviewer’s recent comments (date 15 March 2011). Changes were made to the wording in the abstract and to the limitations section, as described below.

**Discretionary Revision**

**Comment:** Add “compared with baseline” to the first sentence of the results paragraph.

**Revision:** The first paragraph of the results section of the abstract now states (change in red text):

In the completer population, significant improvements (LS mean ±SE [95% CI]) were maintained after 2 years of treatment in A1C (−1.71 ±0.08% [−1.86 to −1.55%]), FPG (−40.1 ±2.9 mg/dL [−45.7 to −34.5 mg/dL]), and body weight (−2.61 ±0.52 kg [−3.64 to −1.58 kg]) compared with baseline.

**Minor Essential Revision**

**Comment:** The authors explain the limitations of the ITT in detail but to be balanced, they must include the limitation of the completers analysis which likely will have an over-representation of subjects who have had good outcomes (ie good glycemic control) as those subjects who are more satisfied with care are more likely to return for follow-up visits. Whereas the subjects who had poor outcomes or are dissatisfied with care, are much more likely not to return and thus will not be included in the completers analysis.

**Revision:** The last paragraph of the discussion was revised to include wording specific to the limitation of completer analyses due to overrepresentation of subjects with favorable outcomes (changes in red text):

Results from both the ITT and completer populations were included in this study, and both populations present certain limitations to the interpretation of the results. For the ITT analysis, using a LOCF method is a conservative approach that accounts for early study withdrawal and provides a prediction of treatment effect for any subject who ever received treatment. The completer analysis mitigates the potentially large variations in treatment exposure by representing the actual efficacy for the full term of drug exposure. The results of the ITT analysis should, thus, be weighed against the results of the completer analysis, as efficacy data collected early in the trial (e.g., from subjects who withdrew early) may not be representative of the true treatment effect, which is established with increased duration of treatment exposure. However, subject retention is often a challenge in long-term trials and the results of the completer analysis may be affected by the composition of the completer population, which often includes a high proportion of subjects who experienced favorable outcomes with treatment and underrepresents subjects who had issues with tolerability or lack of efficacy.
Please contact me with any additional questions or issues.

Sincerely,
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