Author's response to reviews

Title: Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomised, double-blind, placebo-controlled 102-week trial

Authors:

Clifford J Bailey (c.j.bailey@aston.ac.uk)
Jorge L Gross (jorgeluizgross@gmail.com)
Delphine Hennicken (delphine.hennicken@bms.com)
Nayyar Iqbal (nayyar.iqbal@bms.com)
Traci A Mansfield (traci.mansfield@bms.com)
James F List (james.list@bms.com)

Version: 2 Date: 10 December 2012

Author's response to reviews:

On behalf of my coauthors, I appreciate the opportunity to respond to the comments provided subsequent to the peer review of our manuscript "Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomised, double-blind, placebo-controlled 102-week trial," BMC Med manuscript submission 1612843562838606.

Editor's comments:

1. Ethical approval: You mentioned in your manuscript that this study 'was approved by the institutional review board at each site.' Please could you specify, within your methods section, exactly which institutional review boards approved your study.

   Response: There were 80 sites approved in this study, and as noted in the manuscript, the protocol received ethical approval from the review boards at each of these sites. We have published a list of the investigators in the Lancet article (Bailey et al. Lancet 2010, 375:2223-2233).

2. Role of funders: In accordance with the CONSORT guidelines, please could you specify the role of the funders?

   Response: We have edited the Acknowledgments section to clarify that Bristol-Myers Squibb and Astrazeneca were the sponsors who funded for the conduct of the trial.

Reviewer 1:

We appreciate the reviewer’s recognition of our analysis of the side effects and the interpretations thereof. We are delighted that this reviewer has recommended publication. We thank the reviewer for his positive, complimentary remarks about the study and manuscript, and we provide responses to his specific suggestions below.
1. Comment: Comparing a new add-on antidiabetic drug with a placebo is not the most convincing approach: we would have been more interested in a study comparing the new drug to a well-established other compound; the authors stressed in their paper that they avoided using any other drug influencing insulin secretion or action (this is a clever remark): they could have used, for example, an alphaglucosidase inhibitor as a comparator.

Response: The comparison of this test agent (dapagliflozin) against a sulfonylurea has been conducted by another study group (Strojek, et al. Diabetes Obes Metab 2011, 13:928-938) showing that similar reductions in HbA1c are achieved at 1 year and beyond with fewer hypoglycaemic reactions and less weight gain. We are pleased that this reviewer has appreciated the exclusion of interference with other agents; our use of an alphaglucosidase inhibitor +/- pioglitazone was reserved for rescue therapy.

2. Comment: The number of subjects who have not completed the study is quite high, even though comparable in the four groups; we would appreciate having, at least, a comparison of the characteristics and reasons of stopping in the four groups with a test of heterogeneity.

Response: We are pleased that this reviewer has acknowledged the duration of this blinded study and the difficulty in retaining patients without unblinding. Thus, the losses in numbers are not due to withdrawal, but rather, to uptake of rescue therapy consistent with the strict glycaemic targets written into the protocol. Beyond 1 year, patients with HbA1c >7.5% (beyond 76 weeks, patients with HbA1c >7%) were automatically given additional (rescue) therapy to ensure optimal control. There were no apparent differences across the four study groups other than the ability of dapagliflozin to reduce the number of patients requiring rescue therapy, thereby substantiating the long-term efficacy of this agent. We have revised the text on page 9, Discussion paragraph 2 to include this comment:

A greater proportion of dapagliflozin-treated patients remained in the trial throughout the full 2 years, substantiating the durability of the glucose-lowering effect. There were no apparent baseline differences across study groups to explain the variation in glycaemic outcomes; however, treatment-related weight reduction is likely to be a factor in enhancement of glucose reduction.

Reviewer 2:

We thank this reviewer for his comprehensive review and positive comments.

1. Comment: If word count allows would be nice to get the weight reduction data into the abstract but this is not essential.

Response: We are pleased to include the weight-reduction data in the abstract, assuming the editor is comfortable with the additional text. For consistency, we felt the need to add the data for fasting plasma glucose as well.

2. Comment: There are no p values that I can see on tables 1 and 3. For example there is clearly a significant drop in uric acid but not sodium in table 3 - why no overt stats on this either in the table or the text? The authors should either justify this to the editor’s satisfaction or change the manuscript accordingly.
Response: Consistent with other trial protocols of this magnitude, p-values were not provided for these outcomes.

We thank you again for your consideration of this manuscript for publication in BMC Medicine.

Kind regards,
Professor Clifford J. Bailey