Reviewer's report

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

**Reviewer:** Gérard Slama

I have been pleased to review the paper entitled:

Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomised, double-blind, placebo-controlled 102-week trial, by Bailey and Coll. It relates the results on quite long term double blind trial comparing the effects of dapglifozin at 3 different dosages with placebo after 2 years.

I've found the paper quite interesting for many reasons.
- It has been produced by a quite well-established team of authors with a very good reputation.
- The trial has been conducted over the quite long term of 2 years, which was the continuation of 2 intermediate, shorter periods of observation.
- The number of subjects included over 500 patients.
- The interest in knowing more about a new compound about to enter the pharmaceutical market: the more we know, the better it is!
- The type of patient included is quite the ones we treat in routine practice.
- The design and the statistical analysis method were adequate.

The weaknesses of the paper are, in my opinion, the following ones:
+ 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.
+ 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.

The points which deserve to be positively retained in this trial are:
+ the quantification of the undesirable side effects and particularly frequency and severity in genito-urinary infections, significantly but, in my opinion, with
acceptable differences between the placebo and active groups (however
defavourable to the active drug),
+ with an apparently good benefits/risks ratio,
+ in addition, unexpected favourable side effects have been observed: better
cholesterol levels, significant drop in blood pressure, significant decrease in body
weight.

Finally, I found this paper interesting enough to be published after correcting the
text in the discussion paragraph to include those of the above objections which
the editor could find relevant.

Declaration of competing interests:

After carefully reading the recommendations to the peer reviewers I declare that I
have neo conflict of interest concerning neither the topic nor the authors signing
the paper