Reply to Reviewer's comments for manuscript number 9134.

March 31, 2014

Dear Prof. Donald W Bowden,

Please find enclosed the edited manuscript in Word format (file name: 9134-review.doc).

Title: Canagliflozin- current status in the treatment of type 2 diabetes mellitus with focus on clinical trial data

Author: Jagriti Bhatia, Nanda Gamad, Saurabh Bharti, Dharamvir Singh Arya

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 9134

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

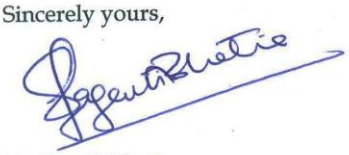
Comment: From the available data, which type of patient is the most suitable candidate for canagliflozin treatment considering the relatively high cost of new drug? According to the context and table 1, obese hypertensive patient not well controlled with SU+MET or pioglitazone + Met may get most benefit. What are the opinions of the CANTATA study researchers?

Response: The authors wish to thank the reviewer for his valuable comments. We have discussed the issue raised below and have also incorporated the same in the manuscript under the subheading "Therapeutic potential". In addition, the table no. 1 has been updated in the manuscript.
CANTATA trials have unveiled various interesting clinical observations of CFZ use in the management of T2DM patients. CFZ improved glycemic control without a concomitant increase in the occurrence of hypoglycemia. It lowered renal threshold for glucose (RT_G) but lowering of RT_G remained above the hypoglycemic threshold (60-70 mg/dL) and since UGE occurs below the RT_G, the incidence as well as risk of hypoglycemia with CFZ was minimal[19,26]. Further, the amplified UGE of 80-120g/day accounted for net loss of calories (~400 kcal/day) that contributed to the weight loss, which was maintained over the trial period of 52 weeks[24,26]. This weight loss was predominantly from loss of fat mass rather than lean body mass[22]. The reversal of glucotoxicity and weight loss together helped to improve beta cell function as indicated in improvement in HOMA-%B[19,21,24,26]. The mechanism for increased LDL-C with CFZ is not known, however, improvement in HDL-C and triglycerides was likely to be due to improved glycemic control and weight loss associated with CFZ[19,21,22]. Mild reduction in BP was also observed in the trial participants. This was due to the mild osmotic diuretic response to UGE and natriuretic effect of CFZ[24]. Thus, in nutshell, CFZ can reduce blood glucose levels and has the least risk of producing hypoglycemia as compared to other antidiabetic agents. In addition, it can also modify the insulin resistance, reduce weight and BP and increase HDL-C. These diverse effects are specific to CFZ and would explain the better outcome with CFZ treated patients as compared to other antidiabetic agent treatment groups. The CANTATA trials have concluded that CFZ could be taken as an initial drug for T2DM patients whose glycemic control is not achieved with diet and exercise; and also as an effective alternative to sulphonylurea, sitagliptin or pioglitazone in dual therapy with metformin.

3 References and typesetting errors have been corrected. All the corrections highlighted/marked on the manuscript have been incorporated.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,



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