Reviewer's report

Title: Safety, Pharmacokinetics and Pharmacodynamics of Remogliflozin Etabonate, a Novel SGLT2 Inhibitor, and Metformin when Co-administered in Subjects with Type 2 Diabetes Mellitus

Version: 2 Date: 22 August 2012

Reviewer: Yutaka Seino

Reviewer's report:

The manuscript entitled “Safety, Pharmacokinetics and Pharmacodynamics of Remogliflozin Etabonate, a Novel SGLT2 Inhibitor, and Metformin when Co-administered in Subjects with Type 2 DM” by Hussey et al. describes the randomized, open-label, repeat-dose, two-sequence, cross-over PK/PD study of SGLT-2 inhibitor remogliflozin etabonate (RE) co-administered with metformin in 13 subjects with T2DM. They demonstrated the lack of effect of RE on steady state metformin pharmacokinetics, and that metformin, likewise, did not affect the AUC of RE, remogliflozin or its active metabolite, GSK279782, although Cmax values were slightly lower for remogliflozin and its metabolite after co-administration with metformin compared with administration of RE alone. They further demonstrated that concomitant administration of RE and metformin was well tolerated with minimal hypoglycemia, no serious adverse events and no increase in lactic acid. Although the current study is well designed and the manuscript is well written, several issues need to be revised before its publication.

Minor Essential Revisions:

1. The authors set “urine protein/creatinine ration >2.5g/gCre” as one of exclusion criteria (Page 5, line 137-139). The value seems much higher than usual cases (e.g. >0.5g/gCre).
2. The authors should provide a Table demonstrating demographic data (e.g. age, gender, BMI, duration, HbA1c, eGFR) on subjects along with their description in the results (Page 11, 293-296).
3. Regarding description on meals (Page 6, line 165), the authors should provide total energy in calorie and ratio among carbohydrate: protein: fat.
4. Regarding PK parameters shown in Table 2, the authors should provide figures demonstrating concentrations of each drug including metformin to
address why AUCs were not affected by metformin despite of reduced Cmax for RE, remogliflozin, and GSK279782. In addition, they should provide concentrations of glucose and insulin to assess effects of RE and RE/Met combination on glycemic control.

5. Tables 3 and 4 should be combined as they deal with the same issue with different drugs.

6. Figure 1 demonstrated that RE BID and MET+RE BID had similar effects on fasting plasma glucose, suggesting little effects of metformin in the current subjects. One possible explanation is a short interval (2 to 15 days) between period 2 and period 3. The authors should discuss these issue in the discussion.

7. The authors should show changes in urinary glucose excretion in graphs.

8. The author should describe severity of hypoglycemia (e.g. mild, moderate and severe) which was observed in the study.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests