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: 15 August 2012

Reviewer: Mark S Fineman

Reviewer's report:

Major Compulsory Revisions

1. Results: Please add baseline FPG values for each treatment to Figure 1 or within the disruption of figure 1. Indicate if there was a sequence effect for FPG especially given the variable washout.

2. As this is a drug interaction study, effects on pharmacodynamic measures are as important as effects on PK, yet limited PD data details are included in the manuscript. Please add a table of urinary glucose excretion and percent of filtered glucose excreted data by treatment to support the no effect statements in the results and discussion section. Please indicate if there was a sequence effect given the variable washout.

3. Discussion: The effect of metformin on the Cmax of remogliflozin deserves some discussion on possible mechanisms and how generalizable the effect may be to the SGLT2 class. Could it be due to metformin’s effects on gastric emptying (Maida et al. Diabetologia. 2011 Feb;54(2):339-49.)? Although the authors claim that a 20% reduction in Cmax is not clinically relevant because the plasma concentration far exceeds the concentration required for full inhibition, it may not be true for lower doses of the SGLT2. In addition, the current study did not utilize maximally allowable doses of metformin and thus the effect may be greater when higher doses of metformin are used.

Minor Essential Revisions

4. Introduction: The authors indicate that GSK279782 is an active metabolite. Is it equipotent to remogliflozin? Please clarify what is known about relative potency and include in the introduction of the manuscript.

5. Results: Authors should add mean, SD, and range for fasting plasma glucose and HbA1c to the demographic section.

6. Results: statements in results and discussion regarding lactic acid data are inconsistent.: results = “no increase”; discussion = “increase or increasing trend during the three day MET BID treatment period”. Please update results accordingly.
Discretionary Revisions

7. Study design, line 169: Suggest rewording “Use of the following concomitant medications, assuming a stable dosing regimen over the 3 months …” to “Use of the following concomitant medications were allowed if the dosing regimen was stable for 3 months prior to study enrollment:…”

8. Statistical analysis, line 272: The language in the statistical section is cumbersome. Suggest rewording parts of it. For example “assuming a within-subject standard deviation …” instead of “under assumption of a within-subject..”

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.