**Reviewer’s report**

**Title:** Pharmacokinetic and pharmacodynamic modelling of oral mitiglinide on glucose lowering in healthy Chinese volunteers

**Version:** 0  **Date:** 17 Jan 2017

**Reviewer:** Melanie Felmlee

**Reviewer's report:**

The manuscript by Liu et al describes the pharmacokinetic analysis of mitiglinide after a single oral dose to healthy volunteers. The design for the PK/PD studies is appropriate; however, I have concerns with the PK/PD analysis and its description in the manuscript.

1. The authors present population equations in the methodology section and diagnostic plots in Figure 3, and have indicated the analysis was conducted in Phoenix WinNonLin. WinNonLin is not population modeling software. Could the authors please clarify if they used Phoenix NLME instead?

2. There is a lack of consistency in the description of the PK model that was used. The authors must clarify what the structure of the final PK model is, and include all relevant parameters in the corresponding table.
   
   a. Figure 1 and the equations within the methods differ with no equation listed to describe oral absorption.
   
   b. The methods section indicates in the second to last paragraph that PK parameter were obtained by simultaneously fitting the mean data. This is not consistent with the population modeling approach presented in the equations
   
   c. In the results section the model is listed as 2-compartment model with Michaelis-Menton elimination; however, there are no nonlinear parameters, and estimation of such parameters would require the administration of a range of doses.
   
   d. Results section: model is listed as having a lag time for absorption, but no lag time is listed in the table or in the model structure. In the discussion (paragraph 1) the absorption kinetics are described as rapid suggesting that a lag time wasn't needed.
   
   e. Conclusion section indicated that a disease progression model was developed; however, this would require data over time in a diabetic population and not a single study in a healthy population.
f. The conclusion section also indicated that there were two sequential absorption process; however, this was not indicated in the structural model in figure 1 or in the equations listed in the methods section.

3. Pharmacokinetics parameters listed in table 2.
   a. Were independent parameters calculated from the individual raw data or were they calculated from the population mean parameters estimates generated from the model.
   b. Cl and CI2 have incorrect units for a clearance parameter
   c. How were Cl/F and Vd/F calculated?
   d. Gamma parameter was listed in the equation section but not in the final parameters
   e. Estimate for the population variability parameters are not included in the table. Please clarify which parameters had population variability in the final model.

4. Results section does not describe the final PD model. A Biophase model is described in figure 1 and table 1, but there was no comments regarding why this particular model was selected.

5. Please revise figure 1 to improve clarity and remove the equations. It would be beneficial to readers for the figure to be generated in software outside of the Phoenix platform.

6. Figure 2: The figure is difficult to read because of size. Please separate so that there are individual figures for the PK and PD data. The results section indicated that the solid line was the best fit line; however, it appears to be just a connection of points. It would be more to have all of the individual data points and then the line of best fit, if a population modeling approach is used.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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