Author’s response to reviews

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

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Author’s response to reviews:

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To:
Editorial Office
BMC Pharmacology and Toxicology

Dear Editor:

Thank you very much for your careful review on our manuscript (PHAT-D-16-00190). I would like to appreciate the comments from you. We have revised the manuscript. Thanks for your interest in our work and we look forward to receiving your good news.

Sincerely yours

Shijia Liu

Reviewer reports:

Reviewer 1: This research has been well planned and conducted, therefore I have only some minor concerns:

- due to the low sample size (18 subjects), it would be ideal to present all your results as median/IQR rather than mean/sd, since you didn't prove that all pk parameters were gaussianly distributed

[Answer] Both individual and population approach were used in the paper, the parameters for individual were presented as mean and SD, and the parameter for population were presented as population mean and inter-individual variability.

- using minutes rather than fractions of hours might be more immediate, all along the text

[Answer] To make consistent with the whole paper, the unit of h for time was used.

- "Mitiglinide produced a statistically significant decrease in glucose levels for a period of 2 h, from 0.2 to 2.2 h after administration (P < 0.05)"; which stat test was used (you need a non-parametric one for the above mentioned reason)? Please, always report p-values with 3 significant digits, never using </> 0.05

[Answer] We have corrected in the text according to the reviewer’s suggestions.
- what about smoking habits in your cohort? Might it affect mitiglinide pk?

[Answer] This study was performed on healthy male subjects who don’t smoke. The data were not collected. We may investigate it in the further research.

- table 1: since you used a 2-comp model, it would be useful to report mitiglinide Kel (or t/2) both for central and peripheral comps

[Answer] Both individual and population approach were used in the paper, Clearence parameterization was used for population approach and related parameters were included.

- figure 2: y-axis should be presented as log rather than linear

[Answer] Plot was updated as attached.

- some typos up and there, please revise the manuscript carefully

[Answer] Other errors detected by us have also been corrected in red.

Reviewer 2: 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?

[Answer] Thanks for this kind reminding. As corrected in the text actually Phoenix NLME was used.

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.

[Answer] It was corrected and clarified in the manuscript according to the reviewer’s suggestions.
a. Figure 1 and the equations within the methods differ with no equation listed to describe oral absorption.

[Answer] Figure 1 and the equations were corrected and added in the attachment.

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.

[Answer] Both individual and population approach were used in the paper and the parameter for population were presented as population mean and inter-individual variability. It was corrected in the manuscript.

c. In the results section the model is listed as 2-compartment model with Michaelis-Menten elimination; however, there are no nonlinear parameters, and estimation of such parameters would require the administration of a range of doses.

[Answer] It was corrected in the first paragraph of results section. The data were fitted with two-compartment model with linear elimination. PK parameters were obtained by simultaneously fitting the plasma concentration data after oral administration of mitiglinide to volunteers using the 2-compartment model.

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.

[Answer] A short lag time was best to describe the data and was included in the model. It was corrected in the results and conclusions section.

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.

[Answer] It was our careless to describe the model wrongly. Actually a model describing the PK/PD for glucose lowering in healthy Chinese volunteers was developed. It was corrected in the conclusion section.
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.

[Answer] It was corrected in the conclusion section in page 13.

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.

[Answer] They were calculated from individual raw data by Non-compartment analysis. It was clarified in the first paragraph of results section

b. Cl and Cl2 have incorrect units for a clearance parameter

[Answer] It has been corrected.

c. How were Cl/F and Vd/F calculated?

[Answer] They were calculated from individual raw data by Non-compartment analysis. It was clarified in the manuscript.

d. Gamma parameter was listed in the equation section but not in the final parameters

[Answer] It was added in the equation section.

e. Estimate for the population variability parameters are not included in the table. Please clarify which parameters had population variability in the final model.

[Answer] It was added and clarified in the Table 1.

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.
Based on the maximum likelihood criterion and visual inspection of the fittings, a two-compartment model of first-order absorption with a lag time and linear elimination was chosen to describe the data. The comments have been added in the results section.

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.

[Answer] Figure 1 is corrected in the attachment according to the reviewer’s suggestions.

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.

[Answer] Figure 2 was corrected in the attachment. And Fig 3 was added to describe the population fitting of plasma mitiglinide concentration and plasma glucose concentration.