Title: Population Pharmacokinetic and Pharmacodynamic Modeling of Transformed Binary Effect Data of Triflusal in Healthy Korean Male Volunteers

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Version: 5
Date: 14 October 2014

Author's response to reviews: see over
Enclosed is a revised manuscript of an original research article entitled “Population pharmacokinetic and pharmacodynamic modeling of transformed binary effect data of triflusol in healthy Korean male volunteers”. On behalf of my colleagues, I would like to submit this manuscript to BMC Pharmacology and Toxicology.

We appreciate all of your efforts for reviewing this manuscript and all the precious comments you gave us. We carefully considered the comments from your reviewer and revised our manuscript. A brief summary of revision outcome is as follows;

**For comments for Reviewer Thorsten Lehr**
1. Discussions on the validity of our model were made.
2. Change from selected covariate to another was made.

This manuscript was read and approved by all authors. We also revised some paragraph because the result of covariate analysis was changed.

Thank you for your time in reviewing this submission. If any questions should arise regarding this submission or during the review process, please contact Seunghoon Han, MD, PhD.

Sincerely yours,

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Responses to Reviewer Thorsten Lehr

We appreciate all of your efforts for reviewing this manuscript and all the precious comments you gave us. We carefully considered your comments and revised our manuscript.

1. Thanks for providing the updated CWRES figure. The plot indicates a trend over time. This is usually caused by a model misspecification. Also the fact that the x-axis is shown in a logarithmic is hiding this trend. Could the authors please comment on this trend? Did this trend disappear if a different distribution model (e.g. 2-compartment) was used? Did the authors test a target mediated drug disposition model? If the drug binds strongly to the target, this may be a valuable model.

Thank you for your kind comment. First of all, we agree to your opinion regarding the misspecification. We also found the trend during our modeling procedures and we thought some outlying values (even though they are not true outliers) seem exaggerate the trend. The observations at 7 hour after the immediate dose were particularly not well-explained. We tried various model structures including 2-compartment model; however, the trend was not improved (the objective function value was also not improved). We could not figure out what the reason for this result was; thus, we could not but stop modeling despite of the unsatisfactory CWRES plot. We also think that your comment on a target mediated drug disposition (TMDD) model is brilliant. But we did not considered the application of TMDD because we could not find any evidence that the drug could be eliminated through target-mediated path. In addition, we have some concerns using TMDD model to explain the PK of HTB – a small molecule drug, because the structure has been generally used for antibody drugs, so far. (Mager DE: Target-mediated drug disposition and dynamics. BiochemPharmacol2006, 72:1-10)

The scale of the x-axis is not in a logarithmic scale but only the time of observation was shown. As you can see the intervals of 0~2 and 2~4 are identical (It is so for those of 4~7 and 7~10).

1. Thanks for adding the CrCl of the population. If I calculate the effect of CrCl on the clearance, the effect seems to be strong. The authors argued, that the population investigated was healthy. However, for a subject with the minimum CrCl of 90 mL/min of
their population the clearance is approximately reduced by 39% compared to a subject with 160 mL/min (maximum value). This results in an increased AUC by 63%. In my opinion the authors should discuss the effect of renal function more.

How much of the variability in Clearance was explained by including CrCl on clearance (i.e. IIIV CI without CRCI compared to IIIV with CRCL)?

We considered that it will be better to make a single response for your two comments above. First of all, we would like to apologize for our serious mistake in the modeling procedures. Thanks to your comment, we could find that the most meaningful covariate was body weight of each subject rather than the calculated creatinine clearance. When the body weight was included in the model, creatinine clearance showed no significance on the model improvement. Thus, we revised all of the parameter estimates accordingly through the whole manuscript and table. In addition, we added some statements in the ‘DISCUSSION’ section regarding the decrease of between-subject variability of corresponding parameters and the meaning of the covariate (line 371 - 384).