Author's response to reviews

Title: Population pharmacokinetic and pharmacodynamic modeling of transformed binary effect data of triflusal in healthy Korean male volunteers

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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 triflusal 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 thoroughly reviewed the comments from your reviewers. A brief summary of revision outcome is as follows;

**For comments for Reviewer Antonello Di Paolo**
1. We could add some valuable statements to enhance the quality of our manuscript.
2. The structure of manuscript was trimmed.

**For comments for Reviewer Thorsten Lehr**
1. Discussions on the validity and clinical implication of our model were made.
2. Justification for the binary data analysis was augmented.

This manuscript was read and approved by all authors. We added a new affiliation (Number 8) for Seunghoon Han according to the policy of Department of Pharmacology, College of Medicine, the Catholic University of Korea. We also improved the quality of written English and trimmed the structure of some paragraph upon your request.

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 Antonello Di Paolo

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.

[Major comments]

1. Page 10, “Population pharmacokinetic model development” section. Model development was performed as usual, but it could be interesting to know whether the Authors evaluated other structural models, for example considering the formation of HTB from triflusal. The transformation of parent drug into the active metabolite could be associated to a delay in plasma appearance of HTB. Another point of discussion is whether the Authors tried to evaluate within-subject variability. In fact, at page 18, lines 338-339 it is stated that “CLCR as a covariate accounted for variability between and within individuals”. Other questions regard both the calculation of shrinkage (Savic RM, Karlsson MO. AAPS J 2009;11:558-69) and the bootstrap analysis (whose final estimate values should be included within table 3).

Thank you for your comment. We fully agree with every points in your comment.

1) We tested various formation structures including zero-order absorption, lag time application, and transit compartments which can reflect the formation and elimination of the parent drug to explain the HTB formation, not knowing the PK of the parent drug. However, no structure gave better outcomes compared to our final model which has first-order formation kinetics without lag time. This is plausible as you can see the rapid increase in HTB concentration on the day of full-PK study (Figure 2). In addition, the rate of concentration increase is fastest at immediate post-dose and decreases thereafter. Thus, our final model is considered to be acceptable and we currently think the statement “The time-concentration profile of HTB over the entire multiple dosing period was best described by a one-compartment model with first-order formation rate constant of HTB.” (line 303-305) may be an acceptable summary of this process. We change the term ‘absorption rate constant’ to ‘formation rate constant’ to avoid confusion and added some statements in the ‘DISCUSSION’ section (line 356-367).

2) We recognize the inappropriateness of mentioning ‘within-individual variability’ for the
comment on covariate. We deleted the sentence.

3) Absolutely, those results should be included in Table 3. We revised the table as you commented. Thank you so much (line 526).

Page 13, line 232. Which were the criteria by which the MPA value of 74 was chosen? A reference to the cited guideline (line 234) seems to be necessary.

Thank you for your adequate comment. We inserted the assay manual as a reference for the corresponding statement (line 228, 481-482)

Page 13, “Covariate analysis” section. Did the Authors adopt a backward exclusion strategy with most stringent criteria (i.e., p < 0.01, OFV decrease > 6.63 points) during covariate analysis? Did the Authors test other relationships for CLCR within the model (i.e., piecewise or linear)?

Your comment is precise. We originally planned the step of backward exclusion in covariate analysis. However, only one clinical variable (CLCR) was selected as a meaningful covariate. Thus, we did not consider the backward exclusion was essential (line 318-320). For CLCR, various structures were compared to explain the relationship between $CL \sim CLCR$. We concluded that the suggested relationship in our manuscript was the optimal structure. So, we revised the sentence to be more clear (line 310).

[Minor comments]

Pages 3-4, “Abstract”. The Authors should include some numerical information about their PK/PD model (i.e., IIV reduction in CL). Furthermore, the daily dose should be mentioned.

We appreciate your kind comment on additional information. We added the estimated values for PK/PD parameters (line 57-59, 61-67) and the information on daily dose in the ‘Methods’ section (line 46-48). We understood that you commented the decrease in the variance of random between-subject variability (BSV) when CLCR was included as a covariate. We revised the term IIV (Inter-individual variability) to BSV to avoid a confusion caused by ‘intra’-individual variability. However, we considered that it will be better to be indicated in the ‘RESULTS’ section of the
manuscript rather than in the ‘ABSTRACT’. Thus, we add a statement on the change in the variance before and after CLCR inclusion in the ‘RESULTS’ section (line 316-318).

Page 14, line 252. The following reference for the Xpose package should be included within the manuscript: Jonsson EN, Karlsson MO. Xpose- an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed 1999;58:51-64

Thank you for your kind comment. We revised the statement regarding Xpose and R (line 257-259).

Page 15. Although stated/described throughout the manuscript, a general “Statistical analyses” section could be added to resume the way how data are presented and the software used to obtain mean, median and SD values, and min-max range.

It is so kind for you to mention an additional section. The section was added from line 287 to 291.

Page 16, “Population PK modeling”. In general, when presenting results from POP/PK analysis, the Authors should include within the text important information regarding the development process of the model, as OFV values for initial and final models, together with initial/final/difference of IIV values for the selected fixed effects.

We completely agree with your comment. However, we considered those values were not essential for our model because the modeling process was not excessively complicated. We applied LRT for every step of parameter addition and only parameters produced > 3.84 decrease in OFV were selected as mentioned in the ‘Methods’. The extent of OFV decrease by random effect parameter was not our major focus in this study. As you commented in the first minor comment, we recognized the necessity for presentation of OFV and BSV decrease by the addition of CLCR as a covariate for CL. Thus, we indicated the values accordingly (line 316-318).

Page 19, line 344. The Cmin,ss and accumulation factor values should be presented for the first time within the result section, thus giving to the reader an overview of PK endpoints and results obtained in the study.
Thanks to your comment, we could improve the composition of our manuscript. We moved the statement regarding $C_{\text{min,ss}}$ and accumulation factor to the ‘Results’ section leaving the combined comments in consideration of $EC_{50}$ where it was.

1 Where Page 19, last paragraph. The Authors correctly list the potential flaws of their study. It could be interesting to explain the effect of these issues and possible solutions to overcome those problems.

   Yes. We revised the last sentence of this paragraph and separated the solution into two parts. The first one discussed the necessity of triflusal concentration measurement for additional information (line 391-396). The second one suggested a condition to overcome current problem related to the binary analysis which was inevitable (line 399-400).

1 Table 3. Remove unit of measure for TETHA4.

   Thank you for the comment. We took the unit away (line 526).
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. The assessment of the final PK model is very difficult. In figure 3 the CWRES should be shown with time after dose and not time elapsed from the first dose.

   We fully agree with your comment. We revised figure 3 as you commented.

2. The authors should discuss their PK findings in relation to other PK studies from trifusal. For example Yun et al (http://www.ncbi.nlm.nih.gov/pubmed/24612881) and Valle et al (http://www.ncbi.nlm.nih.gov/pubmed/15711832) published a PK models for trifusal.

   Thank you for your kind guide for an appropriate evaluation of our PK model. We added a paragraph in the ‘DISCUSSION’ section as a response to this comment. (line 356-367)

3. The authors should discuss also the effect of the kidney more thoroughly. In Line 299 the authors present the relationship. This equation is raising the question of the impact of CrCl on the concentration-time profiles. A simulation may help to answer the question. Further, it may be asked how the increased exposure impacts the pharmacodynamics. In addition, it is unclear (Table 1) which range of CrCl was investigated. Please add the statistic and discuss your population. The authors also select the CrCl based on Baysian estimates. What was the Eta shrinkage? How significant was the covariate effect?

   Your comment on the effect of CLCR on the trifusal PK is precise. We also wished to discuss the influence in detail; however, we could not because of the following reasons;

   1) Our study population was healthy male Koran volunteers. It made the range of CLCR studied stay within clinically normal limits. Thus, no extrapolation could be expected to the population with actual renal impairment who might need dose modification.

   2) In clinical settings, most of the dose modification is made for the patients with decreased renal function. So, major concern should be placed to the increase in the trifusal concentration causing toxicity. In our study, we considered the efficacy of trifusal, which is
the inhibition of platelet aggregation, rather than the toxicity. Thus, we could not mention the outcome of the renal impairment from the results of this study.

We understand your concern on the ETA shrinkage and the covariate effect. We presented the shrinkage value of each ETA in TABLE 2. The covariate effect was shown in line 316-318.

1 It is unclear to me, why the PD measurements were discretized. A graphic (e.g. concentration vs. platelet) aggregation may help. Yun et al also modeled the platelet aggregation. Where is the difference between the two models? Did the authors tested the model from Yun et al?

To assist your understanding, we revised FIGURE 2 to show the distribution of PD observation. We believe this may be a great help for the readers of this article understand the necessity of discretization. Based on the bimodal distribution, we believe our approach is more acceptable compared to the method regarding the platelet aggregation as a continuous variable.

1 Please add a c-value or an ROC-curve for the final PD model. Did the authors perform a covariate analysis of the PD model as well?

We do not understand why c-value or an ROC-curve is required. Instead, we inserted the predicted concentration-probability curve in FIGURE 4. We also performed covariate analysis for EC$_{50}$; however, no meaningful covariate was identified.

[Minor Essential Revisions]

1 Please add the RSE of the IIV estimates in table 3

Thank you for your kind comment. We revised out manuscript as commented (line 526).

1 Please check the order of your tables.

Thank you for your kind comment. We revised out manuscript as commented.