Reviewer's report

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

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Reviewer: Antonello Di Paolo

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The paper of Park and colleagues describes the population pharmacokinetics and the derived pharmacodynamic model regarding the antiaggregant activity of the triflusal active metabolite HTB. Final results show that a one-compartment model describes HTB plasma concentrations in 34 healthy male volunteers, and that the selected dose (600 mg/day) is enough to obtain an antiaggregant effect. The following comments arise from reading the manuscript.

Major

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).

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.

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)?

Minor

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.

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
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.

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.

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.

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.

Table 3. Remove unit of measure for TETHA4.

English language should be revised throughout the manuscript.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I have not competing interests in relation to this paper