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RESPONSE TO LETTER TO THE EDITOR

Response to Physiologically Based Pharmacokinetic Model for Prediction of Leflunomide and Teriflunomide—Should Consideration Be Given to Cannalicular Efflux Transporters?

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To the Editor: We thank Dr Srinivas for the thought-provoking comments and the opportunity to clarify a number of aspects of our work.[1]

With reference to **Figure 2** from RUN8,[2] the residual error model has been weighted by the inverse square root of the number of patients within each study so as to prioritize the impact of studies with higher subject numbers. For example, although the studies that included multiple sclerosis individuals were repeat dose studies (concentrations were therefore higher and the inherent variability was represented across time), given the larger subject numbers, the curve fits were equal or better to those seen with the shorter single-dose studies. Despite this, the effect of poly-pharmacy and varying disease states on teriflunomide concentrations should be explored further, particularly for known inducers or inhibitors of ABCG2, CYP1A2, or CYP2C19.[3]

In response to the model fitting well to the mean teriflunomide concentrations after i.v. administration of teriflunomide (**Figure 2**), it is important to recognize that there was only one representation of this, albeit it seems to indicate the importance of the presystemic components. Nonetheless, given teriflunomide concentrations vary widely after both leflunomide and teriflunomide administration,[4,5] this seems consistent with the enterohepatic system being the chief source of teriflunomide concentration variability.

Dr Srinivas' suggestion to further explore cannalicular transporters is thus an important one, as they may affect the enterohepatic system. The model was developed with the intention of assessing the influence of *ABCG2* genotype, however, no effect was observed. Nonetheless, given the acknowledged limitations of the study, including the relatively low number of participants, we agree that continued exploration is warranted. However, the exploration of such transporter effects *in vivo* can be time-consuming and expensive, and therefore targeted investigation of transporters to which teriflunomide is an indicated substrate is important. Dr Srinivas has also underlined a possible relationship between increased alanine aminotransferase and lowered expression of cannalicular transporters. This highlights the importance of investigating the relationship between the expression of *ABCG2* (and other transporters) and teriflunomide concentrations, and the presented model is ideal to assess these outcomes. Investigating transporter effects on enterohepatic recycling will be assisted by knowledge of teriflunomide concentrations during cholestyramine administration. Without this data, between-subject variability of the enterohepatic recycling system is unidentifiable, thus making covariate identification difficult, as discussed within the original manuscript. As such, we would extend an invitation to collaborate with research groups who may possess such data.

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Conflict of Interest. The authors declare no conflict of interest.

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