Reply to Baklouti et al., "Why Is It Desirable To Do the External Evaluation of a Population Pharmacokinetic Model?"

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We thank Baklouti et al. (1) for commenting on our population pharmacokinetic study of dalbavancin for optimal treatment of adult patients with staphylococcal osteoarticular infections (2) and for suggesting that our model tends to underestimate the concentrations observed in a group of French patients (French group).

Our model was not externally validated, but the model performances were very high as attested by < 20% of residual standard errors for CL and V, consistency between estimated values and those obtained after bootstrap, and adequacy of the VPC (2). Overall, these statistics make our model highly reliable for the tested population, namely that of patients with osteoarticular infections and normal renal function with eGFR ranging between 90 and 120 mL/min/1.73 m². As originally stated in our study, we recognized that the small samples size of our cohort including only patients with normal renal function prevented us to establish any association between eGFR and dalbavancin CL, differently from what observed in previous studies (2). This fact may obviously preclude us to extend our findings to other patients’ populations having different characteristics, namely those with a wider range of renal function and/or with different underlying pathophysiological conditions. Consequently, it is not surprising that the model performance could be suboptimal when dealing with a population having wider variability in renal function and/or different underlying diseases. In this regard, it should not be overlooked that the eGFR range was very much wider in the French group than in our population (43.8-225 vs. 91-105 mL/min/1.73 m²).

Besides, it should also be mentioned that the analysis of Baklouti et al. should not be considered fully appropriate according to the recommendations on how to perform a correct external validation (3). In this regard, it is recommended that the predictive performance is assessed by calculating the mean squared error (MSE) and the root mean square error (RMSE), as measures of bias and precision, respectively. This was not done by Baklouti et al. who simply performed a Monte Carlo simulation by means of the pharmacokinetic parameters that we reported and superimposed the observed concentrations on the simulated concentration-time profiles.
Finally, we could not rule out that some bias could depend also on differences in the analytical methods used by the two labs to measure dalbavancin concentrations, considering that Baklouti et al., differently from us, did not report any adequate details in this regard.

Overall, this debate suggests once more that the findings of any population pharmacokinetic model should be reliably applied only to patients who have the same characteristics of the tested population.
References

