

Physiologically-Based Pharmacokinetic (PBPK) Model-Informed Drug Development for Fenebrutinib: Understanding Complex Enzymatic and Multiple Transporter Related Drug-Drug Interactions

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Objectives: Fenebrutinib (FEN) is a potent and selective reversible antagonist of Bruton's tyrosine kinase under clinical development [1,2]. The *in vitro* data indicated FEN is a CYP3A substrate and time-dependent inhibitor, as well as a BCRP and OATP1B transporter inhibitor [3]. In the clinical FEN–itraconazole (ITZ) DDI study, an unexpected decrease in FEN $C_{\max}$ and a delay in $T_{\max}$ were observed. Deconvoluting the unexpected DDI observation to have a robust estimate of CYP3A contribution (f_{mCYP3A}) is important to assess DDI risk between FEN and other CYP3A perpetrators. In the clinical FEN-rosuvastatin study, DDI involving multiple transporter inhibition was observed. Confirmation of the relative contribution of OATP1B vs. BCRP to the observed DDI is desired to predict FEN DDI with other transporter substrates. A model-based strategy using PBPK approaches was developed with the ultimate goal of understanding complex DDI and recommending co-medications for FEN without additional clinical DDI studies.

Methods: Two novel PBPK approaches are presented: (1) a mechanistic absorption model to incorporate the effect of an excipient in the ITZ solution to rationalize the unexpected clinical DDI observation between ITZ and FEN, and thereafter determine FEN f_{mCYP3A} through retrospective simulations and verification using additional clinical data; (2) the combined use of PBPK model and endogenous biomarker measurements to enhance mechanistic understanding of a clinical DDI involving multiple transporters.

The FEN PBPK model was built in Simcyp® using preclinical ADME data and further refined and verified based on Phase I PK data. The Advanced Dissolution, Absorption and Metabolism (ADAM) model was developed to describe the absorption of FEN. A K_p scalar was applied to match the predicted V_{ss} with the observed value. Total clearance was assigned to hepatic (~95%) and renal (~5%) based FEN disposition data, and hepatic clearance was further assigned to CYP3A pathway in FEN elimination.

Retrospective PBPK modeling was conducted to understand the unexpected decrease in FEN C_{max} in the presence of ITZ. An ADAM absorption model with GI regional P_{eff} predicted from mechanistic permeability module was developed to incorporate a key hypothesis of complexation between FEN and H- β -CD (an excipient in the ITZ solution) [4,5], and to simulate the effect of complexation on the absorption of FEN. Sensitivity analyses on f_{mCYP3A} (0.5 -0.95) and the extent of H- β -CD effect (up to 100x change in P_{eff}) were performed to verify model simulations of the unexpected DDI observations. To understand the relative contribution of OATP1B vs. BCRP inhibition, scenario simulations of DDI (incorporating BCRP and/or OATP1B) were conducted, and results were verified based on the changes of endogenous transporter biomarker (coproporphyrin CP I and III) data from the clinical study [3].

Results: The ADAM absorption model incorporating our hypothesized complexation mechanism (caused ~ 30x decrease of P_{eff} in upper GI) was able to describe the effect of H- β -CD on FEN PK (~50% decrease in absorption). The subsequent DDI simulation using this model was able to capture the observed DDI, with AUC increased ~2.5 fold, C_{max} decreased ~11% and T_{max} delayed ~1hr. The key parameter f_{mCYP3A} was estimated to be 0.8~0.85 based on sensitivity analyses, and this estimate is supported by the totality of evidence, including in vitro phenotyping, human mass balance study and simulated multiple dose PK data.

Scenario simulations suggested that the main contributor to the observed DDI with rosuvastatin (C_{maxR} ~ 5.0, AUCR~ 2.6) is gut BCRP inhibition by FEN. The limited involvement of OATP1B inhibition (C_{maxR} ~ 1.6, AUCR~ 1.4 without BCRP) was further confirmed based on the unchanged plasma concentrations of CP I and III, endogenous substrates of OATP1B.

Conclusion Our PBPK models successfully characterized the unexpected CYP3A DDI observation confounded by the excipient effect, and the relative contribution of OATP1B vs. BCRP inhibition by FEN. This work provided mechanistic insights to deconvolute complex DDIs and increased confidence for using a model-based approach for FEN DDI risk assessment and co-med recommendations. To our knowledge, this is the first attempt using PBPK approach to characterize H- β -CD effect in DDI assessment. This is also one of the early examples for using endogenous biomarker together with PBPK approach to characterize transporter related DDI.

References:

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