A physiologically-based pharmacokinetic model adequately predicted the human pharmacokinetic profiles of YH4808, a novel potassium-competitive acid blocker, to treat gastric acid related diseases

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\textbf{Objectives:} YH4808 is a highly potent, selective and reversible potassium-competitive acid blocker (P-CAB) on H\textsuperscript{+}/K\textsuperscript{+}-ATPase under development for the treatment of gastric acid related diseases including gastroesophageal reflux disease and peptic ulcer disease. The objectives of this study were 1) to develop a human PBPK model optimized by human pharmacokinetic (PK) data and 2) to predict the PK profiles of YH4808 using the PBPK model in various clinical settings.

\textbf{Methods:} A PBPK model was developed using the physicochemical data, in vitro preclinical and clinical data of YH4808, which was further refined using human plasma concentrations obtained from a single-dose ascending phase I clinical trial of YH4808 with the SimCYP\textsuperscript{®} (Certara USA, Inc., Princeton, USA) (Figure. a). Compartments were included for the brain, heart, lung, kidney, muscle, spleen, liver, gastrointestinal (GI) tract, pancreas, and a combined compartment for the remaining tissues. All compartments except the GI tract and liver were assumed to be well-stirred and their clearances were limited by blood flow. The absorption of YH4808 was described by the advanced dissolution, absorption and metabolism (ADAM) model implemented in SimCYP\textsuperscript{®}, which divides the GI tract into nine segments, assuming permeability-limited disposition in the GI tract and liver. Biliary route is the major elimination pathway of YH4808, and the clearance was estimated using in vitro hepatic microsomal intrinsic clearance data.

\textbf{Results:} The pharmacokinetic profile of YH4808 after multiple oral administrations was predicted using a refined PBPK model (Figure. b). YH4808 concentration reached steady state after Day 4 following repeated once daily administrations at 100mg, and the PBPK model adequately predicted the observed concentrations. The PBPK model predicted a dose-dependent linear increase in the maximum plasma drug concentration and the area under the plasma concentration-time curve from time 0 to time of last measurable concentration after a single and multiple administrations of YH4808, similar to what was observed.

\textbf{Conclusions:} The PBPK model adequately predicted observed concentrations of YH4808. Thus, the PBPK model can be used to predict the PK profiles of YH4808 in various clinical settings such as concomitant food intake and drug-drug interactions.

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Figure.png}
\caption{Observed (●) and PBPK model-simulated (-) plasma concentration-time profile of YH4808 in humans after single(a) and repeated (b) oral administration. Observed plasma concentration-time profiles were obtained for a 100mg single(a) and repeated(b) phase I clinical trial of YH4808}
\end{figure}