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Development of PBPK model to predict liver exposure of SRT-015, a next-generation inhibitor of ASK1

Abstract 2740

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1 Introduction

SRT-015 is a novel, clinical-stage, small molecule inhibitor of Apoptosis Signal-regulating Kinase 1 (ASK1) in development for liver diseases, including alcoholic hepatitis (AH), acute-on-chronic liver failure (ACLF), and non-alcoholic steatohepatitis (NASH).

In all preclinical species evaluated, SRT-015 is preferentially distributed to liver, with liver/plasma ratio ranging 10-60x.

2 Aim

We aimed to develop a physiologically based pharmacokinetic (PBPK) model to noninvasively estimate liver exposure of SRT-015 in humans.

3 Method

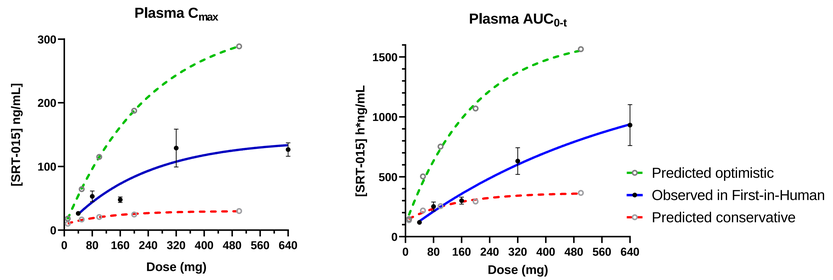
GastroPlus software (Simulation Plus, Lancaster, CA) was used first to build and validate PBPK models for SRT-015 PK mouse, rat, and non-human primates to explain the observed plasma levels vs. time profiles following intravenous (IV) and oral (PO) dose
The model was further expanded with the addition of efficacious liver and plasma concentrations of SRT-015 determined in preclinical models of NASH (DIO-NASH model, Gubra), AH/ACLF and acetaminophen overdose toxicity. Knowledge gained during preclinical PBPK modeling was then applied to build a human PBPK model for SRT-015 and predict First-in-Human (FIH) exposure following oral administration.
Actual plasma exposure of SRT-015 from the FIH study (NCT04887038) was then used to refine the human PBPK model and predict human liver exposure of SRT-015. The established model was also used to simulate human plasma and liver exposure after IV administration of SRT-015.

4 Results

Development of PBPK model from preclinical data

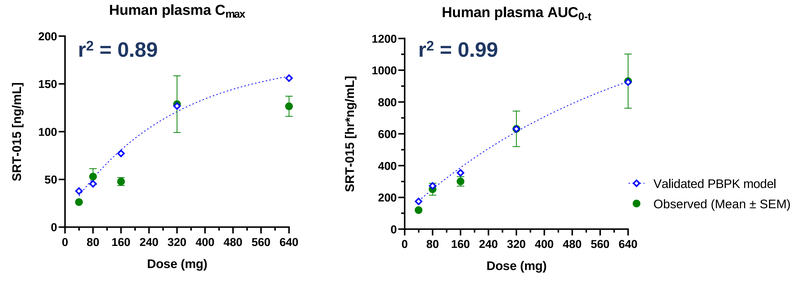
The PBPK model was highly predictive of human SRT-015 plasma exposure.

All observed values of C_{max} and AUC from FIH study within the predicted ranges across all dose levels.

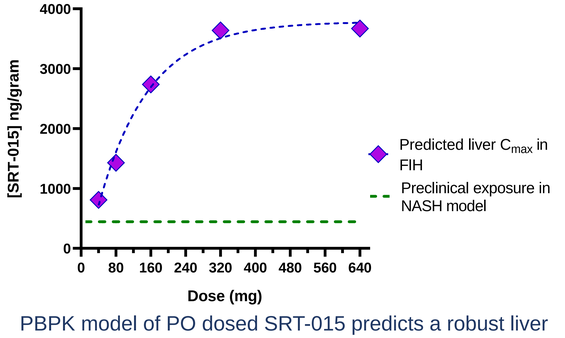


Validation of PBPK model with phase 1 plasma exposure

After further refinement, the C_{max} and AUC values predicted by the model correlated well with the observed in phase 1.

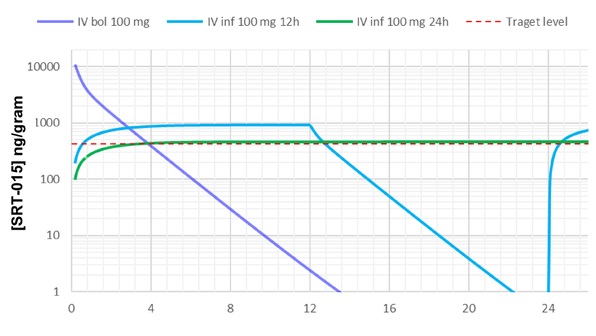


Predicted human liver exposure of SRT-015 (PO dose)



PBPK model of PO dosed SRT-015 predicts a robust liver exposure, well above the efficacious level in preclinical disease models.

Simulation of human liver exposure of SRT-015 (IV dose)



Additionally, the model predicts efficacious exposure with intravenous continuous infusion of SRT-015.

5 Conclusions

- **We have established a highly predictive PBPK model of human SRT-015 exposure.**
- **The model indicates achievement of efficacious exposure in the human liver with all oral doses tested in the phase 1 clinical trial in healthy participants and will help in the dose selection for phase 2 trials.**
- **The model also indicates the feasibility to attain efficacious exposure via IV infusion, which could be a preferred administration route in ACLF patients with impaired consciousness or otherwise unable to swallow an oral drug.**

6 Acknowledgements

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7 Contact information

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