Pharmacokinetic Modeling of EP547 and Simulations of Exposure in Hepatic Impairment

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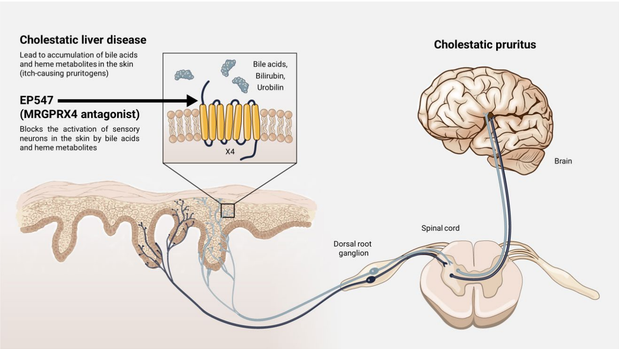
INTRODUCTION

- Mas-related G protein-coupled receptor X4 (MRGPRX4) is a multi-ligand chemosensory receptor expressed on pruriceptive sensory neurons in the skin that is activated by multiple components of bile. Specifically, primary and secondary bile acids and heme metabolites, including bilirubin, are all agonists of MRGPRX4, and their skin accumulation in association with pruritic cholestatic diseases implicates MRGPRX4 in this disease state.[1, 2]
- EP547, a potent and highly selective small-molecule inverse agonist of MRGPRX4 that blocks activation of the receptor by all bile acids and heme metabolites tested, is under development[3] as a once-a-day, orally administered therapy for cholestatic pruritus (Figure 1).[2]
- EP547 is believed to be predominantly cleared by hepatic metabolism and therefore EP547 pharmacokinetics (PK) are anticipated to be affected by impairment of hepatic function.

Figure 1. EP547 is a potent small-molecule MRGPRX4 antagonist in development for the treatment of cholestatic pruritus



AIMS

- **To develop a population PK (PopPK) model of EP547 in healthy subjects (HS) and patients with cholestatic liver disease (CLD)**
- **To apply the PopPK model to predict EP547 exposure in patients with reduced hepatic function to guide dosing in future clinical trials**

METHODS

- PopPK modeling of EP547 was performed following single (5 dose levels from 25 mg through 675 mg) and multiple (25, 75, and 225 mg once a day [QD] for 7 days) oral doses in male and female HS (n=48), following single (75 mg) and multiple (30 mg QD for 7 days) oral doses in patients with CLD (n=7), and following single (75 mg) and multiple (20 mg QD for 7 days) oral doses in patients with uremic pruritus (n=6).
- Modeling and simulations were performed with non-linear mixed effects software Phoenix NLME.
- Model evaluation was based on standard model diagnostics and Goodness of Fit (GOF) criteria (eg, accuracy of parameter estimation [ie, 95% confidence interval excluding 0], successful model convergence) and by looking at pertinent graphical representations of GOF (eg, fitted and observed concentrations vs. time, weighted residuals vs. time).

STUDY DATA

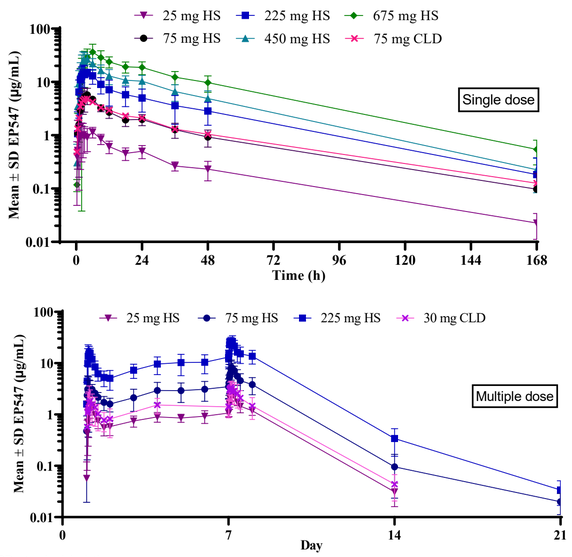
- The PK analysis dataset included 1413 measurable densely-spaced PK observations from 61 unique subjects.
- Of the 61 subjects in the PK dataset, 52.5% were male, 47.5% were female, and 54.1% were Caucasian.
- Patients with CLD had Child-Pugh A liver scores.

RESULTS

Exploratory PK Analysis: HS and Patients with CLD

- The shape of the elimination phase in HS and patients with CLD in semi-log plots suggests 2-compartment kinetics for both populations (Figure 2).

Figure 2. Plasma drug concentration vs time profiles following single and multiple doses in HS and patients with CLD



SD=standard deviation.

Final PopPK Model Parameters

- The first-order conditional estimation – extended least squares (FOCE-ELS) method as implemented in Phoenix NLME was used for model fitting. The final model parameters are in Table 1.
- A 2-compartment model with proportional error, with mixed zero- and first-order absorption and a zero-order lag time was developed to describe EP547 PK.
- Fixed allometric exponents of 0.75 and 1 were applied to the clearance and volume parameters, respectively.

Table 1. Final model parameters

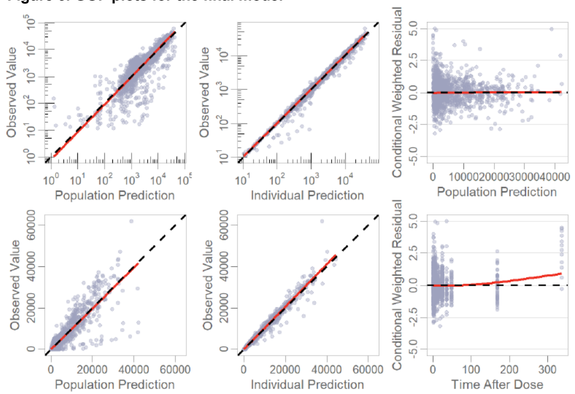
Parameters	Estimates	%RSE	95% CI
CL/F (L/h)	$0.572 \times (\frac{WT}{80.3})^{0.75}$	6.6	0.497 - 0.646
V/F (L)	$12.955 \times (\frac{WT}{80.3})^{1}$	5.7	11.512 - 14.398
CL2/F (L/h)	$1.267 \times (\frac{WT}{80.3})^{0.75}$	12.1	0.967 - 1.567
V2/F (L)	$10.786 \times (\frac{WT}{80.3})^{1}$	8.4	9.007 - 12.565
Dur (h)	1.732	9.6	1.405 - 2.058
Ka (1/h)	0.326	20.8	0.193 - 0.459
Tlag (h)	0.472	5.1	0.425 - 0.52
% (Ka)	0.668	14.2	0.482 - 0.855
Proportional error (%)	18.5	1.6	17.9 - 19.1

CI=confidence interval; CL/F=apparent clearance; CL2/F=apparent peripheral clearance; Dur=zero-order duration; Ka=absorption rate constant; RSE=relative standard error; Tlag=absorption lag time; V/F=apparent central volume of distribution; V2/F=apparent peripheral volume of distribution; WT=weight.

GOF for Final Model

- Observed concentrations and predicted values were distributed along the line of unity with minimal bias. Higher concentrations are slightly over predicted, which is illustrated in the conditional weighted residual vs. time after dose plot (Figure 3).

Figure 3. GOF plots for the final model



Dots are individual data points and solid lines are locally weighted scatterplot smoothing lines. In the leftmost and middle column plots, dashed lines are lines of identity, while in the two rightmost plots, dashed lines indicate normal distribution in plots of the conditional weighted residuals. Concentration units are in ng/mL, while time units are in hours.

Visual Predictive Check (VPC) of EP547 Concentrations

- The observed data generally falls within the simulated ranges as evidenced by the percentage of observed values that fall within the 95% confidence interval (Table 2).

Table 2. Observed data within simulated 95% CI in VPC plot – overall

Number of Obs Values (% of Obs Values)	Bin Midpoint (h)											
	2.5 (n=545)	18 (n=183)	48 (n=138)	146.5 (n=313)	312 (n=20)	480 (n=9)	889 (n=20)	1002 (n=26)	1224.25 (n=26)	1371 (n=76)	1512 (n=57)	Overall (n=1413)
Outside 95% CI	4 (0.7)	1 (0.5)	4 (2.9)	7 (2.2)	0 (0)	0 (0)	2 (10.0)	0 (0)	0 (0)	16 (21.1)	22 (38.6)	56 (4.0)
Within 95% CI	541 (99.3)	182 (99.5)	134 (97.1)	306 (97.8)	20 (100)	9 (100)	18 (90.0)	26 (100)	26 (100)	60 (78.9)	35 (61.4)	1357 (96.0)

CI=confidence interval; n=number of data points; obs=observed.

Simulations for Child-Pugh A and Child-Pugh B Patients

- Simulations of EP547 exposure in hepatically impaired patients were performed by modifying systemic clearance to account for reduced hepatic metabolism and guided by reported changes in blood flow in hepatically impaired patients (Table 3).
- Values used for the percentage change in hepatic blood flow relative to HS were -1.5% and -26.7% for Child-Pugh A and Child-Pugh B, respectively.[4]
- Simulated steady-state EP547 exposures compared favorably with observed exposures in patients with CLD with mildly impaired (Child-Pugh A) hepatic function (Table 4).

Table 3. Simulated EP547 exposure on Day 8 in HS under normal and simulated Child-Pugh A and Child-Pugh B conditions – 75 mg QD

Condition	N	Mean (SD) C_{max} (ng/mL)	C_{min} (ng/mL)	C_{ave} (ng/mL)	AUC_{0-24} (ng*h/mL)	$t_{1/2}$ (h)
HS (no CL reduction)	48	8360 (1910)	3470 (1150)	5120 (1340)	123000 (32200)	27.3 (5.12)
Child-Pugh A (-1.5% CL reduction)	48	8430 (1930)	3540 (1170)	5200 (1360)	125000 (32600)	27.6 (5.19)
Child-Pugh B (-26.7% CL reduction)	48	9900 (2230)	5060 (1530)	6750 (1710)	162000 (41000)	35.8 (6.82)

AUC calculated using linear up/log down method.
AUC_{0-24}=area under the curve from 0 to 24h; C_{ave}=average concentration over the dosing interval; CL=clearance; C_{max}=maximum concentration over the dosing interval; C_{min}=minimum concentration over the dosing interval; N=number of subjects; SD=standard deviation; $t_{1/2}$=half-life.

Table 4. Simulated and observed EP547 exposure on Day 8 in patients with Child-Pugh A hepatic impairment – 30 mg QD

Condition	N	Mean (SD) C_{max} (ng/mL)	AUC_{0-24} (ng*h/mL)	$t_{1/2}$ (h)
Simulated Child-Pugh A in HS (-1.5% CL reduction)	48	3370 (770)	49900 (13100)	27.6 (5.19)
Child-Pugh A CLD patients	2	3490 (940)	53000 (21790)	27.9 (0.880)

AUC calculated using linear up /log down method.
AUC_{0-24}=area under the curve from 0 to 24h; CL=clearance; C_{max}=maximum concentration over the dosing interval; N=number of subjects; SD=standard deviation; $t_{1/2}$=half-life.

CONCLUSION

- **EP547 PK in healthy subjects and patients with CLD were well described by a 2-compartment PopPK model with proportional error, mixed zero- and first-order absorption, and a zero-order lag time.**
- **Adjustment of the clearance parameter value within the PopPK model to simulate the effects of reduced hepatic function may be useful to help inform dose selection in patients with CLD in future clinical trials.**

REFERENCES

1) Dvorak et al., AASLD 2021, Poster Publication Number 1297
2) Yeager et al., AASLD 2021, Poster Publication Number 1262
3) Taylor et al, AASLD 2021, Poster Publication Number 1272
4) Dyvorne et al., 2015, AJR Am J Roentgenol, 204(3):510-18

DISCLOSURES

JB and TK are employees of Escient Pharmaceuticals, Inc. (Escient). CC and DB are employees of Certara. Study EP-547-101 funding was provided by Escient.

This research was funded by Escient Pharmaceuticals, Inc. For more information, contact clinicaltrials@escientpharma.com.

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