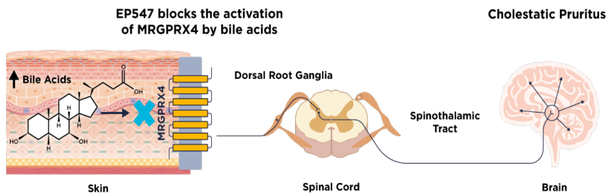
First-in-Human Study of EP547, a Potent and Highly Selective MRGPRX4 Inverse Agonist in Development for Treatment of Cholestatic Pruritus

Kristin Taylor[1], Jennifer Brooks[1], John Hemming[1], Beatrice Ferguson[1], Jaret Malloy[1], Alain Baron[1], Stuart K. Roberts[2], Edward Gane[3]
[1]Escient Pharmaceuticals, San Diego, CA, USA; [2]Alfred Hospital, Melbourne, VIC, Australia; [3]Auckland Clinical Studies, Auckland, New Zealand

INTRODUCTION

- Cholestatic pruritus is a common and often severe and debilitating condition in patients with primary biliary (PBC) and primary sclerosing cholangitis (PSC).
- Current pharmacological treatments for cholestatic pruritus are often unspecific and only modestly effective, and there are no medications that have been developed and approved specifically for CP in patients with PBC and PSC.[1, 2]
- Hence, there is a pressing need for novel therapies that target the underlying pathophysiology of cholestatic pruritus.
- 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.[3-6]
- 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 as a once-a-day, orally administered therapy for patients with cholestatic pruritus (Figure 1).[7]

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



AIM

The main objective of this Phase 1 first-in-human clinical trial was to assess the safety and pharmacokinetics (PK) of EP547 in healthy subjects and in patients with chronic liver disease (CLD) commonly accompanied by cholestatic pruritus.

METHODS

- The study was conducted in Australia and New Zealand and employed a standard single (SAD) and multiple (MAD) ascending dose design in healthy subjects, with additional single- and multiple-dose cohorts in patients with CLD (Table 1).
- Study conduct was overseen by a Safety Review Team that reviewed all emerging data and confirmed patient safety before subsequent cohorts were dosed.
- Subjects and study site personnel were blinded to treatment for all placebo-controlled segments.

Table 1. Study Design

	Healthy Subjects		Patients with CLD	
	SAD	MAD	Single Dose	Multiple Dose
Study population	• Healthy males and females • 18-60 years old		• PBC, PSC, or chronic hepatitis B or C • 18-80 years old • Moderate to severe cholestatic pruritus (multiple dose only)	
Dosing levels	25, 75, 225, 450, 675 mg	25, 75, 225 mg	75 mg	30 mg
Dosing schedule	Single dose	Once daily for 7 days	Single dose	Once daily for 7 days
Allocation/ Randomization	3:1 (active/placebo)	3:1 (active/placebo)	All active	3:1 (active/placebo)

Key Primary and Secondary Outcome Measures:

- Safety and tolerability
- Pharmacokinetics: Plasma and skin PK profiles and PK parameters

RESULTS

Demographics and baseline characteristics were consistent with expectations for the respective populations

- All subjects in the SAD, MAD, single-dose, and multiple-dose phases completed study procedures.
- Baseline characteristics were generally balanced between treatment groups.
- Patients with CLD generally had higher serum total bile acid concentrations than healthy subjects.

Table 2. Demographics and baseline characteristics

	Healthy Subjects		Patients with CLD	
	SAD N=40	MAD N=24	Single Dose N=5	Multiple Dose N=3
Age (years)	31 ± 9	35 ± 14	59 ± 16	52 ± 10
Sex (% Male)	38	71	40	33
Race (% White/Asian/Other)	63/15/28	50/21/33	80/20/20	100/0/0
Weight (kg)	72 ± 15	80 ± 15	83 ± 22	87 ± 28
BMI (kg/m^2)	25 ± 3	26 ± 4	28 ± 5	29 ± 11
Relevant Liver Disease History (n)				
Hepatitis B	NA	NA	1	0
Hepatitis C	NA	NA	3	0
PBC	NA	NA	1	1
PSC	NA	NA	0	2
Liver-Related Laboratory Values				
Child-Pugh score (points)	NA	NA	5 ± 0	5 ± 0
ALT (U/L)	17 ± 7	23 ± 12	28 ± 13	61 ± 35
AST (U/L)	18 ± 3	22 ± 5	28 ± 10	59 ± 32
ALP (U/L)	62 ± 18	70 ± 18	79 ± 52	331 ± 214
Total BAs (mg/dL)	0.14 ± 0.13	0.11 ± 0.09	0.66 ± 0.67	1.15 ± 0.86
Total Bilirubin (mg/dL)	0.41 ± 0.21	0.50 ± 0.25	0.40 ± 0.11	1.01 ± 0.24

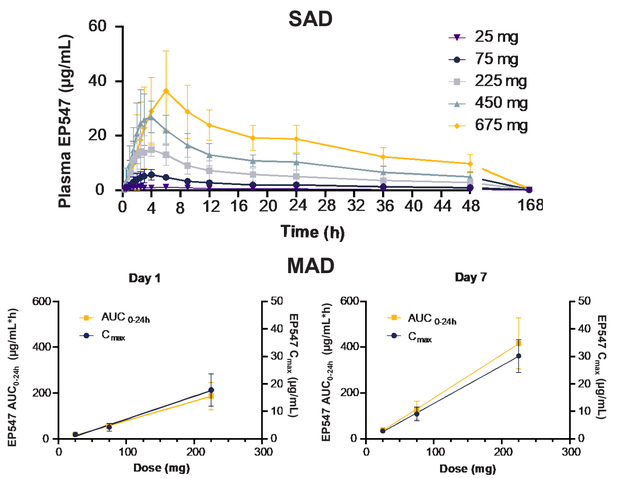
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BA=bile acid; BMI=body mass index; NA=not applicable.
Data are mean ± standard deviation or percent or number of subjects.
Subjects could select more than one race category.

EP547 PK was predictable, dose linear, and supports once-daily oral administration

Healthy Subjects:

- EP547 exposure was dose proportional with an approximately 2-fold increase for maximum plasma concentration (C_{max}) and area under the concentration-time curve from 0 to 24 hours postdose (AUC_{0-24}) on Day 7 relative to Day 1.
- EP547 median time to achieve peak plasma concentration (T_{max}) was achieved at approximately 2.5 to 6 hours postdose with a median terminal half-life ($t_{½}$) between 12 and 34 hours postdose.
- EP547 was confirmed to be present in the skin.

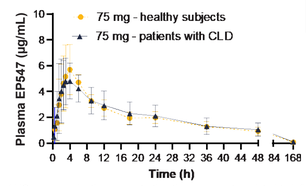
Figure 2. EP547 PK in Healthy Subjects: Dose proportionality for AUC_{0-24} and C_{max}



Data are mean ± standard deviation.
SAD: N=30 (6 per treatment group). MAD: N=18 (6 per treatment group).

Patients with CLD:

Figure 3/Table 3. EP547 exposure is similar between healthy subjects and patients with CLD



75 mg Single Dose EP547 PK Parameters	Healthy Subjects SAD N=6	Patients with CLD Single Dose N=5
C_{max} (µg/mL)	6.4 (1.2) 19%	5.2 (1.6) 31%
T_{max} (h)	4.0 (2.0, 6.0)	3.0 (1.5, 6.0)
AUC_{0-24h} (µg/mL•h)	70 (15) 22%	72 (24) 33%
AUC_{∞} (µg/mL•h)	147 (48) 33%	158 (73) 46%
$t_{½}$ (h)	28 (17, 53)	35 (13, 42)

AUC_{∞}=area under the concentration-time curve extrapolated to infinity.
Left panel: Data are mean ± standard deviation.
Right panel: Data are mean (standard deviation) percent coefficient of variation for C_{max} and AUC; data are median (minimum, maximum) for T_{max} and $t_{½}$.

- Simulations of single-dose data accurately predicted the multiple-dose exposures observed in the multiple-dose patient cohort.

EP547 was well tolerated with no safety signals identified

- EP547 was safe and well tolerated at the doses and durations tested in both populations and showed no apparent dose response or worsening of safety parameters compared to placebo.
- There were no severe adverse events (AEs), no serious AEs (SAEs), and no AEs leading to early withdrawal from the study.
- The most common AEs with EP547 in healthy subjects were mild headache and diarrhea. Mild headache was the only common AE in patients with CLD (Table 4).
- No meaningful changes were observed among safety laboratory measures, electrocardiograms, or vital signs for either population.

Table 4. AEs in Patients with CLD

Preferred Term, n	Single Dose EP547 75 mg (N=5)	Multiple Dose EP547 30 mg (N=2)	Multiple Dose Placebo (N=1)
Any AE	**4**	**1**	**1**
Headache	2	1	0
Back pain	1	0	0
Cough	1	0	0
Thermal burn	1	0	0
Urticaria	0	1	0
Contusion	0	0	1
Dizziness	0	0	1
Vessel puncture site hematoma	0	0	1

CONCLUSION

In this first-in-human study of EP547:

- **EP547, a novel mechanism-of-action targeted investigational treatment to address cholestatic pruritus, a serious, unmet medical need, was safe and well tolerated at the doses and durations tested.**
- **The PK of EP547 is predictable, shows strong dose linearity, and supports once-daily oral administration in future studies.**
- **The results support further clinical evaluation, including studies with a larger sample size and longer treatment duration to further characterize the safety, tolerability, and efficacy of EP547.**

REFERENCES

1) Bassari et al., 2015: World J Gastroenterol, 21:1404-13
2) Mittal, 2016: Curr Probl Dermatol, 50:142-8
3) Meixiong et al., 2019: eLife, 8: e48431
4) Meixiong et al., 2019: PNAS, 116:10525-30
5) Yu et al., 2019: bioRxiv. 2019: eLife, 8:e48431
6) Dvorak et al., AASLD 2021, Poster Publication Number 1297
7) Yeager et al., AASLD 2021, Poster Publication Number 1262

DISCLOSURES

KT, JB, JH, BF, and AB are employees of and hold stock in Escient Pharmaceuticals, Inc. (Escient). JM is a consultant for Escient. SR and EG were principal investigators of Study EP-547-101, the funding of which was provided by Escient.

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