Pharmacokinetics of tropifexor, a potent farnesoid X receptor agonist, are similar in subjects with mild, moderate, and severe hepatic impairment: Results from a multicentre, open-label, single-dose study

PO-534

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Background

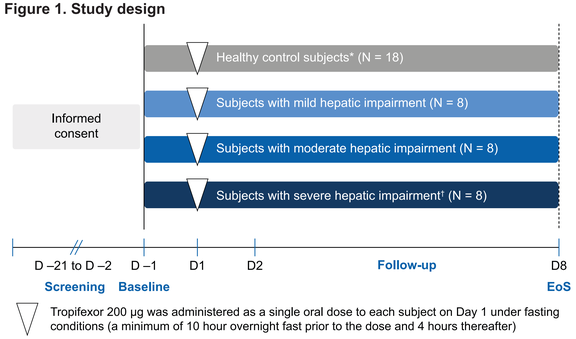
- Tropifexor is a potent farnesoid X receptor (FXR) agonist that is currently under development for the treatment of non-alcoholic steatohepatitis[1,2]
- In the first-in-human study, tropifexor was safe and well-tolerated at single doses up to 3000 µg in healthy volunteers and showed dose-proportional pharmacokinetics with no obvious major enterohepatic circulation[2,3]
- Tropifexor is eliminated predominantly via hepatic metabolism catalysed by cytochrome P450 (CYP)3A4 and CYP2C8 and uridine 5'-diphosphoglucuronosyltransferases (UGT)1A1 and UGT1A3[2,3]
- This study evaluated safety and the effect of hepatic impairment (HI) on the systemic exposure of tropifexor, to support treatment and dosing decisions for patients with varying degrees of HI

Methods

Study design and population

- In this open-label, single-dose, parallel-group study (NCT03681457), 42 subjects were enrolled: 8 each with mild, moderate, or severe HI (Child-Pugh classification) and 18 matched healthy control subjects with normal hepatic function
- Subjects in the control and HI groups were matched with respect to gender, age (± 10 years), body weight (± 10%), and smoking status. Each healthy subject was matched to at least 1 corresponding subject in the HI group
- Tropifexor 200 µg was administered as a single oral dose on the morning of Day 1 under fasting conditions (a minimum of a 10 hour overnight fast prior to the dose and 4 hours thereafter)
- Dosing in the severe HI group commenced after half of the subjects in the mild and moderate HI groups completed the study

Figure 1. Study design



*Healthy subjects were enrolled in 2 sets, the first set after enrolment of subjects in the mild and moderate HI groups and the second set after enrolment of subjects in the severe HI group; †Dosing in the severe HI group commenced after half of subjects in the mild and moderate HI groups completed the study.
D, day; EoS, end-of-study; HI, hepatic impairment.

Objectives

- Primary: To assess the pharmacokinetic (PK) properties of tropifexor in subjects with mild, moderate, or severe HI vs healthy subjects
- Secondary: To assess i) safety and tolerability of tropifexor in subjects with mild, moderate, or severe HI vs healthy subjects; ii) plasma protein binding free fraction of tropifexor (fu) in subjects with HI vs healthy subjects

Assessments

- PK parameters: Serial blood samples were collected from pre-dose and up to 168 h post-dose to assess maximum drug concentration [C_{max}], time to reach C_{max} (T_{max}), area under the concentration-time curve from time zero to i) the time of last quantifiable concentration [AUC_{last}], and ii) infinite time [AUC_{inf}]
- Safety: Vital signs, electrocardiogram (ECG), and adverse events (AEs) were monitored up to 30 days post-dose

Analysis sets

- Safety: All subjects who received any study drug
- PK: Subjects who received study drug with at least one available valid quantifiable postdose PK measurement, and with no protocol deviations that impact the PK data

Results

Subject disposition and baseline demographics

- Of the 42 subjects enrolled, 41 (97.6%) subjects completed the study. One subject in the control group discontinued study due to a family emergency
- The majority of subjects were males (32 [76.2%]) and Caucasian (31 [73.8%]). The mean (SD) age of all subjects was 51.1 (11.06) years
- The mean (SD) weight and body mass index for all subjects were 88.6 (19.11) kg and 29.7 (5.03) kg/m^2, respectively

PK results

- Mean tropifexor concentrations were similar between the mild HI and control groups; they were slightly higher in the moderate HI group vs controls throughout the observation period (**Figure 2**)
- In the severe HI group, mean tropifexor concentrations were lower for the first 12 hours vs controls and were slightly higher thereafter (**Figure 2**)
- Summary statistics for plasma PK parameters of total and unbound tropifexor are summarised in **Table 2**

Effect of HI on PK parameters

- Total tropifexor: Compared to their healthy control groups, a geometric mean C_{max} decrease of 10% in the mild HI group and of 36% in the severe HI group was noted; AUC_{last} and AUC_{inf} were similar in the mild and severe HI groups vs controls. In subjects with moderate HI, AUC_{last} and AUC_{inf} increased by 28% vs controls (**Figure 3A**)
- Unbound tropifexor: In subjects with mild HI, $C_{max,u}$ was similar while $AUC_{last,u}$ and $AUC_{inf,u}$ increased on average by 11% vs controls. $C_{max,u}$ increased on average by 30% in the moderate HI group vs controls; it was comparable between the severe HI and control groups. $AUC_{last,u}$ and $AUC_{inf,u}$ increased on average by 64% in the moderate HI group and 61% in the severe HI group vs controls (**Figure 3B**)

Plasma protein binding of tropifexor

- Plasma protein binding of tropifexor was very high (99.8% to 99.9%) in all groups
- The fu (%) ranged between 0.102%–0.541% in all subjects. Binding was comparable between the healthy and mild HI groups. A small increase in the overall mean fu (%) was observed in the moderate HI (1.4-fold) and the severe HI (1.7-fold) groups vs the healthy/mild HI group

Safety

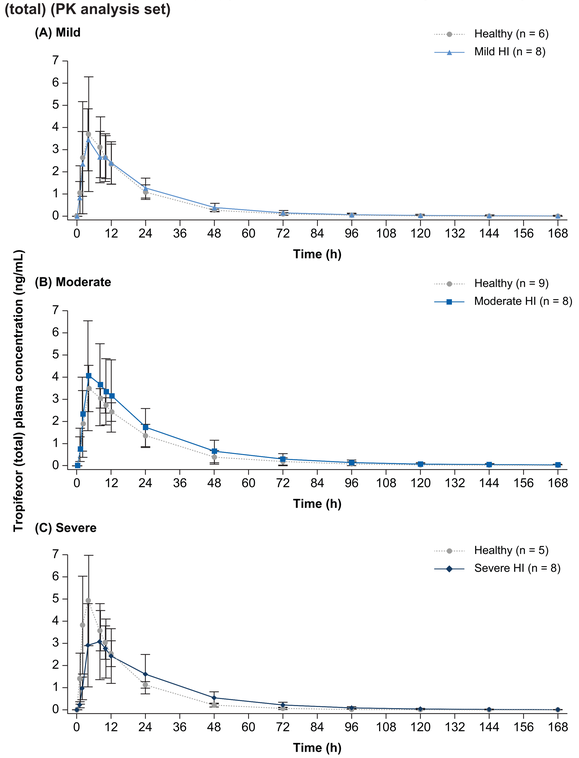
- None of the treatment-emergent AEs, serious AEs were considered related to the study drug or led to study discontinuation
- No clinically significant changes in vital signs or ECGs were observed
- No deaths were reported during the study

Table 1. Baseline demographics (safety analysis set)

	Mild HI (N = 8)	Healthy matched controls[a] (N = 6)	Moderate HI (N = 8)	Healthy matched controls[a] (N = 9)	Severe HI (N = 8)	Healthy matched controls[a] (N = 5)
Age (years), mean (SD)	52.8 (12.01)	50.3 (9.91)	49.8 (13.30)	47.2 (11.53)	56.0 (8.02)	52.6 (10.62)
Gender, n (%)						
Male	7 (87.5)	5 (83.3)	5 (62.5)	6 (66.7)	7 (87.5)	4 (80.0)
Female	1 (12.5)	1 (16.7)	3 (37.5)	3 (33.3)	1 (12.5)	1 (20.0)
Caucasian,n (%)	6 (75.0)	4 (66.7)	6 (75.0)	7 (77.8)	6 (75.0)	3 (60.0)
Weight (kg), mean (SD)	88.4 (14.80)	86.5 (13.82)	96.2 (26.59)	94.6 (24.38)	81.5 (9.24)	81.6 (15.05)
BMI (kg/m^2), mean (SD)	31.1 (3.79)	27.6 (2.60)	31.8 (6.53)	30.9 (6.29)	27.4 (3.28)	26.7 (3.55)

[a]Each healthy subject was matched to at least 1 corresponding subject in the HI group.
BMI, body mass index; HI, hepatic impairment; SD, standard deviation.

Figure 2. Arithmetic mean (SD) plasma concentration-time profiles of tropifexor (total) (PK analysis set)



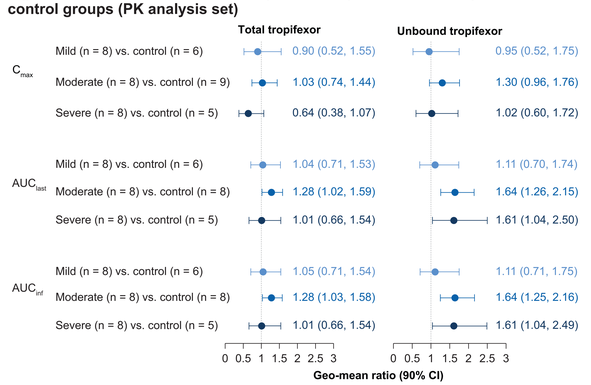
HI, hepatic impairment; PK, pharmacokinetic; SD, standard deviation.

Table 2. Summary statistics for plasma PK parameters of total and unbound tropifexor (PK analysis set)

Parameter Geo-mean (CV%)	Mild HI (N = 8)	Healthy matched controls (N = 6)	Moderate HI (N = 8)	Healthy matched controls (N = 9)	Severe HI (N = 8)	Healthy matched controls (N = 5)
Total tropifexor						
C_{max} (ng/mL)	3.15 (52.7)	3.42 (74.6)	3.81 (59.5)	3.66 (24.1)	2.94 (56.8)	4.61 (48.0)
T_{max} (h)[a]	4.0 (2.0-8.0)	4.0 (4.0-8.0)	6.0 (4.0-10.0)	4.0 (2.0-8.1)	8.0 (4.0-10.0)	4.0 (4.0-8.0)
AUC_{last} (ng*h/mL)	76.9 (46.4)	73.1 (35.9)	104 (50.3)	81.6 (36.7)[b]	83.0 (53.1)	82.3 (19.4)
AUC_{inf} (ng*h/mL)	78.2 (46.5)	73.8 (35.6)	106 (50.0)	82.9 (37.8)[b]	83.8 (52.8)	83.1 (19.1)
Unbound tropifexor						
$C_{max,u}$ (ng/mL)	0.00436 (55.8)	0.00444 (87.8)	0.00663 (59.6)	0.00508 (29.4)	0.00700 (58.5)	0.00689 (49.0)
$AUC_{last,u}$ (ng*h/mL)	0.107 (49.9)	0.0950 (45.6)	0.181 (71.7)	0.110 (35.9)[b]	0.198 (54.4)	0.123 (23.3)
$AUC_{inf,u}$ (ng*h/mL)	0.108 (50.0)	0.0960 (45.4)	0.184 (73.1)	0.112 (37.3)[b]	0.200 (54.1)	0.124 (23.1)
fu (%)	0.138 (5.9)	0.130 (20.6)	0.174 (50.9)	0.138 (22.0)	0.238 (22.7)	0.149 (14.3)

[a]Data presented as median (min-max); [b]n = 8.
AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from predose to infinity; AUC_{last}, AUC from predose to time of last quantifiable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; fu, fraction of tropifexor unbound to protein; HI, hepatic impairment; PK, pharmacokinetic; T_{max}, time to reach C_{max}.

Figure 3. Geometric mean ratios for plasma PK parameters of tropifexor in HI vs control groups (PK analysis set)



A separate linear mixed effects model, with group as a fixed effect and matched pair as random effect, was fitted to compare each HI group with its matching control group for each log-transformed PK parameter. Results were back transformed to obtain geo-mean ratio and 90% CI on the original scale.
AUC, area under the plasma concentration-time curve; AUC_{inf}, AUC from predose to infinity; AUC_{last}, AUC from predose to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; HI, hepatic impairment; PK, pharmacokinetic.

Table 3. Incidence of treatment-emergent AEs (safety analysis set)

	Normal (N = 18)	Mild HI (N = 8)	Moderate HI (N = 8)	Severe HI (N = 8)	Total (N = 42)
Number of subjects with at least one TEAE	2 (11.1)	0 (0.0)	1 (12.5)	2 (25.0)	5 (11.9)
SAEs	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)[a]	2 (4.8)
Incidence of TEAEs by preferred term					
Ascites	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.4)
Constipation	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	1 (2.4)
Hepatic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.4)
Infusion site extravasation	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Multiple fractures	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (2.4)
Vascular procedure complication	1 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)

All data are n (%).[a]One subject reported multiple fractures and one subject reported hepatic encephalopathy; neither SAE was considered by the Investigator to be related to the study drug.
AE, adverse event; SAE, serious AE; HI, hepatic impairment; TEAE, treatment-emergent AE.

Conclusions

- A single oral dose of tropifexor 200 µg was well tolerated in all subjects, with no relevant increase in systemic exposure of total tropifexor across mild, moderate, and severe HI groups
- Although increased exposure to unbound tropifexor was seen in the moderate and severe HI groups, it was within well-tolerated limits seen previously in healthy subjects[2]
- Tropifexor pharmacokinetics were relatively insensitive to changes in HI, offering the potential to treat patients with liver disease without dose adjustment

References

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Disclosures

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