

# The Effect of Hepatic Impairment on the Pharmacokinetics of Intravenously Administered Felcisetrag (TAK-954)

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## Abstract

Felcisetrag (formerly known as TAK-954) is a selective serotonin receptor agonist under investigation for use in patients with postoperative gastrointestinal dysfunction. The safety, tolerability, and pharmacokinetics (PK) of intravenous (i.v.) felcisetrag have been studied, but little is known about the effect of hepatic impairment on the PK of the drug. This phase I, non-randomized, open-label study compared the PK of a single 60-minute i.v. infusion of felcisetrag between healthy individuals ( $n = 8$ ) and patients with moderate ( $n = 10$ ) or severe ( $n = 7$ ) hepatic impairment. The primary study end points were the total and free maximum observed plasma concentration of felcisetrag at the end of infusion ( $C_{max}$ ), area under the concentration–time curve (AUC) from time 0 to the time of the last quantifiable concentration ( $AUC_{last}$ ), and AUC from time 0 to infinity ( $AUC_{inf}$ ). Concentration–time profiles of felcisetrag were similarly shaped between groups but revealed lower concentrations of total plasma felcisetrag with increasing severity of hepatic impairment, whereas concentrations of free felcisetrag increased. The ratios of  $AUC_{last}$  and  $AUC_{inf}$  for patients with severe hepatic impairment were up to 29.3% lower for total felcisetrag and up to 29.2% higher for free felcisetrag than found in healthy individuals ( $P < .05$ ). Infusions were well tolerated with no discontinuations, severe adverse events, or deaths during the study. Overall, the effect of hepatic impairment on exposure to felcisetrag was minimal, suggesting that dose adjustment may be unnecessary in patients with hepatic impairment.

## Keywords

postoperative gastrointestinal dysfunction, felcisetrag, pharmacokinetics, hepatic impairment, safety and tolerability

Postoperative gastrointestinal dysfunction, also known as postoperative ileus, characterized by delayed gastrointestinal recovery following surgery, is reported in 13% to 27% of patients undergoing major abdominal surgery.<sup>1–4</sup> The development of postoperative gastrointestinal dysfunction is associated with increased postoperative morbidity as well as prolonged length of stay in hospital and higher hospital costs.<sup>5,6</sup>

A number of non-pharmacological strategies have been explored for the treatment of postoperative gastrointestinal dysfunction, including enhanced recovery protocols,<sup>7</sup> coffee,<sup>8</sup> chewing gum,<sup>9</sup> and acupuncture,<sup>10</sup> all of which appear to have favorable safety profiles but unclear benefit for actively reducing the disorder. Pharmacological options that have shown promise in treating postoperative gastrointestinal dysfunction include  $\mu$ -opioid antagonists,<sup>11</sup> ghrelin agonists,<sup>12</sup> and serotonin (5-HT) receptor agonists.<sup>13</sup>

Felcisetrag (1-piperidinecarboxylic acid, 4-((4-(((2-(1-methylethyl)-1H-benzimidazol-7-yl)carbonyl)amino)methyl)-1-piperidinyl)methyl)-, methyl ester; previously referred to as TAK-954, Figure 1) is a potent, highly selective 5-HT<sub>4</sub> receptor agonist with demonstrated prokinetic activity throughout the gastrointestinal tract in experimental models.<sup>14,15</sup>

In a study of felcisetrag pharmacokinetics (PK) in healthy participants, after single and multiple daily intravenous (i.v.) infusions of felcisetrag (0.1 or 0.5 mg), approximate dose-proportional increases in the drug were observed on day 1, with steady-state levels achieved by day 3 and minimal accumulation.<sup>16</sup> The mean terminal elimination half-life ( $t_{1/2z}$ ) ranged from

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recent medical history. The Child–Pugh criteria uses 5 clinical and laboratory criteria to categorize patients (serum bilirubin, serum albumin, ascites, neurological disorder, and prothrombin time), with variable points for each criterion based on increasing severity.<sup>19,20</sup> The severity of cirrhosis is classified as mild (Child–Pugh grade A, 5 or 6 points), moderate (Child–Pugh grade B, 7 to 9 points), or severe impairment (Child–Pugh grade C, 10 to 15 points), based on the total score derived from these criteria. Exclusion criteria for participants with hepatic impairment included a history of hepatic carcinoma, hepatorenal syndrome, or presence of liver masses (tumors or abscesses, with no definitive diagnosis) by ultrasound, CT, or MRI, or acute liver disease caused by an infection or drug toxicity, surgical portosystemic shunts, elevated bilirubin levels (>5 times upper normal limit), or renal creatinine clearance  $\leq 50$  mL/min, as calculated by the Cockcroft–Gault formula at screening.<sup>21</sup> Participants with severe hepatic encephalopathy (grade >2) were also excluded.

Healthy participants with normal hepatic function (healthy participants) were chosen to be comparable with the hepatic impairment groups with regards to median age and weight (with approximately 50% of healthy participants on each side of the median age and weight of the enrolled participants with hepatic impairment grouped together), sex, and race. Participants in the healthy control group were chosen to be in general good health as assessed by the investigator, based on a medical history and clinical evaluation (including physical examination, clinical laboratory tests, vital sign measurements, and 12-lead electrocardiogram [ECG]) performed at the screening visit and at check-in on day 1. The main exclusion criteria for healthy participants were history of malignancy or clinically significant endocrine, gastrointestinal (including motility disorder and intestinal obstruction), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases.

### Study Design

This was a phase 1, nonrandomized, open-label study. Approximately 32 participants were planned for non-random assignment to 1 of 4 treatment groups (group 1, mild hepatic impairment; group 2, moderate hepatic impairment; group 3, severe hepatic impairment; group 4, no hepatic impairment [healthy participants]) with a minimum of eight individuals in groups 1, 2, and 4 and a maximum of 8 individuals in group 3.

The groups were enrolled in a staggered fashion, starting with group 2 (moderate hepatic impairment). Initially, the first 2 participants in group 2 received felcisetrag (0.2 mg) administered i.v. as a 60-minute

infusion in 0.9% sodium chloride in a fasted state (after a minimum 8-hour fast), followed by safety and PK assessments. The i.v. dose of felcisetrag 0.2 mg used in this study was within the potentially clinically relevant range of doses previously found to accelerate gastric emptying,<sup>22</sup> and was lower than the maximum multiple i.v. dose (0.5 mg once daily) that has been investigated in PK studies to date, in an attempt to maintain tolerability in case of increased concentrations in patients with hepatic impairment.

Once safety and PK data were available for group 2, study personnel and the investigator reviewed these data and confirmed the 0.2 mg dose of felcisetrag for the remaining six participants in the group. Enrollment of healthy participants (group 4) commenced after the second participant in group 2 had been enrolled. When group 2 was complete, and following an assessment of the PK and safety data from that group, the study personnel decided not to enroll participants in group 1 (mild hepatic impairment), based on the similar exposure to felcisetrag observed in group 2 (moderate hepatic impairment) compared with that seen in a previous study in healthy participants.<sup>23</sup>

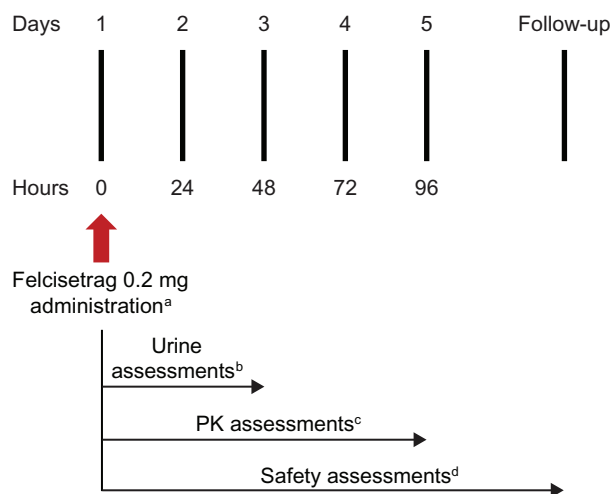
Participants with severe hepatic impairment were enrolled into group 3 and received a single infusion of felcisetrag 0.2 mg administered i.v. over 60 minutes. All participants were confined to the clinic for 4 days (from 1 day before drug infusion, to day 3 post-infusion) or longer at the discretion of the investigator, with two further outpatient visits, and a follow-up visit at 10 to 14 days after dosing.

### Study Objectives

The primary objective of this study was to evaluate the effect of varying degrees of hepatic function on the PK of a single i.v. infusion of felcisetrag. Secondary objectives were to evaluate the safety and tolerability of a single i.v. infusion of felcisetrag in participants with varying degrees of hepatic function.

### Sample Collection

Blood samples (4 mL) for the assessment of plasma concentrations of felcisetrag and its 2 main metabolites (THR-513466 and THR-913682) were collected on day 1 at up to 30 minutes before dosing and up to 96 hours after the start of infusion (Figure 2). Samples were collected in ethylenediaminetetraacetic acid (EDTA) dipotassium salt dihydrate-containing collection tubes and free felcisetrag was extracted using solid-phase extraction on an Oasis MCX 96-well extraction plate (Waters, Milford, Massachusetts). Extracted compounds were injected onto a MonoChrom Si high-performance liquid chromatography column (Agilent, Santa Clara, California) (Supplemental Text S1). Additional samples were collected at 1 hour and



**Figure 2.** Study schedule for felcisetrag administration and sample collection for pharmacokinetic assessments. <sup>a</sup>Single i.v. infusion over 60 minutes. <sup>b</sup>Urine samples collected prior to dosing and at intervals of 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours. <sup>c</sup>Blood samples were collected on day 1 at up to 30 minutes prior to dosing and at 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 6, 12, 24, 36, 48, 72, and 96 hours postdose. <sup>d</sup>Follow-up visits took place up to 14 days after the last PK assessment. i.v., intravenous; PK, pharmacokinetics.

at 12 hours postdose for the ex vivo determination of protein binding subsequently used to calculate unbound concentrations of felcisetrag and corresponding free PK parameters.

Urine samples for the determination of felcisetrag levels and metabolites were collected on day 1 and at intervals up to 48 hours after the start of the infusion (Figure 2).

Plasma and urine samples were analyzed for felcisetrag and its 2 main metabolites (THRX-513466 and THRX-913682) using validated high-performance liquid chromatography with tandem mass spectrometry methods. Separate analytical methods were used for plasma and urine samples. The plasma calibration range was 5.0 to 2000 pg/mL and the lower limit of quantification was 5.0 pg/mL for all analytes. The urine calibration was 10.0 to 10000 ng/mL for all analytes. Further details of the methods used for the quantification of felcisetrag, and its metabolites, are presented in Supplemental Text S1.

#### PK Assessments

All noncompartmental PK analyses, summary tables, and figures were generated using Phoenix WinNonlin 7.0 (Certara, Princeton, New Jersey). The primary study end points (expressed as total [bound and unbound] and free [unbound]) were  $C_{max}$ , area under the concentration–time curve (AUC) from time 0 to the time of the last quantifiable concentration ( $AUC_{last}$ ), and AUC from time 0 to infinity ( $AUC_{inf}$ ), calculated from  $AUC_{last}$  by the addition of the constant  $C_{last}/\lambda_z$ ,

where  $C_{last}$  is the last observed quantifiable concentration and  $\lambda_z$  is the terminal elimination rate constant. Exploratory end points were the level of drug excreted in urine from time 0 to time  $t$  ( $A_{et}$ ), the fraction of administered dose of drug excreted in urine ( $f_e$ ), and renal clearance ( $CL_R$ ).

#### Safety Assessments

Safety was assessed by monitoring for AEs and vital signs, and by conducting ECGs, safety laboratory tests, and physical examinations throughout each dosing period. Safety was assessed from day 1 to the follow-up visit (0 to 14 days after the last PK sample).

#### Statistical Analysis

**Sample Size.** The planned sample size of eight participants per hepatic function group was informed by regulatory guidance for PK studies in patients with impaired hepatic function.<sup>20,24</sup>

**Analysis Sets.** The safety analysis set consisted of all participants who were enrolled and received the study drug. The PK analysis set included all participants who were enrolled and received the correct dose of study drug and had at least one measurable plasma concentration or quantity of drug in the urine for felcisetrag. All participants with valid PK parameter estimates were included in the summaries and analyses for that parameter.

**Statistical Tests.** The PK parameters determined using noncompartmental analysis of felcisetrag concentration–time data were compared between healthy participants and participants with hepatic impairment, classified by Child–Pugh score, and summarized descriptively.

To compare each group of participants with hepatic impairment with healthy participants, an analysis of variance (ANOVA) was performed on log-transformed  $C_{max}$ , AUCs (total and free), and total plasma clearance (CL). To investigate the effect of covariates on the relationship between felcisetrag PK parameters and level of hepatic impairment, an analysis of covariance (ANCOVA) with hepatic function group as a fixed effect, and with age, sex, and body weight as covariates, was performed on log-transformed  $C_{max}$ , AUCs (total and free), and CL data.

The relationships between and among Child–Pugh scores and PK parameters for felcisetrag ( $C_{max}$ ,  $C_{max}$  for unbound drug [ $C_{max_u}$ ],  $AUC_{last}$ ,  $AUC_{last}$  for unbound drug [ $AUC_{last_u}$ ],  $AUC_{inf}$ , and  $AUC_{inf}$  for unbound drug [ $AUC_{inf_u}$ ]) were evaluated using regression analysis, if appropriate. For each PK parameter, regression models with Child–Pugh score, baseline serum bilirubin, albumin, and prothrombin time as covariates

**Table 1.** Demographics and Baseline Characteristics by Hepatic Function Group

	Group 4 (Normal Hepatic Function) (n = 8)	Group 2 (Moderate Hepatic Impairment) (n = 10)	Group 3 (Severe Hepatic Impairment) (n = 7)	Total (N = 25)
Age (years), n (%)				
18 to ≤64	5 (62.5)	8 (80.0)	4 (57.1)	17 (68.0)
65 to ≤75	3 (37.5)	2 (20.0)	3 (42.9)	8 (32.0)
Age, years				
Mean (SD)	58.5 (9.5)	55.6 (12.3)	57.9 (12.88)	57.2 (11.21)
Median (min–max)	59.0 (44–72)	60.0 (37–70)	60.0 (34–71)	60.0 (34–72)
Sex, n (%)				
Male	5 (62.5)	6 (60.0)	6 (85.7)	17 (68.0)
Female	3 (37.5)	4 (40.0)	1 (14.3)	8 (32.0)
Ethnicity, n (%)				
Not Hispanic or Latino	8 (100.0)	10 (100.0)	7 (100.0)	25 (100.0)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)				
White	8 (100.0)	10 (100.0)	7 (100.0)	25 (100.0)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Baseline weight, kg				
Mean (SD)	89.95 (17.1)	86.77 (19.82)	87.19 (21.33)	87.90 (18.67)
Median (min–max)	86.00 (71.4–116.2)	92.00 (55.0–111.0)	84.00 (63.0–119.3)	86.00 (55.0–119.3)
Baseline BMI, kg/m <sup>2</sup>				
Mean (SD)	31.1 (3.18)	30.4 (5.02)	27.9 (6.18)	29.9 (4.87)
Median (min–max)	31.5 (26–35)	33.0 (23–35)	28.0 (20–34)	32.0 (20–35)
Baseline height (cm)				
Mean (SD)	169.8 (11.30)	168.0 (10.47)	176.1 (6.28)	170.8 (10.01)
Median (min–max)	173.0 (153–183)	171.0 (155–181)	176.0 (166–186)	174.0 (153–186)

BMI, body mass index; SD, standard deviation.

were used. Scatter plots were created to examine the relationships between the above PK parameters and the covariates.

All statistical analyses were performed using the SAS System 9.4 (SAS Institute Inc., Cary, North Carolina) and performed at a .05 significance level.

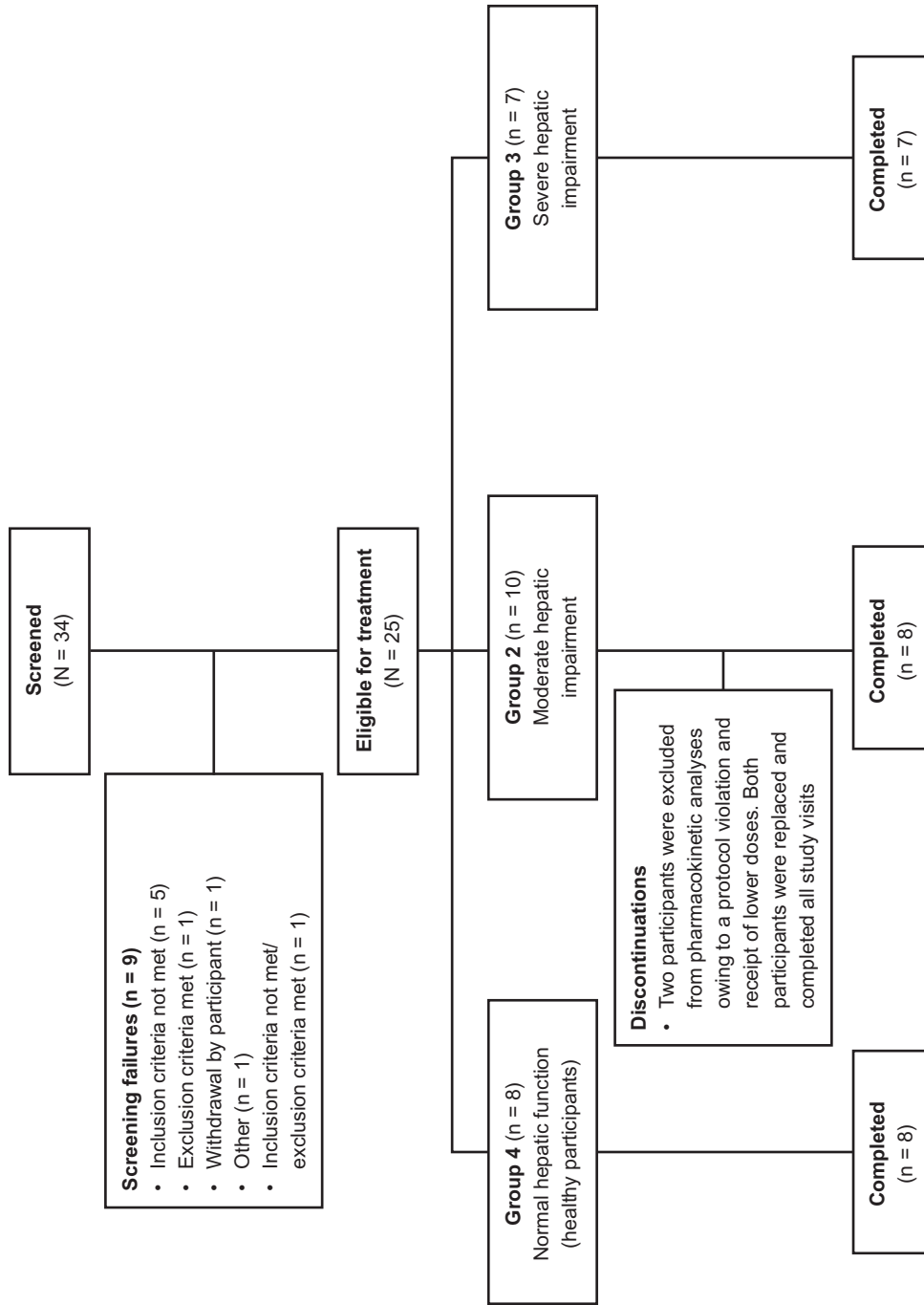
## Results

### Participant Disposition and Demographics

In total, 25 participants were enrolled in the study and assigned to 1 of 3 groups based on their hepatic impairment status: group 2, n = 10 (moderate hepatic impairment) or group 3, n = 7 (severe hepatic impairment), or to a group of age- and sex-matched healthy participants (group 4, n = 8) (Figure 3). No participants were enrolled in the planned group 1 (mild hepatic impairment). The dose of felcisetrag was maintained at 0.2 mg for group 3 based on PK and safety data from group 2. All 25 participants received a single i.v. infusion of felcisetrag (safety

set), and all participants completed the study visit. Two participants in the moderate hepatic impairment group had significant protocol deviations as a result of incorrect installation of the infusion line into the infusion pump through operator error. These participants were replaced and excluded from the PK analysis set (n = 23) because they did not receive the correct dose of felcisetrag.

Baseline characteristics were generally well balanced between the hepatic impairment groups (Table 1). Of the 25 enrolled participants, approximately two-thirds (n = 17) were men. The mean (SD) baseline age across groups was 57.2 (11.21) years and mean (SD) BMI was 29.9 (4.87) kg/m<sup>2</sup>. The mean (SD) Child–Pugh scores at baseline were 8.3 (0.48) for group 2 (moderate hepatic impairment) and 11.3 (1.11) for group 3 (severe hepatic impairment). Details of additional baseline hepatic function test results for participants in group 2 and group 3 are provided in Supplemental Table S1.



**Figure 3.** Disposition of participants. Recruitment for group 1 (mild hepatic impairment) was planned but aborted owing to the similar felcisetrag exposure in group 4 (normal hepatic function) and group 2 (moderate hepatic impairment).



**Table 2.** Pharmacokinetic Parameters for Free and Total Plasma Felcisetrag by Hepatic Function Group

	Group (Hepatic Impairment Status)	Least-squares Mean	Ratio (%)	90%CI for Ratio	P values for Treatment Difference
<b>Free felcisetrag</b>					
AUC <sub>inf</sub> (ng <sup>*</sup> h/mL)	4 (none)	0.50	Reference		
	2 (moderate)	0.63	114.13	(96.04–135.63)	.201
	3 (severe)	0.75	129.15	(108.02–154.41)	.023
AUC <sub>last</sub> (ng <sup>*</sup> h/mL)	4 (none)	0.41	Reference		
	2 (moderate)	0.55	115.72	(98.71–135.67)	.129
	3 (severe)	0.64	126.45	(107.26–149.08)	.023
CL (L/h)	4 (none)	4.80	Reference		
	2 (moderate)	4.67	87.63	(73.76–104.10)	.201
	3 (severe)	4.55	77.40	(64.76–92.51)	.022
C <sub>max</sub> (ng/mL)	4 (none)	–1.98	Reference		
	2 (moderate)	–1.72	130.28	(108.68–156.18)	.020
	3 (severe)	–1.73	128.80	(106.77–155.39)	.031
<b>Total felcisetrag</b>					
AUC <sub>inf</sub> (ng <sup>*</sup> h/mL)	4 (none)	3.44	Reference		
	2 (moderate)	3.24	81.27	(64.48–102.44)	.138
	3 (severe)	3.12	72.18	(56.80–91.73)	.029
AUC <sub>last</sub> (ng <sup>*</sup> h/mL)	4 (none)	3.35	Reference		
	2 (moderate)	3.16	82.50	(66.08–103.01)	.151
	3 (severe)	3.01	70.68	(56.17–88.94)	.017
CL (L/h)	4 (none)	1.86	Reference		
	2 (moderate)	2.06	122.98	(97.55–155.03)	.139
	3 (severe)	2.18	138.43	(108.92–175.94)	.030
C <sub>max</sub> (ng/mL)	4 (none)	0.97	Reference		
	2 (moderate)	0.89	92.83	(73.93–116.56)	.579
	3 (severe)	0.64	72.01	(56.90–91.15)	.026

The PK analysis set comprised 23 participants because two had protocol deviations and received approximately half the dose of felcisetrag. These participants were replaced and excluded from the PK analysis set.

AUC<sub>inf</sub>, area under the concentration–time curve calculated from time zero to infinity; AUC<sub>last</sub>, area under the concentration–time curve from time 0 to time of the last quantifiable concentration; CI, confidence interval; CL, total plasma clearance; C<sub>max</sub>, maximum observed concentration.

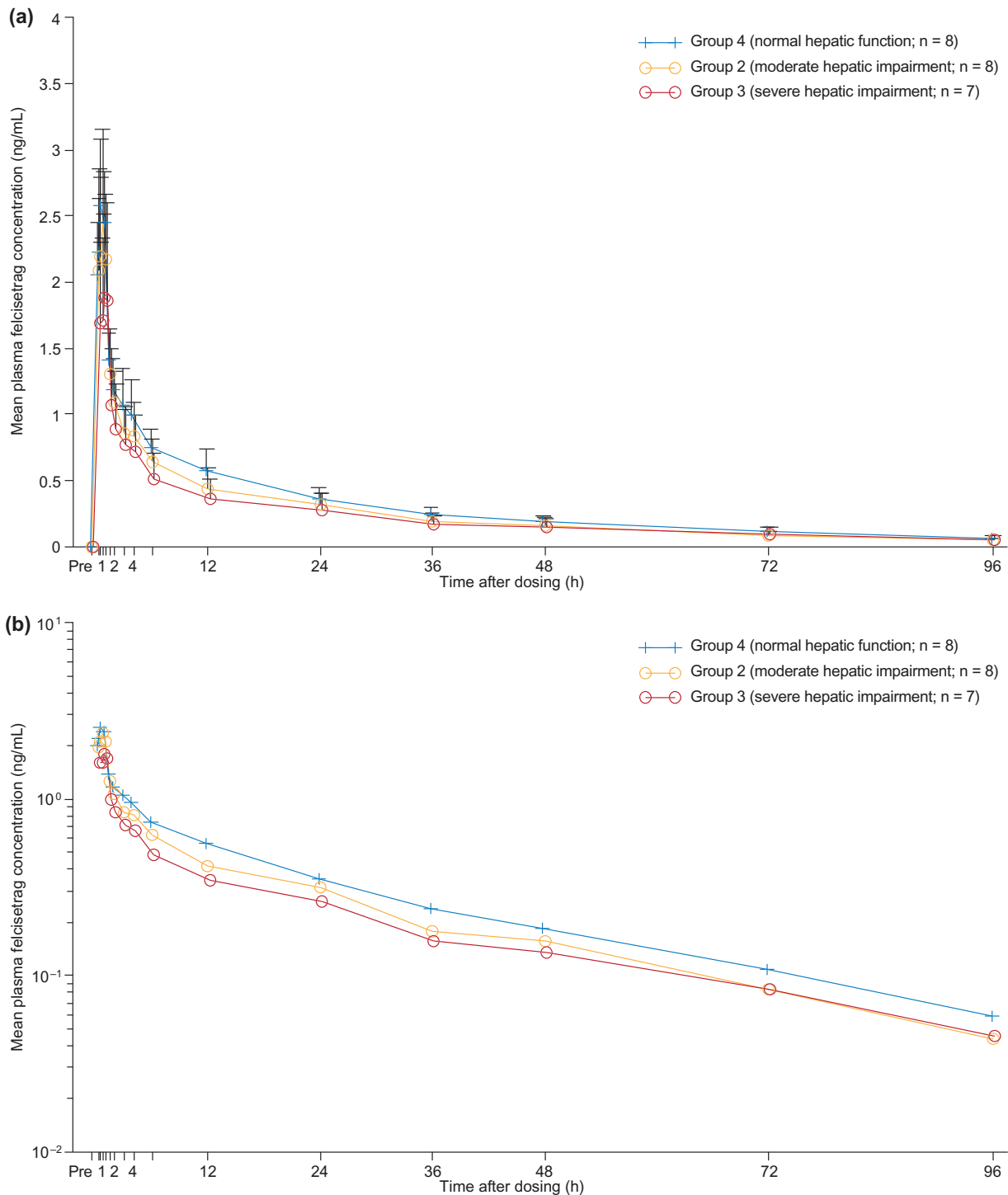
## Pharmacokinetics

**Plasma Pharmacokinetics.** The plasma concentration–time profiles of total plasma felcisetrag were similarly shaped between participants with moderate and severe hepatic impairment (groups 2 and 3) and healthy participants (group 4). Overall, the plasma concentration–time profiles for total plasma felcisetrag were similar across those with hepatic impairment and those who were healthy, but lower concentrations of total plasma felcisetrag were observed with increasing severity of hepatic impairment (Figure 4).

The PK exposure parameters (C<sub>max</sub> and AUC<sub>inf</sub>) for total plasma felcisetrag decreased with decreasing hepatic function, whereas those for free (unbound) felcisetrag increased (Figure 5). The geometric mean (percentage coefficient of variation [%CV]) C<sub>max</sub> for total felcisetrag in plasma decreased from 2.63 (19.1) ng/mL in healthy participants to 2.44 (25.3) ng/mL in those with moderate impairment, and 1.89 (35.4) ng/mL in individuals with severe hepatic impairment. For free felcisetrag, the geometric mean (%CV) C<sub>max</sub> was 0.14 (15.6) ng/mL

in healthy participants and 0.18 (24.4) ng/mL and 0.18 (23.1) ng/mL in those with moderate and severe hepatic impairment, respectively. Values for the geometric mean (%CV) of AUC<sub>inf</sub> for total felcisetrag in plasma decreased from 31.30 (20.1) h\*ng/mL in healthy participants to 25.44 (27.1) h\*ng/mL in those with moderate impairment, and 22.60 (34.3) h\*ng/mL in individuals with severe hepatic impairment. In contrast, the geometric mean (%CV) of AUC<sub>inf</sub> for free felcisetrag was increased in participants with severe (2.12 [21.8] h\*ng/mL) and moderate (1.88 [24.0] h\*ng/mL) hepatic impairment, compared with healthy participants (1.64 [13.8] h\*ng/mL). The total and free t<sub>1/2z</sub> and the volume of distribution (V<sub>z</sub>) parameters for each group are provided in Supplemental Table S2.

The ratios of the estimated means of AUC<sub>inf</sub> and C<sub>max</sub> for total felcisetrag in plasma decreased with an increase in hepatic impairment, compared with healthy participants, and were lower for total plasma felcisetrag than for free felcisetrag (Table 2). In participants with moderate or severe hepatic impairment, the estimated ratios for AUC<sub>inf</sub> were 18.7% and 27.8%



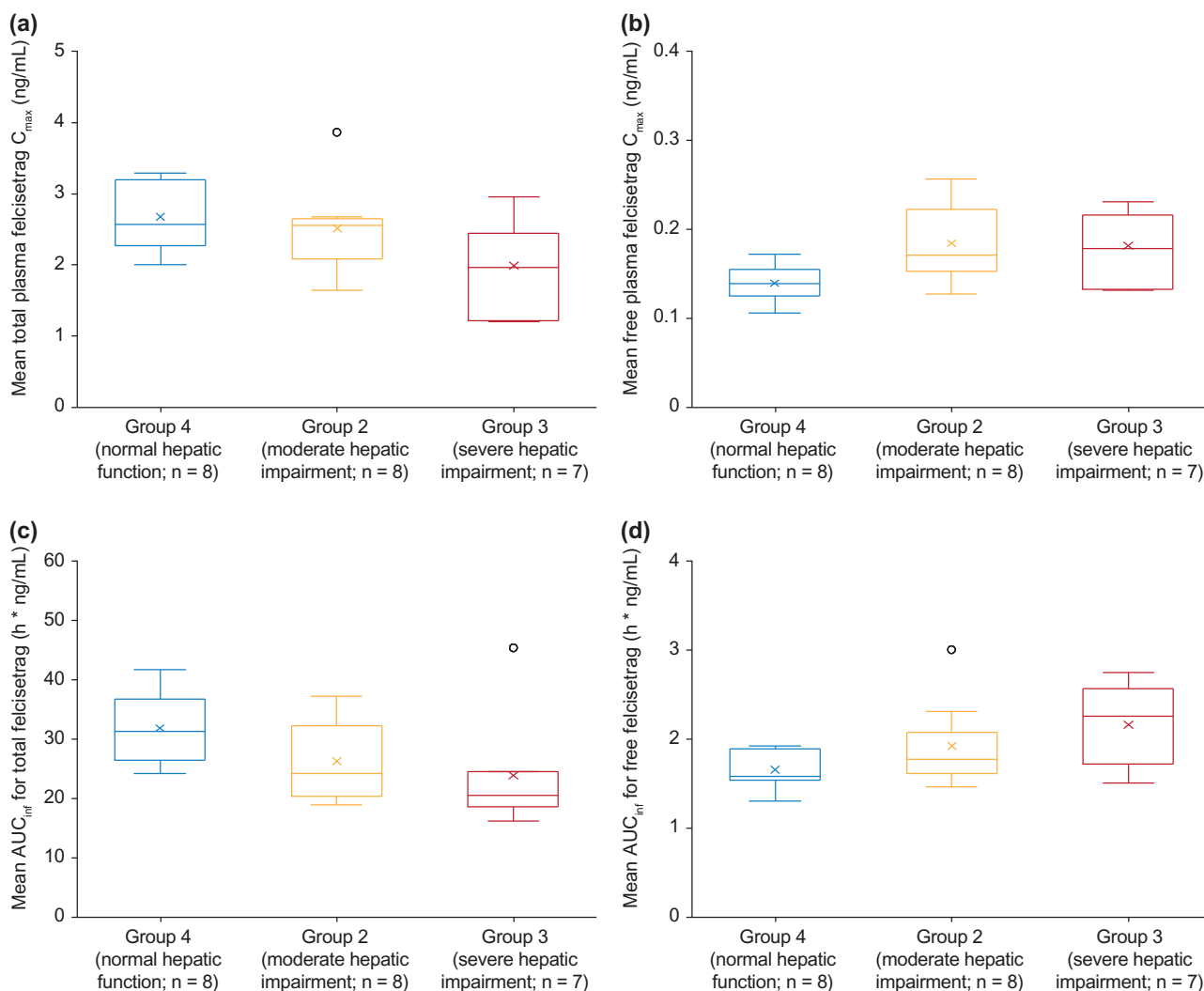
**Figure 4.** Mean plasma concentration of felcisetrag over time on a linear scale (a) and a semi-log scale (b) by hepatic function (moderate or severe group) and in healthy participants. Error bars indicate standard deviation. h, hour; Pre, pre-dose measurements were made within 30 minutes of receiving felcisetrag.

lower than for healthy participants, respectively, for total felcisetrag, and 14.1% and 29.2% higher, respectively, for free felcisetrag. For  $C_{max}$ , the estimated ratios for total felcisetrag were 7.2% and 30.0% lower, respectively, in participants with moderate and se-

vere hepatic impairment than in healthy participants, and 30.3% and 28.0%, higher, respectively, for free felcisetrag.

The ratios for free  $AUC_{inf}$  and  $AUC_{last}$  for felcisetrag suggested a slightly higher, but nonsignificant ( $P > .05$ ),





**Figure 5.** Pharmacokinetic parameters ( $C_{\max}$  and  $AUC_{\text{inf}}$ ) for total and free felcisetrag by hepatic function group. Circles indicate outliers. Crosses indicate mean values. Horizontal dividing lines indicate median values. Upper and lower box boundaries indicate third and first quartiles, respectively. Upper and lower whiskers indicate maximum and minimum values, respectively.  $AUC_{\text{inf}}$ , area under the concentration–time curve calculated from time zero to infinity;  $C_{\max}$ , maximum observed concentration.

exposure to felcisetrag in participants with moderate hepatic impairment than in healthy participants (up to 15.7%), whereas in contrast the ratios for total  $AUC_{\text{inf}}$  and  $AUC_{\text{last}}$  were lower (by up to  $-18.7\%$ ) (Table 2). In participants with severe hepatic impairment, the ratios for  $AUC_{\text{inf}}$  and  $AUC_{\text{last}}$  were significantly higher for free felcisetrag exposure (by up to 29.15%) and lower (by up to  $-29.3\%$ ) for total felcisetrag than in healthy participants (Table 2). There were similar changes observed for  $C_{\max}$  ratios, with free felcisetrag 30.28% higher and total felcisetrag 7.2% lower in participants with moderate hepatic impairment than in healthy individuals. In participants with severe hepatic impairment, the free  $C_{\max}$  ratio was higher (28.80%) and the total  $C_{\max}$  ratio was lower ( $-27.99\%$ ) than in healthy subjects (Table 2).

Free CL ratios were 12.37% lower for participants with moderate hepatic impairment and 22.6% lower for participants with severe hepatic impairment, when compared with healthy participants. For total CL ratios, values were 22.98% higher for participants with moderate hepatic impairment and 38.4% higher for participants with severe hepatic impairment, compared with healthy participants (Table 2).

Regression analysis on the PK of felcisetrag demonstrated a significant effect of both total bilirubin and serum albumin on total  $AUC_{\text{inf}}$ ,  $AUC_{\text{last}}$ , and  $C_{\max}$ , with exposure parameters decreasing with increasing total bilirubin ( $P < .05$ ) and increasing with increasing serum albumin ( $P < .05$ ) (Supplemental Table S3). These observations were, however, not observed with free felcisetrag. Significant decreases in total  $AUC_{\text{inf}}$ ,

**Table 3.** Overview of Treatment-Emergent Adverse Events by Hepatic Function Group

	Group 4 (Normal Hepatic Function) (n = 8)		Group 2 (Moderate Hepatic Impairment) (n = 10)		Group 3 (Severe Hepatic Impairment) (n = 7)		Total (N = 25)	
	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)	Events, n	Participants, n (%)
TEAEs	2	2 (25.0)	3	3 (30.0)	1	1 (14.3)	6	6 (24.0)
Not related	1	1 (12.5)	0	0 (0.0)	0	0 (0.0)	1	1 (4.0)
Related	1	1 (12.5)	3	3 (30.0)	1	1 (14.3)	5	5 (20.0)
Mild	1	1 (12.5)	2	2 (20.0)	1	1 (14.3)	4	4 (16.0)
Moderate	1	1 (12.5)	1	1 (10.0)	0	0 (0.0)	2	2 (8.0)
Severe	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Leading to discontinuation	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Serious AEs								
Not related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Related	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Leading to discontinuation	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

AE, adverse event; TEAE, treatment-emergent adverse event.

$AUC_{last}$ , and  $C_{max}$  with increasing hepatic impairment (increasing Child–Pugh score) were also observed ( $P < .05$ ) (Supplemental Table S4).

In addition, ANCOVA analysis of the effect of covariates on the relationship between hepatic function and felcisetrag PK parameters demonstrated a significant effect of body weight on total ( $P < .001$ ) and free ( $P = .028$ )  $C_{max}$  (Supplemental Table S4). There was also a significant effect of age as a covariate for total  $AUC_{inf}$  ( $P = .011$ ),  $AUC_{last}$  ( $P = .020$ ), and  $C_{max}$  ( $P = .031$ ), and a significant effect of sex for free  $AUC_{inf}$  ( $P = .021$ ) and  $AUC_{last}$  ( $P = .028$ ).

**Urine Pharmacokinetics.** There was no apparent effect of hepatic impairment on urine PK parameters ( $A_{et}$ ,  $f_e$ , and  $CL_R$ ) in participants with moderate hepatic impairment, compared with healthy individuals, but these PK parameters were increased in those with severe hepatic impairment, compared with healthy participants (Supplemental Table 5). A higher proportion of the administered felcisetrag 0.2 mg was excreted in participants with severe hepatic impairment than in those with moderate hepatic impairment or in healthy participants. Although the geometric mean renal clearance ( $CL_R$ ) of felcisetrag 0.2 mg was increased by 68% in participants with severe hepatic impairment and by 19% in those with moderate hepatic impairment, compared with healthy participants, the %CV values (40.9% to 90.8%) indicate a large percentage of variability in the data, with individual values overlapping

in the three groups. Given the small increase in the fraction of administered dose excreted in urine by participants with severe hepatic impairment, relative to healthy participants (26.8% vs 23.0%, respectively), the increase in geometric mean  $CL_R$  does not appear to be clinically meaningful.

**Metabolite Pharmacokinetics.** Plasma concentrations of the two metabolites of felcisetrag (THR513466 and THR913682) were below the limit of quantification (BLQ) at all but one time point (1 hour, group 2, moderate impairment), and therefore no estimates of PK parameters for these metabolites were possible. Given the expectation for diminished metabolic potential in participants with hepatic impairment, it was decided not to analyze urine samples for these 2 metabolites.

### Safety

The safety analysis set included 25 participants who received felcisetrag. In total, 6 (24%) patients reported six treatment-emergent AEs (TEAEs) (Table 3). There was no apparent pattern observed in the incidence or severity of TEAEs between participants with normal ( $n = 2$ ) or with increasing hepatic impairment (moderate impairment,  $n = 3$ ; severe impairment,  $n = 1$ ). All reported TEAEs were either moderate (2 participants [8%], 2 TEAEs) or mild (4 participants [16%], 4 TEAEs) in severity. The only AE reported in more than one participant was diarrhea (1 [12.5%] healthy participant,

2 [20%] participants with moderate hepatic impairment, and 1 [14.3%] participant with severe hepatic impairment). No participants prematurely discontinued from participating in the study owing to AEs and no deaths were reported.

## Discussion

The results of this study support that an increasing severity of hepatic impairment has minimal effect on the PK of a single i.v. infusion of felcisetrag 0.2 mg. Furthermore, no safety or tolerability concerns were observed in association with the use of felcisetrag 0.2 mg in participants with varying degrees of hepatic impairment.

Reduced hepatic function resulted in minimal differences in the mean plasma concentration–time profiles of felcisetrag compared with those in healthy individuals. Total exposure to felcisetrag was reduced as the severity of hepatic impairment increased, with  $C_{max}$ ,  $AUC_{last}$ , and  $AUC_{inf}$  values for total plasma felcisetrag decreasing by up to 29.3%. In contrast, exposure of free felcisetrag increased by up to 30.3% with increasing severity of hepatic impairment. This may be partially explained by levels of CYP3A4, the enzyme primarily responsible for felcisetrag metabolism, which is known to be reduced most markedly in patients with severe hepatic impairment.<sup>25</sup> Furthermore, felcisetrag primarily binds to albumin, and patients with severe hepatic impairment had lower baseline serum albumin levels, meaning that levels of free felcisetrag would be expected to increase, resulting in changes to  $V_z$  and subsequent changes for total felcisetrag concentrations. The mean  $V_z$  for total felcisetrag in participants with severe hepatic impairment was approximately 50% greater than for healthy participants (411.3 vs 270.5, respectively) (Supplemental Table S2). The quantity of felcisetrag excreted via urine was similar in participants with moderate hepatic impairment and in healthy individuals, but was increased, relative to healthy participants, in those with severe hepatic impairment.

The increased exposure to free felcisetrag in participants with hepatic impairment was not associated with any increase in the incidence or severity of TEAEs, compared with healthy participants. The safety profile was as expected for an i.v. infusion of felcisetrag 0.2 mg based on previous clinical data and no safety concerns were observed as severity of hepatic impairment increased. A single dose of i.v. felcisetrag 0.5 mg has previously been shown to not be associated with an increase in adverse events in critically ill patients with enteral feeding intolerance, despite demonstrated efficacy in accelerating gastric emptying.<sup>17</sup> There was a low frequency of TEAEs across all groups and the most frequently reported TEAE in all groups was

diarrhea. All TEAEs were mild or moderate in severity. Overall, these data suggest that dose adjustment of felcisetrag may not be required in patients with hepatic impairment.

The felcisetrag exposure–response relationship was not investigated in the current trial, but the i.v. infusion of felcisetrag 0.2 mg investigated was chosen as it was predicted to be within the clinically relevant range and was lower than the maximum multiple i.v. infusion dose (0.5 mg once daily) that has been evaluated in healthy individuals. The exposure levels observed in the present study are expected to be within therapeutic levels, and the findings from this study are therefore considered clinically relevant.

## Conclusion

Despite a reduction in exposure to total felcisetrag and an increase in exposure to free felcisetrag with increasing severity of hepatic impairment, the overall effect of varying degrees of hepatic impairment on exposure to felcisetrag was minimal. A single i.v. infusion of felcisetrag 0.2 mg was well tolerated with no serious AEs or deaths reported.

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## Conflicts of Interest

R.C. is an employee of Takeda Pharmaceutical Company Ltd. B.C. is an employee of PRA Health Sciences, Prague, Czech Republic. V.K. is a contractor to Summit Clinical Research, LLC. M.R. was an employee of the Takeda Development Center Americas Inc. at the time of the study and is now an employee of Syros Pharmaceuticals Inc, Cambridge, Massachusetts. R.L. was a consultant to the Takeda Development Center when this research was undertaken. C.D. is an employee of Takeda Pharmaceutical Company Ltd. G.D. was a contractor to Takeda Pharmaceutical International Company Ltd. at the time of the study and is now an employee at Ironwood Pharmaceuticals, Boston, Massachusetts.

## Data Sharing

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.