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Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of INT-787, a Novel Farnesoid X Receptor Agonist, in Healthy Volunteers: A Phase 1 Trial

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ABSTRACT

Aberrant farnesoid X receptor (FXR) signaling is implicated in cholestatic, inflammatory, and fibrotic liver diseases. In preclinical/clinical studies, semisynthetic bile acid-derived FXR agonists markedly improved hepatic function in various conditions. INT-787, a novel hydrophilic semisynthetic bile acid FXR agonist, has demonstrated a reduction in inflammatory and fibrotic markers and regulation of bile acid/lipid metabolism. This first-in-human, randomized, placebo-controlled phase 1 study assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of INT-787 and its equipotent metabolites in healthy volunteers by evaluating single ascending doses (SAD), multiple ascending doses (MAD), and food effect. Participants ($n = 130$) across all study portions were similar in age, race, and body mass index. In the SAD and MAD portions, the maximum plasma concentration (C_{max}) and area under the curve (AUC) for total INT-787 generally increased with dose. In the Food Effect portion, the mean C_{max} of total INT-787 was almost 2-fold higher under fasted conditions compared with fed conditions; $AUC_{0\text{-inf}}$ was unchanged. Steady state for total INT-787 was reached by Day 7. In cohorts receiving ≥ 50 mg doses, the half-life of total INT-787 ranged from 21 to 55 h. INT-787 metabolites exhibited increased concentrations after mealtimes despite morning dosing, consistent with endogenous bile acid behavior. Following single and multiple doses of INT-787, decreases in C4 and increases in FGF-19 levels were observed. Single and multiple oral doses were generally well tolerated; 4 adverse events of mild, transient pruritus not requiring interventions were reported at higher doses. These results warrant further investigation of INT-787 in patients with liver-related disorders.

1 | Introduction

Farnesoid X receptor (FXR) signaling plays a critical role in bile acid, glucose, and lipid homeostasis and impacts the intestinal microbiome and mucosal integrity [1, 2]. Disruption of FXR signaling is considered to play a role in cholestatic, inflammatory, and fibrotic liver diseases [3, 4]. INT-787 (3α,7α,11β-Trihydroxy-6α-ethyl-5β-cholan-24-oic Acid) is a novel hydrophilic semisynthetic bile acid FXR agonist derived from the primary bile acid chenodeoxycholic acid (CDCA), with the potential to treat liver-related diseases, including alcohol-related liver disease (ALD), chronic cholestatic liver disease, and nonalcoholic steatohepatitis (NASH), now referred to as metabolic dysfunction–associated steatohepatitis (MASH) [4–7]. As described by Pellicciari et al. (2016), the addition of a β hydroxy group at position C11 of obeticholic acid (OCA) resulted in a compound equipotent to OCA on the FXR without any activity on the Takeda G protein-coupled receptor 5 (TGR5) [6], potentially avoiding side effects

Summary

- What is the current knowledge on the topic?
  - Farnesoid X receptor agonists, including obeticholic acid (OCA), have shown efficacy in the treatment of liver-related diseases.
  - Preclinical studies of INT-787, a novel, semisynthetic primary bile acid derived from chenodeoxycholic acid, have demonstrated superior effectiveness compared to OCA.
- What question did this study address?
  - This research explored the safety, tolerability, pharmacokinetics, and pharmacodynamics of INT-787 and its equipotent active metabolites with single ascending dose (SAD) and multiple ascending dose (MAD) schemes in healthy human volunteers, as well as the effect of fasted versus fed conditions.
- What does this study add to our knowledge?
  - This first-in-human study of INT-787 found that in both SAD and MAD dosing schemes, the maximum plasma concentration and area under the curve for total INT-787 generally increased with increasing doses as expected, with rapid absorption and dose-dependent exposure.
  - All dosings of INT-787 were generally well tolerated, and no serious treatment-emergent adverse events were reported.
- How might this change clinical pharmacology or translational science?
  - These findings support further investigation of INT-787 in patients with liver-related disorders.

associated with TGR5 activation, such as itching [8]. INT-787 has high selectivity for the FXR and improved hydrophilicity (16-fold higher than OCA). INT-787 has a critical micellular concentration that is on par with ursodeoxycholic acid (UDCA), resulting in a low detergency and the potential for reduced toxicity [6].

Preclinical studies of FXR agonists, including OCA, have shown improvements in hepatic steatosis, cholestasis, inflammation, fibrosis, and intestinal mucosal integrity, as well as reductions in bile acids and pro-fibrotic cytokines in various animal models of liver-related diseases [9–13]. When directly compared with OCA in diet-induced obese mouse models of MASH, INT-787 was superior to OCA in the reduction of plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and circulating bile acids [14]. INT-787 was also found to regulate more genes associated with FXR signaling, bile acid regulation, lipid metabolism, and fibrosis compared with OCA [14]. The benefit of using INT-787 rather than OCA has also been demonstrated by INT-787's superiority of its impact on liver steatosis, inflammatory markers, and fibrotic genes [14, 15]. In addition, INT-787 exhibits 4X higher tolerability vs. OCA, with a maximum dose of 120 mg/kg/day, compared to 30 mg/kg/day that has typically been observed with OCA [14, 15]. INT-787 also preserves intestinal barrier integrity and promotes intestinal microbial reshaping in a mouse model of obstructed bile acid flow [16]. In a phase 1, open-label study of healthy male subjects, INT-787 exhibited low intestinal absorption and high gut localization [17]. These data on INT-787 and related FXR agonists provide a foundation for clinical investigation of INT-787 as a potential treatment for liver-related disorders.

The objective of this first-in-human phase 1 study was to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of INT-787 and its equipotent major metabolites (glyco- and tauro-INT-787, which are typical of bile acid metabolism) with single ascending doses (SAD) and multiple ascending doses (MAD) in healthy human volunteers. The effect of food (fasted vs. fed) and gender was also evaluated.

2 | Methods

2.1 | Participants

Participants were aged 18–55 years and in good health based on medical history, physical examination, and routine laboratory tests. Study candidates were excluded if they had smoked tobacco within 3 months of screening; had a history of inflammatory bowel disease, cholecystectomy, or surgery of the gastrointestinal tract; or had a history of drug or alcohol abuse or addiction within the last 2 years. A complete list of inclusion and exclusion criteria can be found in the Supporting Information.

2.2 | Study Design

This was a 3-part, phase 1, randomized, placebo-controlled dose-escalation study conducted in accordance with the principles of the Declaration of Helsinki and in compliance with the International Council for Harmonization Guideline for Good Clinical Practice and European Union Clinical Trial Directive 2001/20/EC (European Union Drug Regulating Authorities Clinical Trials Database Number: 2021–001025-43; ethical approving body for the Netherlands site: The Independent Ethics Committee of the Foundation 'Evaluation of Ethics in Biomedical Research' [Beoordeling Ethiek Biomedisch Onderzoek], Assen, Netherlands; ethical approving body for the Hungarian site: Medical Research Council Ethics Committee for Clinical Pharmacology [Egészségügyi Tudományos Tanács Klinikai Farmakológiai Etikai Bizottság], Budapest, Hungary). All subjects provided written informed consent prior to any study-related procedures.

As this was a first-in-human study, the initial dose of INT-787 was selected according to published guidelines from the US Food and Drug Administration [18] and European Medicines Agency [19] on the overall safety and tolerability profile of INT-787 established in the nonclinical program and previous experience with steroidal FXR agonists, including OCA. Dose escalation was guided by blinded data review by the study investigator and the Intercept Global Safety Committee and was made by joint decision of the investigator and sponsor. No formal sample size calculation was performed for this study; the number of participants planned was deemed appropriate from similar first-in-human studies. Participants were randomized according to a randomly generated list. In the SAD portion of the study, participants in each of 9 dose cohorts were randomized (5:1 ratio for the 2.5 mg cohort, and 6:2 ratio for all others),

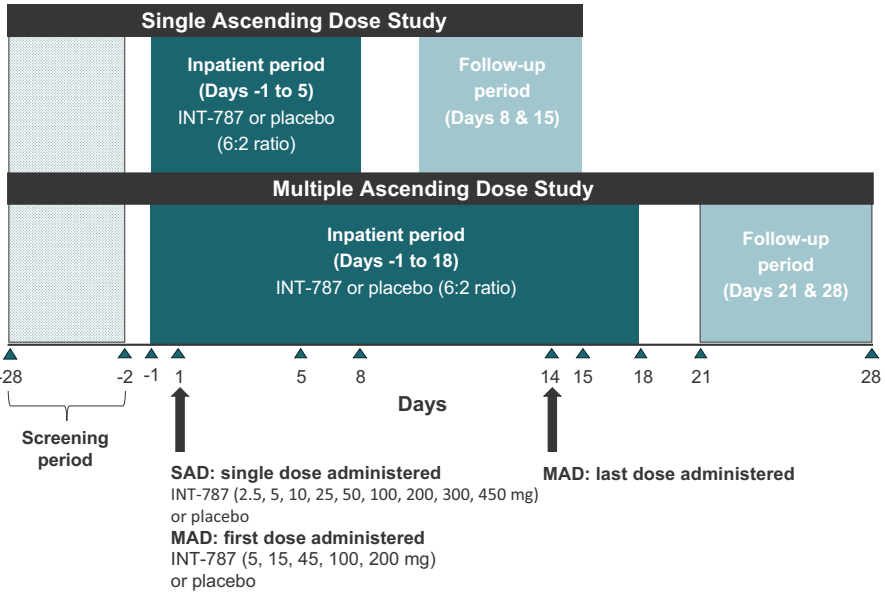

FIGURE 1 | Study design – single ascending dose (SAD) and multiple ascending dose (MAD) portions of the study. Subjects were screened for up to 28 days prior to Day 1. Those meeting the inclusion/criteria were randomized to receive escalating doses of INT-787 or placebo. All cohorts were randomized in a 6:2 ratio, except for the 2.5 mg cohort, which was randomized in a 5:1 ratio. In the SAD portion, a single oral dose (2.5, 5, 10, 25, 50, 100, 200, 300, or 450 mg) of INT-787 or placebo was administered to participants the morning of Day 1, following an overnight fast; participants continued fasting for an additional 4 h after dosing. Blood and urine samples for PK analysis were collected predose and at various time points postdose throughout Day 1. Participants returned on Days 8 and 15 for the collection of PK samples and safety assessments. In the MAD portion, participants received multiple oral administrations of INT-787 (5, 15, 45, 100, or 200 mg) or placebo each day for 14 days. On Days 1, 7, and 14, participants fasted for 10 h prior to dosing until 4 h after dosing. Blood and urine samples were collected predose and at various time points postdose on Days 1, 7, and 14. Participants returned on Days 21 and 28 for the collection of safety and PK/PD samples. MAD, multiple ascending dose; PD, pharmacodynamic; PK, pharmacokinetic; SAD, single ascending dose. *Participants were randomized in a 5:1 ratio for the 2.5 mg cohort.

with a sentinel dosing strategy for optimal safety, to receive a single oral dose of INT-787 or placebo in a fasted state; gender effect was assessed by a single oral dose of 100 mg or placebo (6:2 ratio; Figure 1). In the MAD portion of the study, participants in each of 5 dose cohorts were randomized (6:2 ratio) to receive oral doses of INT-787 or placebo once daily for 14 days (Figure 1). Participants were randomized (4:5 ratio) in the Food Effect portion of the study to receive 2 single doses (28 days apart) of 50 mg INT-787: 1 dose under fasted conditions and 1 dose under fed conditions in a cross-over manner (Figure S1). The fed state included a high-calorie, high-fat breakfast approximately 30 min before INT-787 administration.

2.3 | Analytical Methods

The details of the analytical methods are provided in the Supporting Information.

2.4 | Pharmacokinetic Analyses

Blood and urine samples were collected for PK analysis of INT-787, glyco-INT-787, and tauro-INT-787 and assessed using standard noncompartmental analysis (Phoenix WinNonlin Version 8 or higher). Since INT-787, glyco-INT-787, and tauro-INT-787 have all been shown to stimulate FXR activity [12], results are reported as total-INT-787 (the summation of INT-787 and its active metabolites) and as INT-787 equivalents. Individual PK assessments of INT-787, glyco-INT-787, and tauro-INT-787 were also made.

2.4.1 | SAD Portion of the Study

Serial blood sampling for the PK evaluation in the SAD portion of the study was performed on Day 1 predose, at various time points postdose, and at follow-up on Days 8 and 15. The PK urine samples were collected predose and at several time increments postdose. The following PK parameters were assessed in the SAD study: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve across time ($AUC_{0\text{-}inf}$), and half-life ($t_{1/2}$). Urine PK parameters included renal clearance (CL_R), cumulative drug excreted in urine (Ae_{urine}), and the fraction of dose administered excreted in urine (Fe_{urine}).

2.4.2 | MAD Portion of the Study

Serial blood sampling for the PK evaluation in the MAD portion of the study was performed at the following time points: Day 1 and 7—predose and at several time points postdose; Days 3 to 6 and 9 to 13—predose only; Day 14—predose and at several time points postdose; and Days 21 and 28 (follow-up visit). PK urine samples were collected at the following time points: Days 1 and 7—predose and at several time increments postdose; Day 14—predose and at several time increments postdose. Spot urine

samples were performed at follow-up on Days 21 and 28. The following PK parameters were assessed in the MAD portion of the study: C_{max}, t_{max}, $t_{1/2}$, $AUC_{0\text{-inf}}$, and AUC during a dosing interval (AUC_{tau}); urine PK parameters included CL_R, Ae_{urine}, and Fe_{urine}.

2.4.3 | Food Effect Portion of the Study

Blood samples for the PK analysis in the Food Effect portion of the study were collected on Day 1 predose, at several time points postdose, and at follow-up on Days 8 and 15. The following PK parameters were assessed in the Food Effect study: C_{max}, t_{max}, $t_{1/2}$, AUC from time 0 to 6 h ($AUC_{0\text{-}6h}$), and $AUC_{0\text{-inf}}$.

2.5 | Pharmacodynamic Analyses

Blood samples were collected for PD analysis of FXR activation biomarkers C4, FGF-19, and endogenous bile acids (unconjugated, glyco-, and tauro-conjugates of CA, CDCA, DCA, LCA, and UDCA). In the SAD portion of the study, FGF-19 and endogenous bile acid samples were taken predose and at 24, 48, and 72 h postdose; C4 samples were taken predose and at 24, 48, 72, and 96 h postdose. In the MAD portion of the study, FGF-19, endogenous bile acid, and C4 samples were taken predose on Days 1, 3, 7, 14, 16 (48 h post final dose), 21 (168 h post final dose), and 28 (336 h post final dose). In the Food Effect portion of the study, FGF-19 and endogenous bile acid samples were taken predose and at 24, 48, and 72 h postdose; C4 samples were taken predose and at 24, 48, 72, and 96 h postdose.

2.6 | Exploratory Renal Biomarkers

As higher-than-anticipated concentrations of glyco-INT-787 were observed in the urine of early study groups, and given the sponsor's intent to study INT-787 in populations with severe liver disease known to have kidney injury, the protocol was amended to include an assessment of exploratory renal safety biomarkers (IL-18, KIM-1, NGAL, and L-FABP-1) to better evaluate any impact on renal physiology. Urine samples collected for PK analysis were also used for this assessment.

2.7 | Safety Analyses

Safety was monitored by a medical monitor from the sponsored contract research organization throughout the study using standard measures, including adverse event monitoring, physical examination, ECG, orthostatic vital signs, and clinical laboratory evaluations. The severity of treatment-emergent adverse events (TEAEs) was rated as mild, moderate, severe, life-threatening, or death using the Common Terminology Criteria for Adverse Events Version 5.0.

2.8 | Statistical Analyses

All statistical analyses were performed using the statistical software SAS for Windows Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina, USA). Analysis of covariance (ANCOVA) was used for C_{max} and AUCs to determine dose proportionality in the SAD and MAD portions of the study and to determine the effect of gender and food. The PK parameters were estimated using a standard noncompartmental analysis (Phoenix WinNonlin Version 8 or higher).

2.9 | Data Monitoring

The sponsor and other authorized third parties acting on behalf of the sponsor could be authorized to be granted direct access to the medical records and to study data without violating the confidentiality to the extent permitted by the applicable laws and regulations.

3 | Results

3.1 | Study Time Frame and Participants

The study was carried out from 11 June 2021 (date of first screening) to 07 February 2023 (date of last follow-up). The safety population included all participants who received ≥1 dose of the study drug or matching placebo. In total, 130 subjects were included in the safety population: 80 participants from the SAD portion of the study, 41 participants from the MAD portion of the study, and 9 participants from the Food Effect portion of the study. Of these participants, 74, 40, and 8 completed the study as per protocol, respectively (Figure S2). The PK population included all participants who received ≥ 1 dose of INT-787 and had sufficient PK data without any major protocol deviations (SAD, $n = 60$; MAD, $n = 30$; Food Effect, $n = 9$).

Baseline demographics and clinical characteristics by dose for all 3 study parts are presented in Tables S1–S3. In the SAD portion of the study, 81.3% of participants were male, the mean age was 30 years, and the mean BMI was 24.2 kg/m^2. Six female participants were included in the gender effect cohort (INT-787 100 mg) and compared to the 8 male participants in the original INT-787 100 mg SAD cohort. In the 450 mg cohort, all 6 participants receiving INT-787 were female, whereas 1 female participant and 1 male participant received placebo. All other SAD cohorts included only male participants. The MAD portion of the study included 58.5% male participants, the mean age was 31 years, and the mean BMI was 22.9 kg/m^2. In the Food Effect portion of the study, 55.6% of participants were male, the mean age was 39 years, and the mean BMI was 24.4 kg/m^2. Across all 3 study parts, male and female participants were similar in age, race, and BMI.

3.2 | Pharmacokinetics

The mean concentration over time profiles for total INT-787 are summarized for the SAD (Figure 2A), MAD (Figure 2B), and Food Effect (Figure S4A) portions of the study. PK parameters are summarized for the SAD (Table 1), MAD (Table 2), and Food Effect (Table S6) portions of the study. The mean concentration over time profiles for unconjugated, glyco-, and tauro-INT-787 are summarized in Figures S3 and S4B–D, and the PK

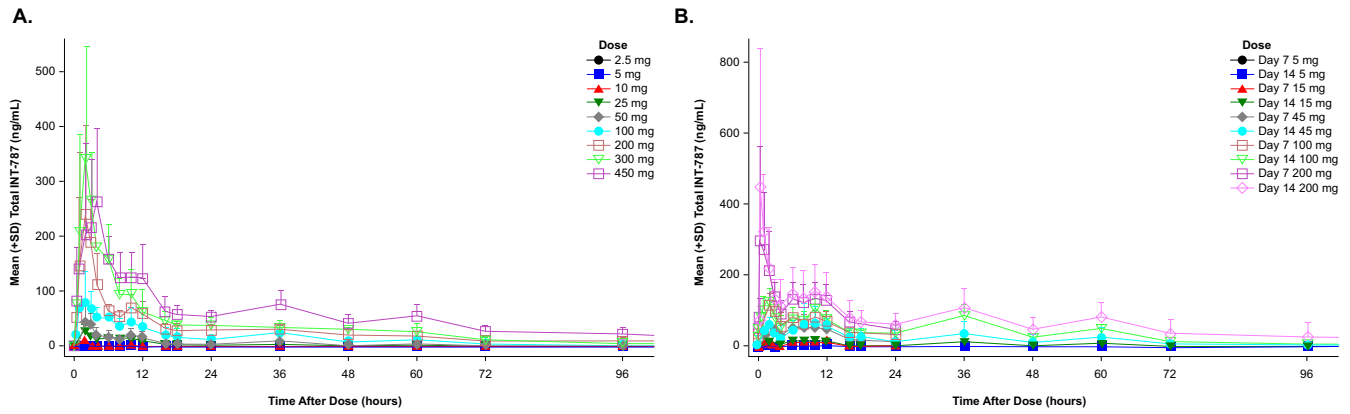

FIGURE 2 | Mean (±SD) plasma concentration-time profiles of total INT-787 following (A) single ascending doses and (B) multiple ascending doses. Participants received escalating oral doses of INT-787 or placebo in a fasted state. In the MAD portion, doses were administered once daily for 14 days; data shown are for Days 7 and 14. Blood samples were collected predose and at predefined time points postdose. Plasma concentrations (ng/mL) are plotted on a linear scale. MAD, multiple ascending dose; SAD, single ascending dose.

parameters for unconjugated, glycol-, and tauro-INT-787 are summarized in Tables S4–S6.

In the SAD portion of the study, total INT-787 was rapidly absorbed, with detectable plasma concentrations at 0.5 h postdose and median t_{max} observed within 1.5 to 3.5 h postdose. Unconjugated INT-787 appeared at the earliest time point (0.25 h; Figure S3 and Table S4). The geometric mean half-life ranged between 4.23 and 37.5 h across all SAD dose cohorts. Based on geometric mean plasma concentration-time profiles for total INT-787, dose-dependent increases in concentration were observed across all SAD cohorts. Overall, C_{max} and $AUC_{0\text{-inf}}$ for total INT-787 increased with increasing doses; however, C_{max} did not continue to increase beyond the 300 mg dose. Increases in total INT-787 concentration as measured by C_{max} were less than dose proportional, whereas the increase in $AUC_{0\text{-inf}}$ was slightly more than dose proportional (Table S7); in ad hoc analyses with trimmed INT-787 dose ranges (5–300 mg, 10–200 mg, and 25–200 mg), increases of C_{max} and $AUC_{0\text{-inf}}$ for total INT-787 were dose proportional (Table S8). Following single-dose administration of INT-787, mean CL_R of total INT-787 decreased with increasing doses, while AE_{urine} of total INT-787 increased with increasing doses. The mean cumulative fraction excreted in urine of total INT-787 ranged between 1.93% and 5.00%, which was composed primarily of glyco-INT-787 and is consistent with the known excretion patterns of bile acids. Overall, although there was a small number of subjects in the gender analysis, C_{max} and $AUC_{0\text{-inf}}$ of total INT-787 were not notably different between male and female participants (Table S9).

In the MAD portion of the study, total INT-787 was rapidly absorbed, with peak concentration between 1.0 and 2.0 h postdose on Day 1, between 0.8 and 6.0 h postdose on Day 7, and between 0.8 and 2.0 h postdose on Day 14 across all MAD dose cohorts. The geometric mean $t_{1/2}$ of total INT-787 ranged from 15.8 to 55.1 h postdose on Day 14 across all MAD dose cohorts. Based on geometric mean plasma concentration-time profiles for total INT-787, dose-dependent increases in concentration were observed across all MAD dose cohorts. Overall, C_{max} and AUC_{tau} for total INT-787 increased with increasing doses on Days 1, 7, and 14. There was no evidence of deviation from dose proportionality for the increase in C_{max} for total INT-787 (Table S10). The accumulation ratio for AUC_{tau} for total INT-787 from Day 1 to Day 7 was approximately 1.4- to 3-fold, with greater accumulation at the lower doses, and with no further notable increases between Days 7 and 14 (Table S11). On Day 14, mean CL_R of total INT-787 decreased with increasing doses, while AE_{urine} increased with increasing doses. The mean cumulative fraction excreted in urine of total INT-787 after Day 14 ranged between 2.69% and 5.10%, which also consisted mostly of glyco-INT-787. The PK urine analysis was only performed for the 45, 100, and 200 mg INT-787 MAD cohorts.

In the Food Effect portion of the study, compared with fed conditions, the geometric mean C_{max} of total INT-787 was almost 2-fold higher under fasted conditions (Figure S4 and Table S6). The geometric least squares mean plasma exposure of total INT-787 was 2- to 3-fold higher during the first 6 h postdose after administration in fasted conditions compared to fed conditions (187.5 vs. 83.2 h•ng/mL, respectively), whereas $AUC_{0\text{-inf}}$ was not notably different between conditions. The $t_{1/2}$ was approximately 2-fold longer under fed conditions compared with fasted conditions.

3.3 | Pharmacodynamics

Only participants who received INT-787 were included in the plasma C4 and FGF-19 analysis, while placebo and INT-787 recipients were included in the bile acid analysis. Following single-dose administration of INT-787 doses of 25 mg or higher, the expected decreases in C4 and increases in FGF-19 concentrations were observed at 24 h postdose and all measured time points thereafter (Figure 3A,B). During multiple-dose administration of INT-787 through Day 14, with doses of 45 mg or higher, substantial decreases in C4 concentrations and increases in FGF-19 concentrations were observed up to Day 14 (Figure 3C,D). Of note, the 15 mg cohort had a single outlier that skewed the data toward no effect. Overall, decreases in C4 and increases in FGF-19 concentrations were more prominent with higher doses of INT-787. Due to high variability, no meaningful changes from baseline or differences between doses were

TABLE 1 | Summary statistics of pharmacokinetic parameters for total INT 787 in plasma and urine—single ascending dose portion of the study.

Parameter	Statistic	2.5 mg (M = 4, F = 0)	5 mg (M = 6, F = 0)	10 mg (M = 6, F = 0)	25 mg (M = 6, F = 0)	50 mg (M = 6, F = 0)	100 mg (M = 8, F = 0)	100 mg (M = 0, F = 6)	200 mg (M = 6, F = 0)	300 mg (M = 6, F = 0)	450 mg (M = 0, F = 6)
$AUC_{0\text{-inf}}$ (h•ng/mL)[a]	*n*	1	4	6	5	6	8	6	6	6	6
	Geo. Mean	14.4	66.4	92.5	347	607	1490	1380	3550	4130	6750
	Geo. CV (%)	NA	81.7	67.5	41.3	51.3	46.7	32.1	41.1	18.1	21.9
C_{max} (ng/mL)	*n*	4	6	6	6	6	8	6	6	6	6
	Geo. Mean	4.38	7.41	17.6	32.3	55.0	108	111	317	421	304
	Geo. CV (%)	25.3	25.6	16.6	32.4	29.6	55.8	49.5	41.0	30.0	43.9
$t_{1/2}$ (h)	*n*	1	4	6	5	6	8	6	6	6	6
	Geo. Mean	4.23	19.6	11.0	20.1	22.8	17.6	21.5	37.5	22.6	26.3
	Geo. CV (%)	NA	238	98.1	12.0	46.8	66.4	39.8	62.7	70.5	36.6
t_{max} (h)	*n*	4	6	6	6	6	8	6	6	6	6
	Median	1.50	1.50	2.00	2.00	2.03	2.01	2.51	2.05	2.03	3.53
	Min, Max	1.00, 2.00	0.500, 2.00	0.500, 2.02	1.00, 3.00	2.02, 3.02	1.00, 6.02	1.00, 8.00	1.02, 4.03	1.03, 4.03	1.03, 4.03
CL_R (L/h)	*n*	4	6	6	6	6	6	6	6	6	6
	Mean (SD)	18.1 (8.54)	8.67 (4.13)	6.02 (1.71)	3.54 (0.826)	3.24 (1.07)	2.29 (1.20)	1.88 (0.582)	1.64 (0.222)	1.75 (0.293)	1.49 (0.209)
	CV (%)	47.1	47.6	28.4	23.3	33.0	52.4	30.9	13.5	16.7	14.0
Ae_{urine} (μg)	*n*	4	6	6	6	6	6	6	6	6	6
	Mean (SD)	107 (38.2)	194 (94.3)	500 (268)	1090 (366)	1770 (424)	3230 (1620)	2540 (1210)	4810 (1250)	6990 (2410)	8700 (2090)
	CV (%)	35.8	48.6	53.7	33.7	23.9	50.1	47.7	26.1	34.5	24.0

(Continues)

TABLE 1 | (Continued)

Parameter	Statistic	2.5 mg (M = 4, F = 0)	5 mg (M = 6, F = 0)	10 mg (M = 6, F = 0)	25 mg (M = 6, F = 0)	50 mg (M = 6, F = 0)	100 mg (M = 8, F = 0)	100 mg (M = 0, F = 6)	200 mg (M = 6, F = 0)	300 mg (M = 6, F = 0)	450 mg (M = 0, F = 6)
Fe_{urine} (%)	*n*	4	6	6	6	6	6	6	6	6	6
	Mean (SD)	4.27 (1.53)	3.88 (1.89)	5.00 (2.68)	4.34 (1.47)	3.55 (0.847)	3.23 (1.62)	2.54 (1.21)	2.40 (0.626)	2.33 (0.804)	1.93 (0.464)
	CV (%)	35.8	48.6	53.7	33.7	23.9	50.1	47.7	26.1	34.5	24.0

Abbreviations: Ae_{urine}, cumulative drug excreted in urine; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; CL_R, renal clearance; C_{max}, maximum plasma concentration of a drug; CV, coefficient of variation; F, female; Fe_{urine}, fraction of dose administered excreted in urine unchanged; Geo. CV, geometric coefficient of variation; Geo. Mean, geometric mean; h, hours; M, male; Max, maximum; Min, minimum; *n*, number of subjects; NA, not applicable; SD, standard deviation; $t_{1/2}$, time required for the drug concentration to be reduced to exactly half of its starting concentration; t_{max}, time required for drug to reach maximum concentration.

[a]Because of the enterohepatic recirculation, extrapolated values like $AUC_{0\text{-}inf}$ are more likely to vary.

observed in CDCA, DCA, LCA, or UDCA following single or multiple-dose administration of INT-787; meaningful decreases from baseline in total C4 concentrations were observed at 24 h postdose in the SAD portion of the study (data not shown). No meaningful differences in the effects on C4, FGF-19, or bile acids were observed between males and females (data not shown). In the Food Effect portion of the study, changes from baseline in C4 and FGF-19 concentrations were similar at all measured time points following administration of INT-787 under fasted vs. fed conditions (data not shown).

3.4 | Exploratory Renal Biomarkers

Exploratory renal safety biomarker data were only available for the 450 mg INT-787 and gender effect (100 mg INT-787) cohorts in the SAD portion of the study and for the 45 mg, 100 mg, and 200 mg INT-787 cohorts in the MAD portion of the study. Excretion of L-FABP-1, KIM-1 (data uncorrected), and NGAL in urine was increased compared to placebo following single-dose administration of 100 and 450 mg INT-787; differences in IL-18 excretion were unremarkable (data not shown). Following multiple-dose administration of INT-787, the amount of L-FABP-1 excreted in urine within 24 h postdose increased slightly from Day 1 to Day 14 and decreased after dosing completion; no meaningful differences were observed between dose cohorts (data not shown). No apparent trends over time or differences between dose groups in the amounts of IL-18, KIM-1, and NGAL excreted in urine were observed, although excreted amounts of KIM-1 and NGAL were increased compared to placebo (data not shown). Variability in excreted amounts of L-FABP-1, IL-18, KIM-1, and NGAL in urine was high across participants; thus, the clinical significance of increases in these renal safety biomarkers remains to be determined.

3.5 | Safety and Tolerability

Treatment-emergent adverse events (TEAEs) are summarized for the SAD (Table 3), MAD (Table 4), and Food Effect (Table S12) portions of the study. In the SAD portion of the study, 63 nonserious TEAEs were reported by 41 (51.3%) participants. Of these, 17 TEAEs reported by 10 (12.5%) participants were considered possibly related to treatment, of which headache, diarrhea, and dizziness were the most common. It is worth noting that caffeine consumption was limited in the study (average of no more than 5 servings per day prior to screening and complete restriction from 48 h prior to the [first] dosing of investigational product until collection of the last PK sample), which may contribute to the emergence of some TEAEs such as headache. The majority of TEAEs were mild. In the MAD portion of the study, 89 nonserious TEAEs were reported by 33 (80.5%) participants. Of these, 3 TEAEs reported by 3 (7.3%) participants were considered possibly related to INT-787: 1 TEAE of pruritus after multiple doses of 100 mg, and 1 TEAE of pruritus and 1 TEAE of increased liver function test after multiple doses of 200 mg. All treatment-related TEAEs were mild. In the Food Effect portion of the study, 8 nonserious TEAEs were reported by 4 (44.4%) participants; the proportion of participants reporting TEAEs was

TABLE 2 | Summary statistics of pharmacokinetic parameters for total INT-787 in plasma and urine[a,b] – multiple ascending dose portion of the study.

Analysis Day	Parameter	Statistic	5 mg (M = 6, F = 0)	15 mg (M = 5, F = 1)	45 mg (M = 2, F = 4)	100 mg (M = 1, F = 5)	200 mg (M = 2, F = 4)
1	$AUC_{0\text{-}inf}$ (h•ng/mL)	*n*	5	6	6	6	6
		Geo. Mean	29.0	100	343	1180	1860
		Geo. CV (%)	22.9	30.3	39.1	49.6	40.4
	C_{max} (ng/mL)	*n*	6	6	6	6	6
		Geo. Mean	8.41	24.3	59.7	146	302
		Geo. CV (%)	36.6	39.5	12.6	27.4	58.1
	$t_{1/2}$ (h)	*n*	5	6	6	6	6
		Geo. Mean	4.89	5.90	4.46	8.23	7.72
		Geo. CV (%)	29.2	23.3	59.5	37.4	19.9
	t_{max} (h)	*n*	6	6	6	6	6
		Median	2.00	1.01	1.51	2.02	1.00
		Min, Max	0.517, 3.02	0.500, 4.02	1.02, 8.03	2.02, 4.02	0.500, 2.02
7	AUC_{tau} (h•ng/mL)	*n*	6	6	6	6	6
		Geo. Mean	62.8	222	726	1380	2510
		Geo. CV (%)	66.8	39.2	57.6	31.1	37.3
	C_{max} (ng/mL)	*n*	6	6	6	6	6
		Geo. Mean	7.85	25.2	82.3	134	366
		Geo. CV (%)	22.7	51.9	45.5	25.3	65.4
	$t_{1/2}$ (h)	*n*	5	6	5	6	6
		Geo. Mean	5.67	4.23	6.95	10.7	9.47
		Geo. CV (%)	44.8	32.7	70.0	39.3	22.5
	t_{max} (h)	*n*	6	6	6	6	6
		Median	1.53	6.00	5.50	2.01	0.759
		Min, Max	0.517, 16.0	1.02, 10.0	1.02, 12.1	1.00, 3.00	0.517, 2.00

(Continues)

TABLE 2 | (Continued)

Analysis Day	Parameter	Statistic	5 mg (M = 6, F = 0)	15 mg (M = 5, F = 1)	45 mg (M = 2, F = 4)	100 mg (M = 1, F = 5)	200 mg (M = 2, F = 4)
14	AUC_{tau} (h•ng/mL)	*n*	5	6	6	6	6
		Geo. Mean	66.1	234	849	1510	2760
		Geo. CV (%)	63.8	33.5	66.1	27.1	48.4
	C_{max} (ng/mL)	*n*	5	6	6	6	6
		Geo. Mean	8.32	29.0	92.9	144	485
		Geo. CV (%)	31.7	47.1	43.6	12.9	83.7
	$t_{1/2}$ (h)	*n*	5	6	6	6	6
		Geo. Mean	15.8	21.4	30.5	55.1	46.0
		Geo. CV (%)	273	63.0	60.6	69.0	50.8
	t_{max} (h)	*n*	5	6	6	6	6
		Median	1.00	1.00	2.01	2.02	0.767
		Min, Max	1.00, 2.00	0.500, 1.02	1.02, 2.02	0.500, 2.02	0.500, 2.00
	CL_R (L/h)	*n*	NA	NA	6	6	6
		Mean (SD)	NA	NA	1.11 (0.386)	0.910 (0.196)	0.766 (0.143)
		CV (%)	NA	NA	34.6	21.6	18.6
	Ae_{urine} (μg)	*n*	NA	NA	6	6	6
		Mean (SD)	NA	NA	2290 (1650)	3870 (1880)	5370 (2140)
		CV (%)	NA	NA	72.0	48.6	39.9
	Fe_{urine} (%)	*n*	NA	NA	6	6	6
		Mean (SD)	NA	NA	5.10 (3.67)	3.87 (1.88)	2.69 (1.07)
		CV (%)	NA	NA	72.0	48.6	39.9

Abbreviations: Ae_{urine}, cumulative drug excreted in urine; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; AUC_{tau}, area under the curve limited to the end of a dosing interval; CL_R, renal clearance; C_{max}, maximum plasma concentration of a drug; CV, coefficient of variation; F, female; Fe_{urine}, fraction of dose administered excreted in urine unchanged; Geo. CV, geometric coefficient of variation; Geo. Mean, geometric mean; h, hours; M, male; MAD, multiple ascending dose; Max, maximum; Min, minimum; *n*, number of subjects; NA, not applicable; PK, pharmacokinetics; SD, standard deviation; $t_{1/2}$, time required for the drug concentration to be reduced to exactly half of its starting concentration; t_{max}, time required for the drug to reach maximum concentration.

[a]Urine parameters (CL_R, Ae_{urine}, Fe_{urine}) were only assessed on Day 14.

[b]PK urine analysis was included for Part B as of CSP Version 7.0; thus, PK urine analysis was only performed for MAD 45, 100, and 200 mg INT-787 dose cohorts.

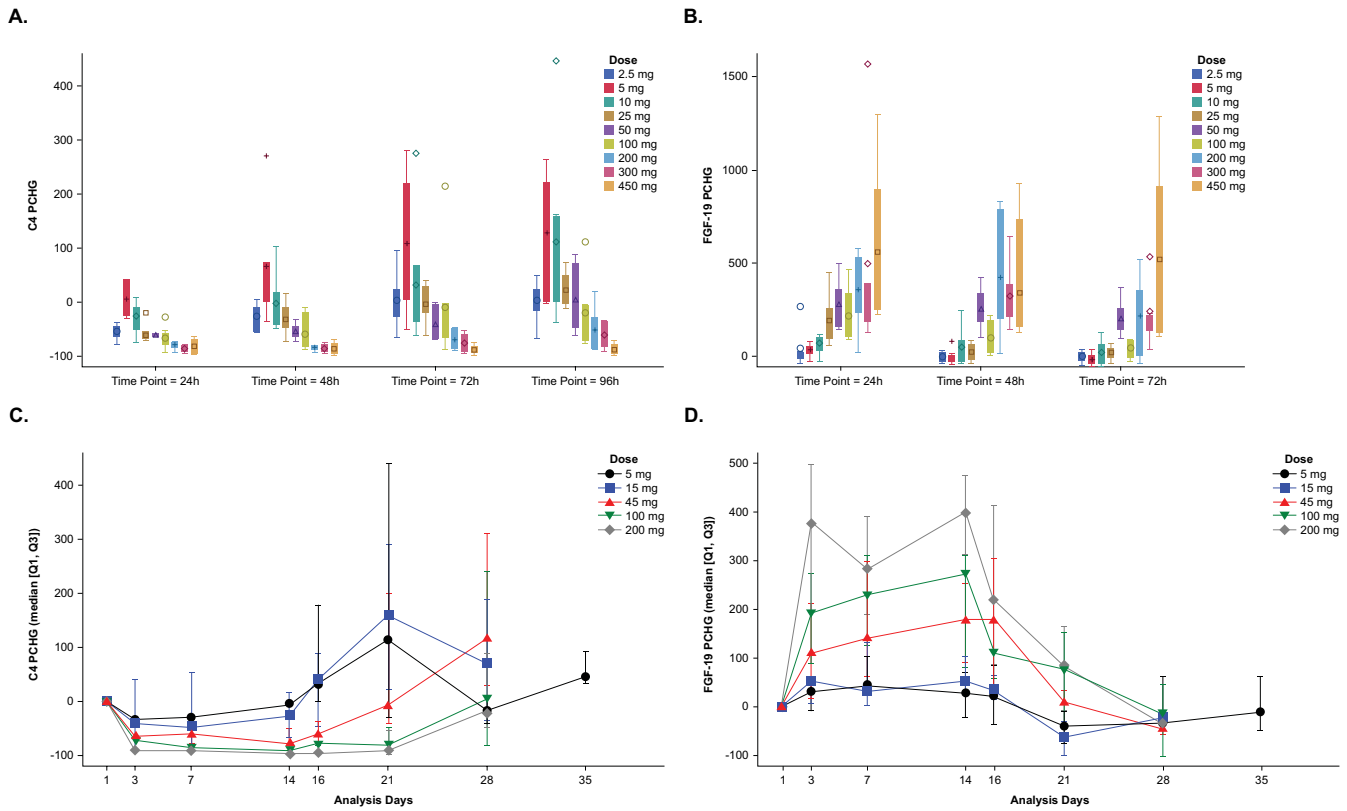

FIGURE 3 | Pharmacodynamics of INT-787 following single and multiple dose administration. (A, B) Mean percent change from baseline over time in C4 and FGF-19 plasma levels for the single ascending dose portion of the study. For C4, plasma concentrations were measured for up to 96 h postdose. For FGF-19, plasma concentrations were measured for up to 72 h postdose. (C, D) Median (Q1, Q3) percent change from baseline over time in C4 and FGF-19 plasma levels for the multiple ascending dose portion. Plasma concentrations of C4 and FGF-19 were measured predose on Days 1, 3, 7, 14, 16, 21, 28, and 35 (5 mg dose only). C4, 7α-Hydroxy-4-Cholesten-3-one; CI, confidence interval; FGF-19, fibroblast growth factor-19; IQR, interquartile range; PCHG, percent change; Q, quartile. Any values outside the maximum whisker represent outliers that are outside Q3 + 1.5*IQR.

44.4% when treatment was administered under fasted conditions versus 12.5% when administered under fed conditions. See Table S13 for a listing of all adverse events by de-identified participant.

Pruritus and drug-induced liver injury (DILI) were considered AEs of special interest (AESIs) for this study. Two TEAEs of pruritus were considered possibly related to treatment with INT-787 (after multiple doses of 100 mg and 200 mg). All AESIs of pruritus resolved during the study, and no TEAEs of DILI were reported. No deaths or serious TEAEs occurred during any of the 3 portions of the study. There were no clinically meaningful findings or trends in clinical laboratory parameters, vital signs, ECGs, and physical examinations. Of note, in the MAD portion of the study, 1 participant in the 200 mg group experienced mild, transient elevations in ALP, AST, and ALT at Days 18 and 21 postdosing that returned to normal limits after dosing completion (Figure S5). Two participants (1 in the SAD portion of the study who received 450 mg INT-787 and 1 in the MAD portion of the study who received doses of 200 mg INT-787) had < 3× upper limit of normal transient increases in ALP and AST at several time points postdose, which returned to normal after dosing completion. Neither the 100 mg nor 200 mg cohort of the MAD portion of the study had concomitant increases in total bilirubin, direct bilirubin, or GGT (data not shown).

4 | Discussion

The results of this phase I study in healthy volunteers demonstrated that irrespective of dosing, maximum plasma concentrations of total INT-787 occurred rapidly postdose. The half-life of total INT-787 ranged from 21 to 55 h in cohorts with consistent exposure (i.e., from doses of 50 mg upwards, wherein the drug concentrations in the plasma samples were consistently measurable and interpretable). The results of the SAD dose proportionality analysis suggested that the observed increases in AUCs and C_{max} deviated from dose proportionality. However, in ad hoc analyses, when disregarding the lower doses that had fewer measurable concentrations, the increase in C_{max} and $AUC_{0\text{-inf}}$ for total INT-787 was dose proportional. In contrast to the SAD results, the MAD dose proportionality analysis did not indicate a saturation effect for C_{max}. The increase of C_{max} for total INT-787 on all PK days did not deviate from dose proportionality. Total INT-787 increases observed in AUC_{tau} from Day 1 to Day 7 but not from Day 7 to Day 14 implied that a steady state was reached by Day 7. No meaningful difference in total INT-787 plasma exposure between male and female participants was observed.

The results of the Food Effect portion of the study suggested that administering INT-787 in a fasted state may increase the rate of absorption due to an approximately 2- to 3-fold higher $AUC_{0\text{-}6h}$ for

TABLE 3 | Summary of TEAEs – single ascending dose portion of the study.

	2.5 mg ($n=5$)	5 mg ($n=6$)	10 mg ($n=6$)	25 mg ($n=6$)	50 mg ($n=6$)	100 mg ($n=14$)	200 mg ($n=6$)	300 mg ($n=6$)	450 mg ($n=6$)	PBO ($n=19$)	Overall ($N=80$)
Total # of subjects with ≥ 1 TEAE, *n* (%)	5 (100.0)	5 (83.3)	4 (66.7)	1 (16.7)	0	9 (64.3)	3 (50.0)	2 (33.3)	2 (33.3)	10 (52.6)	41 (51.3)
Total number of TEAEs	7	8	7	1	0	15	3	3	5	14	63
Serious TEAEs	0	0	0	0	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0	0	0	0	0
TEAEs by severity, *n* (%)[a]											
Grade 1: mild	5 (100.0)	5 (83.3)	4 (66.7)	1 (16.7)	0	9 (64.3)	3 (50.0)	2 (33.3)	1 (16.7)	10 (52.6)	40 (50.0)
Grade 2: moderate	0	0	0	0	0	0	0	0	1 (16.7)	0	1 (1.3)
Grade 3: severe	0	0	0	0	0	0	0	0	0	0	0
Grade 4: life-threatening	0	0	0	0	0	0	0	0	0	0	0
Grade 5: death	0	0	0	0	0	0	0	0	0	0	0
TEAEs by relationship to study drug, *n* (%)[b]											
Related (possibly or probably)	1 (20.0)	3 (50.0)	2 (33.3)	0	0	1 (7.1)	0	0	2 (33.3)	1 (5.3)	10 (12.5)
Not related (or unlikely)	4 (80.0)	2 (33.3)	2 (33.3)	1 (16.7)	0	8 (57.1)	3 (50.0)	2 (33.3)	0	9 (47.4)	31 (38.8)
TEAEs leading to discontinuation of study drug	0	0	0	0	0	2 (14.3)	0	0	0	1 (5.3)	3 (3.8)
TEAEs by MedDRA class (≥ 3% of subjects)											
GI disorders, *n* (%)	4 (80.0)	2 (33.3)	2 (33.3)	0	0	3 (21.4)	0	2 (33.3)	0	3 (15.8)	16 (20.0)
Abdominal pain	2 (40.0)	0	0	0	0	1 (7.1)	0	0	0	1 (5.3)	4 (5.0)
Diarrhea	0	2 (33.3)	0	0	0	0	0	1 (16.7)	0	0	3 (3.8)
Dyspepsia	0	0	0	0	0	1 (7.1)	0	0	0	0	1 (1.3)
Nausea	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (1.3)

(Continues)

TABLE 3 | (Continued)

	2.5 mg (*n* = 5)	5 mg (*n* = 6)	10 mg (*n* = 6)	25 mg (*n* = 6)	50 mg (*n* = 6)	100 mg (*n* = 14)	200 mg (*n* = 6)	300 mg (*n* = 6)	450 mg (*n* = 6)	PBO (*n* = 19)	Overall (*N* = 80)
Nervous system disorders	0	2 (33.3)	2 (33.3)	0	0	2 (14.3)	0	0	2 (33.3)	2 (10.5)	10 (12.5)
Headache	0	2 (33.3)	2 (33.3)	0	0	2 (14.3)	0	0	0	2 (10.5)	8 (10.0)
Infections and infestations	1 (20.0)	2 (33.3)	0	0	0	3 (21.4)	2 (33.3)	0	0	2 (10.5)	10 (12.5)
Nasopharyngitis	1 (20.0)	0	0	0	0	1 (7.1)	1 (16.7)	0	0	0	3 (3.8)
Asymptomatic COVID-19	0	1 (16.7)	0	0	0	0	0	0	0	1 (5.3)	2 (2.5)
General disorders and administration site conditions	0	1 (16.7)	0	1 (16.7)	0	0	0	0	0	0	2 (2.5)
Vessel	0	0	0	1 (16.7)	0	0	0	0	0	0	1 (1.3)
Skin and subcutaneous tissue disorder[c]	1 (20.0)	1 (16.7)	0	0	0	0	0	0	0	2 (10.5)	4 (5.0)
Dermatitis contact	0	0	0	0	0	0	0	0	0	2 (10.5)	2 (2.5)
AESIs											
DILI	0	0	0	0	0	0	0	0	0	0	0
Pruritus	0	1 (16.7)	0	0	0	0	0	0	0	0	1 (1.3)

Note: Percentages are based on the number of subjects in the Safety Population within each treatment group.
Abbreviations: AESI, adverse event of special interest; DILI, drug-induced liver injury; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; PBO, placebo; TEAE, treatment-emergent adverse event.
[a]Participants reporting > 1 adverse event were counted only once using the highest severity.
[b]Participants reporting > 1 adverse event were counted only once using the closest relationship to the study drug.
[c]Includes treatment-emergent pruritus.

TABLE 4 | Summary of TEAEs – multiple ascending dose portion of the study.

	5 mg (*n* = 6)	15 mg (*n* = 6)	45 mg (*n* = 6)	100 mg (*n* = 6)	200 mg (*n* = 6)	PBO (*n* = 11)	Overall (*N* = 41)
Total # of subjects with ≥ 1 TEAE, *n* (%)	5 (83.3)	2 (33.3)	5 (83.3)	6 (100)	6 (100)	9 (81.8)	33 (80.5)
Total number of TEAEs	10	7	7	21	14	30	89
Serious TEAEs	0	0	0	0	0	0	0
TEAE leading to death	0	0	0	0	0	0	0
TEAEs by severity, *n* (%)[a]							
Grade 1: mild	5 (83.3)	2 (33.3)	5 (83.3)	6 (100)	6 (100)	8 (72.7)	32 (78.0)
Grade 2: moderate	0	0	0	0	0	1 (9.1)	1 (2.4)
Grade 3: severe	0	0	0	0	0	0	0
Grade 4: life-threatening	0	0	0	0	0	0	0
Grade 5: death	0	0	0	0	0	0	0
TEAEs by relationship to study drug, *n* (%)[b]							
Related (possibly or probably)	0	0	0	1 (16.7)	2 (33.3)	0	3 (7.3)
Not related (or unlikely)	5 (83.3)	2 (33.3)	5 (33.3)	5 (83.3)	4 (66.7)	9 (81.8)	30 (73.2)
TEAEs leading to discontinuation of study drug	0	0	0	0	0	1 (9.1)	1 (2.4)
TEAEs by MedDRA class (≥ 3% of subjects)							
GI disorders, *n* (%)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	2 (33.3)	6 (54.5)	16 (39.0)
Abdominal pain	1 (16.7)	0	0	0	0	1 (9.1)	2 (4.9)
Diarrhea	0	0	0	0	0	4 (36.4)	4 (9.8)
Dyspepsia	0	2 (33.3)	0	0	0	3 (27.3)	5 (12.2)
Nausea	1 (16.7)	0	0	2 (33.3)	0	0	3 (7.3)
Nervous system disorders	2 (33.3)	0	1 (16.7)	0	3 (50.0)	5 (45.5)	11 (26.8)
Headache	2 (33.3)	0	1 (16.7)	0	3 (50.0)	4 (36.4)	10 (24.4)
Infections and infestations	1 (16.7)	0	1 (16.7)	3 (50.0)	0	4 (36.4)	9 (22.0)
Nasopharyngitis	0	0	1 (16.7)	1 (16.7)	0	2 (18.2)	4 (9.8)
Asymptomatic COVID-19	0	0	0	0	0	1 (9.1)	1 (2.4)

(Continues)

TABLE 4 | (Continued)

	5 mg (*n* = 6)	15 mg (*n* = 6)	45 mg (*n* = 6)	100 mg (*n* = 6)	200 mg (*n* = 6)	PBO (*n* = 11)	Overall (*N* = 41)
General disorders and administration site conditions	2 (33.3)	1 (16.7)	1 (16.7)	3 (50.0)	4 (66.7)	5 (45.5)	16 (39.0)
Catheter	1 (16.7)	0	1 (16.7)	0	0	2 (18.2)	4 (9.8)
Skin and subcutaneous tissue disorder[c]	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)	1 (9.1)	7 (17.1)
Dermatitis contact	0	1 (16.7)	1 (16.7)	0	0	0	2 (4.9)
AESIs							
DILI	0	0	0	0	0	0	0
Pruritus	0	0	0	1 (16.7)	1 (16.7)	0	2 (4.9)

Note: Percentages are based on the number of subjects in the Safety Population within each treatment group.
Abbreviations: AESI, adverse event of special interest; DILI, drug-induced liver injury; GI, gastrointestinal; MedDRA, Medical Dictionary of Regulatory Activities; PBO, placebo; TEAE, treatment-emergent adverse event.
[a]Participants reporting > 1 adverse event were counted only once using the highest severity.
[b]Participants reporting > 1 adverse event were counted only once using the closest relationship to the study drug.
[c]Includes treatment-emergent pruritus.

total INT-787. Mean concentration-time plots revealed that glyco- and tauro-INT-787 concentrations were consistently higher during dinner time, indicating that food may have an impact on exposure to INT-787 and its metabolites, consistent with bile acid biology and known postprandial elevations or the known diurnal variation in conjugated bile acid levels throughout the day [20]. Further testing with a larger group of participants will be needed to confirm these findings. Additionally, given the enterohepatic circulation of endogenous bile acids and other semi-synthetic bile acid derivatives, studying the PK of INT-787 in patients with hepatic impairment will be essential, particularly as it is being explored for the treatment of various hepatic diseases.

Consistent with FXR activation, single and multiple dose administration of INT-787 decreased plasma concentrations of C4 and increased FGF-19. The clinical significance of any increase in exploratory renal safety biomarkers remains to be determined; due to substantial variability, no firm conclusions could be drawn.

Single and multiple oral doses of INT-787 were generally well tolerated, with no apparent relationship observed between INT-787 dose and the number of TEAEs or the number of participants reporting TEAEs. Pruritus is a well-recognized class effect of FXR agonists; however, the mechanism of pruritus induction by FXR agonists is not well understood [21]. Recent preclinical studies suggest that activation of TGR5 stimulates the release of transmitters that cause pruritus [6, 22]. Other preclinical studies suggest that activation of the Mas-related G protein–coupled receptor (MRGPR)X4 via bile acids or bilirubin may be a possible contributor to pruritus [21, 23]. These are two of many possible scenarios whereby pruritus may develop, whether directly or indirectly via drugs or metabolites [21]. In the present study, pruritus was not notably reported across the whole range of INT-787 doses (3 treatment-related events in 3 participants), potentially owing to its high specificity for FXR and lack of activity on TGR5 or MRGPRX4. However, these findings also need to be further validated in larger cohorts of patients treated with INT-787 for longer durations and in patients with liver disease who are predisposed to pruritus.

The observed transient increases in serum ALP, AST, and ALT with high doses of INT-787 (100 mg and 200 mg cohorts of the MAD portion of the study) were mild (Grade 1: 1.25–2.5 × ULN) and not indicative of liver injury [24]. Additionally, since ALP is also produced outside of the liver by organs such as bone, kidneys, and intestines, its plasma levels may be elevated in the presence of normal liver health [24]. Concurrent increases in GGT and/or total and direct bilirubin were not observed and remained within normal limits after exposure to INT-787. Mild, transient increases in serum ALP are anticipated with FXR agonism and have been reported in clinical studies of both bile acid–based and non-steroidal FXR agonists [25–27].

There are some strengths and limitations to this study. Its division into both single and multiple dosing schemes allows for comprehensive insight into the effects of dosing types, and the added gender effect portion provides more nuanced data on gender variability; however, considering the small number of subjects included in this exploratory analysis, no firm conclusions on gender effects can be drawn. Other limitations include small sample size in each cohort and high variability of PD data across participants.

In conclusion, INT-787 is a biologically active, well-tolerated compound with rapid absorption and dose-dependent exposure in healthy volunteers. The demonstrated safety, tolerability, and pharmacodynamic activity of INT-787 support further investigation in patients with liver-related disorders. A phase 2a proof-of-concept study with INT-787 at a starting dose of 5 mg (FRESH; NCT05639543) is currently enrolling patients with severe alcohol-associated hepatitis.

Author Contributions

T.C., J.B., J.V.D.W., R.K., J.C., L.K., and M.E. wrote the manuscript. T.C., J.B., J.C., L.K., and M.E. designed the research. T.C., J.B., J.C., L.K., and M.E. performed the research. T.C., J.B., J.C., L.K., and M.E. analyzed the data.

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Disclosure

T.C., J.B., J.C., L.K., M.E.: Employees of Intercept Pharmaceuticals Inc. J.V.D.W., R.K.: Employees of ICON plc.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.