CLINICAL STUDY REPORT

A THREE-PART, PHASE 1, RANDOMIZED, CONTROLLED, DOSE-ESCALATION STUDY OF INT-787 FOLLOWING SINGLE OR MULTIPLE DOSE ADMINISTRATION IN HEALTHY SUBJECTS

CONFIDENTIAL

Sponsor code: 787-124
ICON code: IPT20804-20804X
EudraCT number: 2021-001025-43

Investigational product:	INT-787
Clinical phase:	Phase 1 study
Indication to be studied:	Not applicable
Study period:	11 Jun 2021 (first screening) to 07 Feb 2023 (last follow-up)
Sponsor:	Intercept Pharmaceuticals, Inc 305 Madison Avenue, Morristown, NJ 07960 USA
Contract Research Organization and clinical site:	ICON – Early Development Services Van Swietenlaan 6, 9728 NZ Groningen The Netherlands
Other clinical site:	ICON - Pharmaceutical Research Associates Magyarország Kft. Rottenbiller Utca 13, H-1077 Budapest Hungary
Coordinating Investigator:	Renger Tiessen, MD, PhD (replacing Jeroen van de Wetering, MD, as of 20 Dec 2022) Phone: +31 50 402 2386 E-mail: Renger.Tiessen@iconplc.com

Final, 26 Jan 2024

This study was performed in compliance with the principles of Good Clinical Practice, including the archiving of essential documents.
This report was written in compliance with the International Council for Harmonisation guidelines.

Name of Sponsor/Company: Intercept Pharmaceuticals, Inc.	**Individual Study Table Referring to Part .. of the Dossier**	**(For National Authority Use Only)**
Name of Finished Product: INT-787	**Volume ..**	
Name of Active Ingredient(s): 3α,7α,11β-trihydroxy-6α-ethyl-5β-cholan-24-oic acid	**Page ..**	

2. SYNOPSIS

Study Title
A THREE-PART, PHASE 1, RANDOMIZED, CONTROLLED, DOSE-ESCALATION STUDY OF INT-787 FOLLOWING SINGLE OR MULTIPLE DOSE ADMINISTRATION IN HEALTHY SUBJECTS

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Contract Research Organization and Clinical Site
ICON - Early Development Services, Van Swietenlaan 6, 9728 NZ Groningen, The Netherlands

Other Clinical Site (as of Clinical Study Protocol Version 5.0)
ICON - Pharmaceutical Research Associates Magyarország Kft., Rottenbiller Utca 13, H-1077 Budapest, Hungary

Principal Investigators
Renger Tiessen, MD, PhD (replacing Jeroen van de Wetering, MD, as of 20 Dec 2022) (Groningen clinical site, The Netherlands)
Vendel Kemény, MD, PhD (Budapest clinical site, Hungary)

Coordinating Investigator
Renger Tiessen, MD, PhD (replacing Jeroen van de Wetering, MD, as of 20 Dec 2022)

Publication : Capozza T, et al. Safety, tolerability, and pharmacokinetics of oral INT-787, a novel modified bile acid FXR agonist, in healthy volunteers. Hepatology 2022; 76: S1507-S1508.

Study Period : Date of first screening to last follow-up: 11 Jun 2021 to 07 Feb 2023

Clinical Phase : Phase 1

Objectives
Part A (Single Dose Administration and Gender Effect):
Primary : To evaluate the safety and tolerability of single ascending doses of INT-787 capsule(s) administered orally to healthy subjects.
Secondary : To evaluate the pharmacokinetics (PK) of INT-787 and its tauro- and glyco-conjugates (and other metabolites as applicable) following administration of single ascending doses of INT-787 capsule(s) administered orally to healthy subjects.
To assess the gender effect on the PK of INT-787 and its tauro- and glyco-conjugates (and other metabolites as applicable) following administration of a single dose of INT-787 capsule(s) administered orally to healthy subjects.

To explore the possible relationships between dose, exposure, and farnesoid X receptor (FXR) activation biomarker responses as well as biomarkers of kidney function (as of clinical study protocol [CSP] Version 7.0) after single ascending doses of INT-787.

Part B (Multiple Dose Administration):

Primary : To evaluate the safety and tolerability of multiple ascending doses of INT-787 capsule(s) administered orally for 14 days to healthy subjects.

Secondary : To evaluate the PK of INT-787 and its tauro- and glyco-conjugates (and other metabolites as applicable) following administration of multiple ascending doses of INT-787 capsule(s) administered orally to healthy subjects.
To explore the possible relationships between dose, exposure, and FXR activation biomarker responses as well as biomarkers of kidney function (as of CSP Version 7.0) after multiple ascending doses of INT-787.

Part C (Food Effect):

Primary : To assess the food effect on the PK of INT-787 and its tauro- and glyco-conjugates (and other metabolites as applicable) following administration of a single dose of INT-787 capsule(s) administered orally to healthy subjects.

Secondary : To evaluate the safety and tolerability of a single dose of INT-787 capsule(s) administered orally to healthy subjects in fasted and fed conditions.

Design and Treatments

This was a 3-part, Phase 1, randomized, placebo-controlled dose-escalation study to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of INT-787 after single and multiple ascending doses (Parts A and B, respectively) and to assess the effect of food (fasted vs fed) on the PK of INT-787 (Part C) in healthy subjects. The effect of gender on the PK of INT-787 was also evaluated (Part A).

Part A (Single Dose Administration and Gender Effect)

Part A had a randomized, double-blind, placebo-controlled design to evaluate the safety, tolerability, PK, and PD of INT-787 after single ascending doses (SAD) and to assess the effect of gender on the PK of INT-787 in healthy subjects. Part A was conducted in 9 sequential single dose level (SDL) groups, and in an additional gender effect group including only female subjects.

In each group, it was intended to randomize 8 subjects in a 3:1 ratio to receive a single dose of INT-787 (6 subjects) or matching placebo (2 subjects). However, due to recruitment issues, Group SDL1 only included 6 subjects (5 on INT-787 treatment and 1 on placebo treatment). In Group SDL6, 2 subjects were added to replace discontinued subjects, resulting in 10 subjects in this group (8 on INT-787 treatment and 2 on placebo treatment).

In each SDL group, except for the gender effect group, a sentinel dosing strategy was used to ensure optimal safety.

INT-787 or placebo were administered as oral capsules in the fasted state. Dose escalation was guided by prespecified stopping criteria, blinded data review by the Investigator and the Intercept Global Safety Committee (GSC), and only proceeded after no objection on the dose escalation report (DER) by the Independent Ethics Committee (IEC).

The following treatments were administered, according to the randomization code:

Group SDL1:	a single dose of 2.5 mg INT-787 (n=5) or placebo (n=1)
Group SDL2:	a single dose of 5 mg INT-787 (n=6) or placebo (n=2)
Group SDL3:	a single dose of 10 mg INT-787 (n=6) or placebo (n=2)
Group SDL4:	a single dose of 25 mg INT-787 (n=6) or placebo (n=2)
Group SDL5:	a single dose of 50 mg INT-787 (n=6) or placebo (n=2)
Group SDL6:	a single dose of 100 mg INT-787 (n=8) or placebo (n=2)
Group SDL7:	a single dose of 200 mg INT-787 (n=6) or placebo (n=2)
Group SDL8:	a single dose of 300 mg INT-787 (n=6) or placebo (n=2)
Group SDL9:	a single dose of 450 mg INT-787 (n=6) or placebo (n=2)
Gender effect group:	a single dose of 100 mg INT-787 (n=6) or placebo (n=2)

Groups SDL1 to SDL6 and the gender effect group were performed at the Groningen clinical site, except for 1 replacement subject in Group SDL6 who participated at the Budapest clinical site. Groups SDL7 to SDL9 were performed at the Budapest clinical site.

The originally planned 10th SDL group was removed, per CSP Version 8.0. Preliminary PK analysis indicated that a sufficiently high exposure was reached and that the C_{max} had plateaued from 200 to 450 mg. Therefore, the Sponsor decided not to further escalate to 600 mg.

Part B (Multiple Dose Administration)

Part B had a randomized, double-blind, placebo-controlled design to evaluate the safety, tolerability, PK, and PD of INT-787 after multiple ascending doses (MAD) in healthy subjects. Part B was conducted in 5 sequential multiple dose level (MDL) groups.

In each group, it was intended to randomize 8 subjects in a 3:1 ratio to receive INT-787 (6 subjects) or matching placebo (2 subjects) once daily for 14 days. In Group MDL2, 1 subject was added to replace a discontinued subject, resulting in 9 subjects in this group (6 on INT-787 treatment and 3 on placebo treatment).

In the first MDL group, a sentinel dosing strategy was used to ensure optimal safety.

INT-787 or placebo were administered as oral capsules in the fasted state. The first dose level was initiated at a time and dose deemed appropriate by the Sponsor based on available safety and PK data from completed dose levels in Part A. Dose escalation was guided by prespecified stopping criteria, blinded data review by the Investigator and the Intercept GSC, and only proceeded after no objection on the DER by the IEC.

The following treatments were administered, according to the randomization code:

Group MDL1:	a dose of 5 mg INT-787 (n=6) or placebo (n=2) once daily for 14 days
Group MDL2:	a dose of 15 mg INT-787 (n=6) or placebo (n=3) once daily for 14 days
Group MDL3:	a dose of 45 mg INT-787 (n=6) or placebo (n=2) once daily for 14 days
Group MDL4:	a dose of 100 mg INT-787 (n=6) or placebo (n=2) once daily for 14 days
Group MDL5:	a dose of 200 mg INT-787 (n=6) or placebo (n=2) once daily for 14 days

Part B was conducted at the Groningen clinical site.

Originally, only 4 MDL groups were planned. However, a 5th MDL group was added to allow investigating higher PK exposures that could be reached in future studies in patients with hepatic impairment. Based on a mouse PK study (Study 00661150), hepatic impairment could increase systemic exposure by 10 times in males and 5 times in females. This is consistent with the fact that hepatic impairment is known to increase systemic concentrations of bile acids in general and INT-787 is a bile acid derivative that behaves like an endogenous bile acid.

Part C (Food Effect)

Part C had a 2-period, randomized, crossover design to assess the effect of food on the PK of INT-787 in healthy subjects. Subjects received 2 single oral doses of INT-787; 1 dose under fasted conditions and 1 dose under fed conditions (ie, after a high fat, high-calorie meal).

It was intended to randomize 8 subjects in a 1:1 ratio to either the fed-fasted group (4 subjects) or the fasted-fed group (4 subjects). In between study drug administrations, there was a 4-week washout period. In the fasted-fed group, 1 subject was added to replace a discontinued subject, resulting in 5 subjects in this group.

In Part C, no sentinel dosing strategy was used.

INT-787 was administered as oral capsules under fasted and fed conditions. The following treatments were administered, according to the randomization code:

Fed-fasted group (n=4):

- Period 1: a single dose of 50 mg INT-787 under fed conditions
- Period 2: a single dose of 50 mg INT-787 under fasted conditions

Fasted-fed group (n=5):

- Period 1: a single dose of 50 mg INT-787 under fasted conditions
- Period 2: a single dose of 50 mg INT-787 under fed conditions

Part C was conducted at the Groningen clinical site.

Study Schedule

Screening	: Between Day -28 and Day -2.
Treatment period	: Part A: 1 period in the clinic from Day -1 (admission) until Day 5. Up to CSP Version 6.0, the subjects returned to the clinical research center for outpatient visits on Days 8, 15, and 22 for the collection of PK samples and safety assessments. As of CSP Version 6.0, the subjects returned to the clinical research center only on Day 8. Part B: 1 period in the clinic from Day -1 (admission) until Day 18. Up to CSP Version 6.0, the subjects returned to the clinical research center for outpatient visits on Days 21, 28, and 35 for the collection of PK samples and safety assessments. As of CSP Version 6.0, the subjects returned to the clinical research center only on Day 21. Part C: 2 periods in the clinic, each from Day -1 (admission) until Day 5. The subjects returned to the clinical research center only on Day 8 of each period.
Follow-up	: Up to CSP Version 6.0 (applicable to Parts A and B only), follow-up assessments were performed approximately 4 weeks after (the last) administration of study drug. As of CSP Version 6.0, follow-up assessments for all parts were performed approximately 2 weeks after (the last) administration of study drug.

Subjects

Part A	: 80 healthy subjects
Part B	: 41 healthy subjects
Part C	: 9 healthy subjects

Main Criteria for Inclusion

Sex	: Male and/or female subjects. Initially, females were only allowed to participate in the gender effect group in Part A, provided that they were postmenopausal, surgically sterile, or of nonchildbearing potential. However, as of CSP Version 6.0, females were allowed to participate in all parts/groups, provided that they were postmenopausal, surgically sterile, or prepared to use at least 1 highly effective method of contraception.
Age	: 18 to 55 years, inclusive, at screening. Up to CSP Version 5.0, the upper age was 50 years for males.
Body mass index (BMI)	: 18.0 to 30.0 kg/m^2, inclusive, at screening
Healthy status	: Healthy

Investigational Products

Active Medication

Active substance	: INT-787
Activity	: FXR-mediated activity
In development for	: Alcohol-associated hepatitis
Strength (unit dose)	: 2.5 to 75 mg per capsule[a]
Dosage form	: Oral capsule
Manufacturer	: Pharmacy at ICON
Batch number drug substance[b]	: CF0997 and CG1135 (the latter only for Group MDL5)

Placebo (Visually Matching Active Medication)

Substance	: microcrystalline cellulose
Activity	: Not applicable
In development for	: Not applicable
Strength (unit dose)	: Not applicable
Dosage form	: Oral capsule
Manufacturer	: Pharmacy at ICON
Batch number drug Substance[b]	: Not applicable

[a] Multiple capsules were used to achieve the higher dose levels.
[b] The batch numbers of the drug product (active medication and placebo) can be found in the manufacturing batch records, which are available on file.

Variables

Safety variables	: Adverse events (AEs), clinical laboratory, standard and extensive 12-lead electrocardiogram (ECG), vital signs, and physical examination.
PK variables	: Plasma PK parameters for total, unconjugated, glyco-, and tauro-INT-787 (total INT-787 is sum of unconjugated, glyco-, and tauro-INT-787) estimated using noncompartmental analysis, as appropriate: $AUC_{0\text{-}6h}$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}96h}$,

		$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, dose-adjusted AUCs and C_{max}, C_{trough}, T_{max}, T_{last}, $t_{1/2}$, metabolite to parent ratio (AUCs and C_{max}), and R_{ac} (AUCs and C_{max}). Urine PK parameters for total, unconjugated, glyco-, and tauro-INT-787 estimated using noncompartmental analysis, as appropriate (Parts A and B [as of CSP Version 7.0] only): CL_R, Ae_{urine}, and Fe_{urine}.
PD variables	:	Plasma concentrations of FXR activation biomarkers: 7α-hydroxy-4-cholesten-3-one (C4), fibroblast growth factor-19 (FGF-19), and endogenous bile acids (total, unconjugated, glyco-, and tauro-conjugates of ursodeoxycholic acid [UDCA], chenodeoxycholic acid [CDCA], deoxycholic acid [DCA], cholic acid [CA], and lithocholic acid [LCA]). Urine concentrations of renal safety biomarkers (as of CSP Version 7.0, for Parts A and B only): interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), liver-type fatty acid binding protein-1 (L-FABP-1), and neutrophil gelatinase-associated lipocalin (NGAL).
Pharmacogenomic variables	:	Potential genotyping of DNA sequence variants in subjects who consented for genotyping, if analyzed.
Exploratory variables	:	Potential microbiome/metabolome analyses, if analyzed.

Statistical Methods

Sample size calculation	:	No formal sample size calculation was performed for this study. The number of subjects planned for each part of the study is commonly used in similar first-in-human Phase 1 studies and was deemed appropriate to fulfill the primary and secondary objectives of this study.
Safety parameters	:	Descriptive statistics.
PK parameters	:	Descriptive statistics. Analysis of variance on C_{max} and AUCs to determine dose proportionality (Parts A and B), gender effect (Part A), and food effect (Part C).
PD parameters	:	Descriptive statistics.

Results

Subject Disposition

In total, 349 potentially eligible subjects were screened (283 subjects at the Groningen clinical site and 66 subjects at the Budapest clinical site), and 130 of these subjects were included in the study: 80 subjects in Part A, 41 subjects in Part B, and 9 subjects in Part C. Seventy-four (74) subjects in Part A, 40 subjects in Part B, and 8 subjects in Part C completed the study as per protocol. An overview of the disposition of subjects is provided in Table S1.

Table S1 Disposition of Subjects

	Part A (N=80) n (%)	Part B (N=41) n (%)	Part C (N=9) n (%)
Safety Population	80	41	9
Pharmacokinetic Population	60 (75.0)	30 (73.2)	9 (100.0)
Subjects Who Completed the Study	74 (92.5)	40 (97.6)	8 (88.9)
Subjects Who Discontinued from the Study	6 (7.5)	1 (2.4)	1 (11.1)
Reason for Discontinuation from the Study			
Adverse Event	3 (3.8)	1 (2.4)	1 (11.1)
Withdrawal by Subject	1 (1.3)		
Lost to Follow-up	1 (1.3)		
Other	1 (1.3)		

Demographics

In Part A, 65 (81.3%) male and 15 (18.8%) female subjects between 18 and 54 years of age and with a BMI between 18.4 and 29.9 kg/m^2 participated in the study. In the gender effect group, only females were included to compare to the males in Group SDL6 (both on 100-mg INT-787 treatment). In Group SDL9, all 6 subjects receiving INT-787 were female whereas 1 female and 1 male received placebo in this group. All other groups solely included males. Overall, male and female subjects were similar in age, race, and BMI.

In Part B, 24 (58.5%) male and 17 (41.5%) female subjects between 18 and 49 years of age and with a BMI between 18.5 and 29.2 kg/m^2 participated in the study.

In Part C, 5 (55.6%) male and 4 (44.4%) female subjects between 19 and 55 years of age and with a BMI between 20.9 and 29.4 kg/m^2 participated in the study.

Safety

Part A (Single Dose Administration and Gender Effect)

All SDLs of INT-787 were generally well tolerated. Three (3) treatment-emergent adverse events (TEAEs) in 3 (3.8%) subjects led to discontinuation from the study: 2 TEAEs of positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test after a single dose of 100 mg INT-787, and 1 TEAE of coronavirus disease 2019 (COVID-19) infection after a single dose of placebo, all considered unrelated to the study treatment. There were no deaths and no serious or severe TEAEs.

Sixty-three (63) TEAEs were reported by 41 (51.3%) subjects. The percentage of subjects reporting TEAEs was not different in the INT-787 groups (ranging from 0% to 100.0%) vs. the pooled placebo group (52.6%). There was no apparent relationship between the INT-787 dose and the number of TEAEs or the number of subjects reporting TEAEs. The most frequently reported TEAEs for all subjects, including placebo, by preferred term (PT) (ie, reported by ≥5% of subjects) were headache (10.0%) and abdominal pain (5.0%). The most frequently reported TEAEs in the pooled placebo group by PT (ie, reported by ≥10% of placebo subjects) were headache (10.5%) and dermatitis contact (10.5%). Except for 1 TEAE of nasopharyngitis, which was first reported at follow-up, all TEAEs were resolved/recovered or resolving/recovering at follow-up.

Out of 63 TEAEs, 17 TEAEs reported by 10 (12.5%) subjects were considered possibly related to the study treatment. Sixteen (16) of these related TEAEs were reported in the INT-787 groups. The most frequently reported possibly related TEAEs (ie, reported at least twice) were headache, diarrhea, and dizziness.

The majority of TEAEs (61 TEAEs in 40 [50.0%] subjects) were of mild intensity. The only 2 TEAEs of moderate intensity were TEAEs of orthostatic hypotension in 1 (1.3%) subject after a single dose of 450 mg INT-787. These events of moderate orthostatic hypotension were considered probably or possibly related to the study treatment.

Part B (Multiple Dose Administration)

All MDLs of INT-787 were generally well tolerated. Two (2) TEAEs in 1 (2.4%) subject on placebo led to discontinuation from the study: 1 TEAE of upper respiratory tract infection and 1 TEAE of dyspepsia, both considered unrelated to the study treatment. There were no deaths and no serious or severe TEAEs.

Eighty-nine (89) TEAEs were reported by 33 (80.5%) subjects. The percentage of subjects reporting TEAEs was not different in the INT-787 groups (ranging from 33.3% to 100.0%) vs. the pooled placebo group (81.8%). There was no apparent relationship between the INT-787 dose and the number of TEAEs or the number of subjects reporting TEAEs. The most frequently reported TEAEs for all subjects, including placebo,

by PT (ie, reported by ≥5% of subjects) were headache (24.4%), dyspepsia (12.2%), diarrhea, catheter site hematoma, and nasopharyngitis (9.8% each), and frequent bowel movements, nausea, catheter site pain, and medical device site reaction (7.3% each). The most frequently reported TEAEs in the pooled placebo group by PT (ie, reported by ≥25% of placebo subjects) were diarrhea (36.4%), headache (36.4%), and dyspepsia (27.3%). All TEAEs were resolved/recovered at follow-up.

Out of 89 TEAEs, 3 TEAEs reported by 3 (7.3%) subjects were considered possibly related to the study treatment: 1 TEAE of pruritus after multiple doses of 100 mg INT-787, and 1 TEAE of pruritus and 1 TEAE of increased liver function test after multiple doses of 200 mg INT-787.

The majority of TEAEs (88 TEAEs in 32 [78.0%] subjects) were of mild intensity. The only TEAE of moderate intensity was a TEAE of upper respiratory tract infection in 1 (2.4%) subject after multiple doses of placebo, which resulted in discontinuation of the subject from the study.

Part C (Food Effect)
Single doses of 50 mg INT-787 were generally well tolerated, both under fasted and fed conditions. One (1) TEAE in 1 (11.1%) subject led to discontinuation from the study. This was a TEAE of COVID-19 infection, which was considered unrelated to the study treatment. There were no deaths and no serious or severe TEAEs.

Eight (8) TEAEs were reported by 4 (44.4%) subjects. The percentage of subjects reporting TEAEs was 44.4% when administered under fasted conditions vs. 12.5% when administered under fed conditions. Except for nasopharyngitis which was reported twice, all TEAEs by PT (asymptomatic COVID-19, anemia, abdominal pain, constipation, musculoskeletal stiffness, and headache) were reported once. All TEAEs were resolved/recovered or resolving/recovering at follow-up.

All 8 TEAEs were considered unrelated or unlikely related to the study treatment, and all 8 TEAEs were of mild intensity.

Adverse Events of Special Interest
Pruritus and drug-induced liver injury (DILI) were considered as AEs of special interest (AESIs) for this study. In Part A, 1 TEAE of mild scattered pruritus, considered possibly related to the study treatment, was reported in 1 subject (1.3%) after a single dose of 5 mg INT-787. In Part B, 4 TEAEs of mild pruritus were reported in 3 subjects (7.3%) after multiple doses of 100 mg or 200 mg INT-787. Two (2) TEAEs of pruritus were considered possibly related to the study treatment (generalized pruritus intermittent in 1 subject after multiple doses of 100 mg INT-787 and itching skin in 1 subject after multiple doses of 200 mg INT-787), whereas 2 TEAEs of application site pruritus were considered related to the study procedure. No TEAEs of pruritus were reported in Part C. All AESIs of pruritus were recovered or resolved during the study. No TEAEs of DILI were reported in Parts A, B, and C. Of note, 2 subjects (1 subject after a single dose of 450 mg INT-787 and 1 subject after multiple doses of 200 mg INT-787) had mild (<3 upper limit of normal), transient increases in aspartate aminotransferase and alanine aminotransferase at several timepoints postdose, which had returned to normal after dosing completion. Neither subject had concomitant increases in total or direct bilirubin, alkaline phosphatase, or gamma glutamyl transferase.

Other Safety Findings
There were no other clinically relevant findings or trends in clinical laboratory parameters, vital signs, ECG, and physical examination in Parts A, B, or C.

Pharmacokinetics

Part A (Single Dose Administration)

Descriptive statistics of the main PK parameters for total, unconjugated, glyco-, and tauro-INT-787 following single dose administration of 2.5 to 450 mg INT-787 are provided in Table S2. Overall, C_{max} and $AUC_{0\text{-}inf}$ for total, unconjugated, glyco-, and tauro-INT-787 increased with ascending single INT-787 doses. However, C_{max} for total and unconjugated INT-787 did not further increase after the 300 mg dose level. Based on AUCs, unconjugated and glyco-INT-787 were overall more abundant in plasma than tauro-INT-787. Overall, the exposure of all components was highly variable.

Data of all SDL groups of Part A, data of the gender effect group of Part A, and data collected under fasted conditions in Part C were used in the SAD dose proportionality analysis. For the increase of C_{max}, no evidence of deviation from dose proportionality was found for glyco-INT-787 (slope of 0.9361 [95% confidence interval [CI]: 0.844; 1.028]). For total, unconjugated, and tauro-INT-787, the increase in C_{max} was less than dose proportional (total INT-787: slope of 0.8952 [95% CI: 0.827; 0.963]; unconjugated INT-787: slope of 0.8729 [95% CI: 0.801; 0.945]; tauro-INT-787: slope of 0.6008 [95% CI: 0.466; 0.736]).

For the increase of $AUC_{0\text{-}inf}$, no evidence of deviation from dose proportionality was found for unconjugated INT-787 (slope of 0.9703 [95% CI: 0.756; 1.185]). For total INT-787, the increase in $AUC_{0\text{-}inf}$ was slightly more than dose proportional (slope of 1.096 [95% CI: 1.017; 1.175]), whereas for glyco-INT-787 and tauro-INT-787, the increase in $AUC_{0\text{-}inf}$ was less than dose proportional (glyco-INT-787: slope of 0.7598 [95% CI: 0.639; 0.881]; tauro-INT-787: slope of 0.2174 [95% CI: -0.023; 0.458]).

Ad-hoc dose-proportionality analysis was performed with trimmed INT-787 dose ranges (5 to 300 mg, 10 to 200 mg, and 25 to 200 mg), ie, zooming in on the presumed range of dosing for actual treatment and disregarding the lower doses which had fewer measurable concentrations. For the trimmed INT-787 dose ranges, the increase of C_{max} and $AUC_{0\text{-}inf}$ for total and unconjugated INT-787 and the increase of C_{max} for glyco-INT 787 were dose proportional. The increase of $AUC_{0\text{-}inf}$ for glyco-INT-787 and the increase of C_{max} and $AUC_{0\text{-}inf}$ for tauro-INT-787 were (extremely) unlikely to be dose proportional.

Following single dose administration of INT-787, the mean cumulative fraction excreted in urine of total INT-787 ranged between 1.9% and 5.0%, with glyco-INT-787 being the most prominent analyte in urine with a mean cumulative fraction excreted ranging between 1.8% and 4.6%.

Part A (Gender Effect)

Descriptive statistics of the main PK parameters for total, unconjugated, glyco-, and tauro-INT-787 following single dose administration of 100 mg INT-787 by males (in Group SDL6 of Part A) vs. females (in the gender effect group of Part A) are provided in Table S2. Overall, C_{max} and $AUC_{0\text{-}inf}$ of total and unconjugated INT-787 were not notably different between males and females.

In the gender effect analysis, none of the 90% CIs for the ratios of geometric least-squares means (LSMeans) of C_{max} and AUCs for total, unconjugated, glyco-, and tauro-INT-787 were fully contained within the 80% to 125% window (Figure S1), and thus a gender effect cannot be fully excluded. However, considering the small number of subjects included in this exploratory analysis, no firm conclusions on gender effects can be drawn. If any gender effect would be present, the effect would be less than 2-fold, as the 90% CIs for the ratios are roughly contained within the 50% to 200% window.

Table S2 Summary Statistics of Pharmacokinetic Parameters for INT-787 in Plasma – Part A (Single Dose Administration and Gender Effect)

			Dose									
Analyte	**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)**
Total INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	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
Unconjugated INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	0	0	0	4	4	8	6	6	6	6
		Geo. Mean	NA	NA	NA	223	666[a]	805	623	1950	2210	3180
		Geo. CV (%)	NA	NA	NA	405	104	49.5	70.5	39.9	12.9	11.2
	C_{max} (ng/mL)	n	4	6	6	6	6	8	6	6	6	6
		Geo. Mean	4.38	7.41	17.6	31.9	54.1	101	98.2	304	382	276
		Geo. CV (%)	25.3	25.6	16.6	31.2	28.6	57.3	60.4	41.4	30.8	43.7
Glyco-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	0	1	4	6	6	8	6	6	6	6
		Geo. Mean	NA	125	128	350	374	688	564	1540	1810	2950
		Geo. CV (%)	NA	NA	59.1	98.1	55.0	50.9	45.8	34.7	36.4	32.5
	C_{max} (ng/mL)	n	2	6	6	6	6	8	6	6	6	6
		Geo. Mean	1.06	1.65	3.65	11.4	13.3	32.1	29.5	60.4	110	105
		Geo. CV (%)	5.45	25.3	98.8	47.5	55.4	66.9	46.5	27.3	54.6	46.5
Tauro-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	0	0	1	3	4	6	5	6	6	6
		Geo. Mean	NA	NA	566	496	210	497	448	418	494	1210
		Geo. CV (%)	NA	NA	NA	74.0	55.6	105	77.0	63.7	50.7	52.6
	C_{max} (ng/mL)	n	0	2	6	6	6	8	6	6	6	6
		Geo. Mean	NA	1.35	1.85	4.93	5.81	9.01	13.6	10.7	16.3	24.1
		Geo. CV (%)	NA	44.7	43.5	56.8	59.7	92.8	134	49.3	49.3	53.7

F=female; Geo. CV=geometric coefficient of variation; Geo. Mean=geometric mean; M=male; Max=maximum; Min=minimum; NA=not applicable; n=number of subjects

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

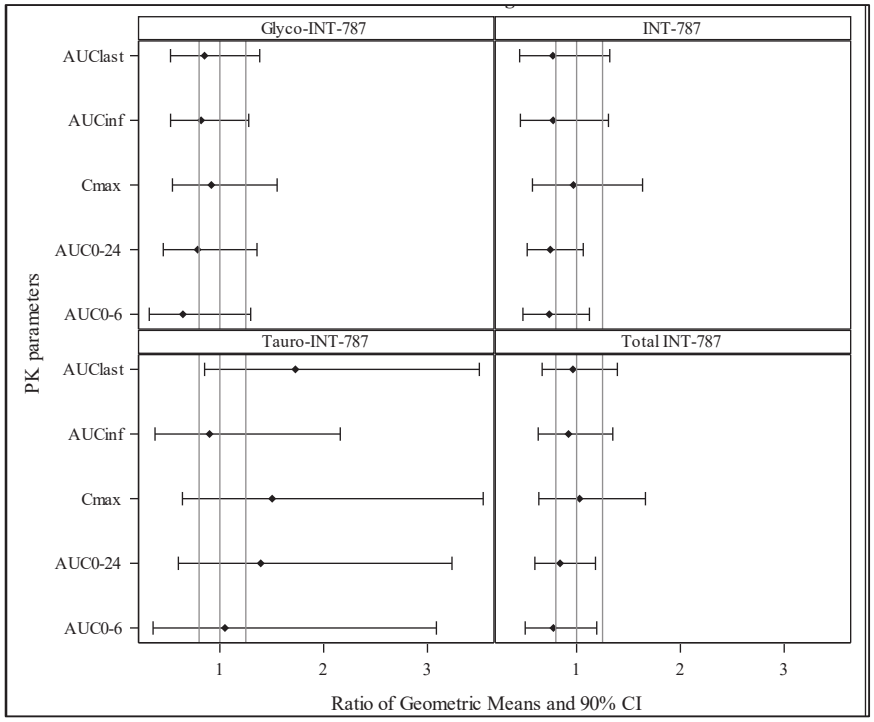

Figure S1 Forest Plot of the Effect of Gender on Pharmacokinetic Parameters for INT-787 in Plasma – Part A (Gender Effect)

CI=confidence interval; LSMeans=least-squares means; PK=pharmacokinetic
Note: A gender effect was not rejected if the 90% CI for the ratio of geometric LSMeans was not contained within 80% and 125%.

Part B (Multiple Dose Administration)

Descriptive statistics of the main PK parameters for total, unconjugated, glyco-, and tauro-INT-787 following multiple dose administration of 5 to 200 mg INT-787 once daily for 14 days are provided in Table S3. Overall, C_{max} and AUC_{tau} for total, unconjugated, glyco- and tauro-INT-787 increased with ascending INT-787 doses on Days 1, 7, and 14. However, C_{max} and AUC_{tau} of tauro-INT-787 did not always further increase after the 100 mg dose level. Based on AUCs, unconjugated and glyco-INT-787 were overall more abundant in plasma than tauro-INT-787. Furthermore, AUC_{tau} for total, unconjugated, glyco-, and tauro-INT-787 overall increased from Day 1 to Day 7 by 1.2 to 5.2-fold. AUC_{tau} for total, unconjugated, glyco-, and tauro-INT-787 did not further increase between Day 7 and Day 14. C_{max} remained more or less constant over 14 days per dose level for total, unconjugated, and glyco-INT-787. However, for tauro-INT-787, which generally had lower concentrations, the C_{max} increased by 2.0 to 4.7-fold from Day 1 to Day 7 across the dose range.

Data of all MDL groups of Part B were used in the MAD dose proportionality analysis. For the increase of C_{max} on Days 1, 7, and 14, no evidence of deviation from dose proportionality was found for total and unconjugated INT-787 (with slopes of 0.9612, 1.008, and 1.045 on Days 1, 7, and 14, respectively, for total INT-787 and slopes of 0.9457, 1.037, and 1.037 on Days 1, 7, and 14, respectively, for unconjugated INT-787).

For total INT-787, the increase in AUC_{tau} was more than dose proportional on Day 1 (slope of 1.196 [95% CI: 1.096; 1.297]), whereas there was no evidence of deviation from dose proportionality found on Days 7 and 14 (with slopes of 0.9993 and 1.010 on Days 7 and 14, respectively). For unconjugated INT-787, the

increases in AUC_{tau} were more than dose proportional on Days 1, 7, and 14 (Day 1: slope of 1.194 [95% CI: 1.106; 1.281]; Day 7: slope of 1.209 [95% CI: 1.114; 1.304]; Day 14: slope of 1.280 [95% CI: 1.183; 1.376]).

For both glyco- and tauro-INT-787, no evidence of deviation from dose proportionality was found for the increase in C_{max} on Day 1. On Days 7 and 14, the increases in C_{max} of glyco- and tauro-INT-787 were less than dose proportional. For tauro-INT-787, no evidence of deviation from dose proportionality was found for the increase in AUC_{tau} on Days 1, 7, and 14. For glyco-INT-787, the increase in AUC_{tau} was more than dose proportional on Day 1, not deviating from dose proportionality on Day 7, and less than dose proportional on Day 14.

Table S3 Summary Statistics of Pharmacokinetic Parameters for INT-787 in Plasma – Part B (Multiple Dose Administration)

				Dose				
Analysis Day	**Analyte**	**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	Total INT-787	$AUC_{0\text{-}inf}$ (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
	Unconjugated INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	0	0	5	6	6
			Geo. Mean	NA	NA	143	494	973
			Geo. CV (%)	NA	NA	41.1	39.8	33.2
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	8.41	22.8	54.6	139	281
			Geo. CV (%)	36.6	39.2	17.0	27.0	61.8
	Glyco-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	1	5	5	5	5
			Geo. Mean	30.6	60.3	179	578	710
			Geo. CV (%)	NA	38.0	38.4	64.7	77.1
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	1.87	4.67	17.5	45.5	62.1
			Geo. CV (%)	35.3	29.8	58.2	53.8	59.8
	Tauro-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	0	0	4	3	3
			Geo. Mean	NA	NA	116	177	296
			Geo. CV (%)	NA	NA	48.6	97.7	38.3
		C_{max} (ng/mL)	n	0	6	6	6	6
			Geo. Mean	NA	2.02	10.0	15.8	15.3
			Geo. CV (%)	NA	50.5	66.4	92.3	34.0
7	Total INT-787	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
	Unconjugated INT-787	AUC_{tau} (h*ng/mL)	n	6	6	6	6	6
			Geo. Mean	14.9	55.7	212	541	1310
			Geo. CV (%)	53.2	34.7	37.8	24.8	27.3
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	6.44	18.8	50.0	121	325
			Geo. CV (%)	21.2	55.5	52.0	25.6	65.0
	Glyco-INT-787	AUC_{tau} (h*ng/mL)	n	6	6	6	6	6
			Geo. Mean	40.7	115	285	509	960
			Geo. CV (%)	69.5	64.3	48.0	54.7	93.4
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	4.69	11.9	30.3	48.5	79.3
			Geo. CV (%)	43.9	52.3	32.9	52.0	86.3
	Tauro-INT-787		n	6	6	6	6	6

Analysis Day	Analyte	Parameter	Statistic	Dose 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)
		AUC_{tau} (h*ng/mL)	Geo. Mean	12.8	77.0	278	379	333
			Geo. CV (%)	126	32.0	118	90.5	40.0
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	2.04	9.53	32.5	37.6	30.4
			Geo. CV (%)	56.9	22.9	113	62.0	40.0
14	Total INT-787	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
	Unconjugated INT-787	AUC_{tau} (h*ng/mL)	n	5	6	6	6	6
			Geo. Mean	12.6	54.1	270	553	1470
			Geo. CV (%)	39.0	26.8	35.3	26.2	40.0
		C_{max} (ng/mL)	n	5	6	6	6	6
			Geo. Mean	7.15	25.6	58.7	120	426
			Geo. CV (%)	18.6	43.8	38.3	19.5	88.7
	Glyco-INT-787	AUC_{tau} (h*ng/mL)	n	6	6	6	6	6
			Geo. Mean	43.9	117	284	553	946
			Geo. CV (%)	60.0	50.3	61.5	52.4	106
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	4.90	12.4	28.9	53.1	80.7
			Geo. CV (%)	36.0	33.1	58.7	56.5	91.7
	Tauro-INT-787	AUC_{tau} (h*ng/mL)	n	6	6	6	6	6
			Geo. Mean	18.6	91.1	355	444	446
			Geo. CV (%)	112	44.7	128	109	48.8
		C_{max} (ng/mL)	n	6	6	6	6	6
			Geo. Mean	2.68	11.6	35.9	50.1	44.5
			Geo. CV (%)	58.9	26.4	125	77.7	40.0

F=female; Geo. CV=geometric coefficient of variation; Geo. Mean=geometric mean; M=male; Max=maximum; Min=minimum; NA=not applicable; n=number of subjects

PK urine analysis was included for Part B as of CSP Version 7.0. Thus, PK urine analysis was only performed for Groups MDL3 (45 mg INT-787), MDL4 (100 mg INT-787), and MDL5 (200 mg INT-787).

Following multiple dose administration of 45 to 200 mg INT-787, the mean cumulative fraction excreted in urine of total INT-787 ranged between 2.7% and 5.1%, with glyco-INT-787 being the most prominent analyte in urine with a mean cumulative fraction excreted ranging between 2.3% and 3.8%.

Part C (Food Effect)

Descriptive statistics of the main PK parameters for total, unconjugated, glyco-, and tauro-INT-787 following single dose administration of 50 mg INT-787 under fasted vs. fed conditions are provided in Table S4.

In the food effect analysis, the 90% CIs for the ratios of geometric LSMeans of AUC_{0-6h} for total, unconjugated, and glyco-INT-787, of C_{max} for unconjugated INT-787, and of AUC_{0-inf} for tauro-INT-787 were fully below the 80% and 125% window, whereas the 90% CIs for the ratio of AUC_{0-24h} for total, unconjugated, and glyco-INT-787, of AUC_{0-t} for unconjugated and glyco-INT-787, and of C_{max} for tauro-INT-787 were fully within the 80% to 125% window (Figure S2). This indicates that a possible food effect cannot be excluded for the rate of absorption of INT-787, based on the statistical analysis of this small group where there was an approximately 2-fold higher C_{max} for unconjugated INT-787 and an approximately 2 to 3-fold higher AUC_{0-6h} for total, unconjugated, and glyco-INT-787 under fasted vs. fed conditions, which seemed to disappear over time.

Table S4 Summary Statistics of Pharmacokinetic Parameters for INT-787 in Plasma - Part C (Food Effect)

			Food Regimen	
Analyte	**Parameter**	**Statistic**	**Fasted**	**Fed**
Total INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	9	8
		Geo. Mean	720	776
		Geo. CV (%)	52.0	42.0
	C_{max} (ng/mL)	n	9	8
		Geo. Mean	72.1	42.0
		Geo. CV (%)	44.6	55.4
Unconjugated INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	9	7
		Geo. Mean	310	376
		Geo. CV (%)	45.4	47.3
	C_{max} (ng/mL)	n	9	8
		Geo. Mean	65.6	33.8
		Geo. CV (%)	37.1	61.7
Glyco-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	9	8
		Geo. Mean	394	469
		Geo. CV (%)	65.2	81.0
	C_{max} (ng/mL)	n	9	8
		Geo. Mean	19.8	14.4
		Geo. CV (%)	125	97.7
	MPR $AUC_{0\text{-}24h}$	n	9	8
		Geo. Mean	0.771	0.621
		Geo. CV (%)	65.7	58.9
	MPR C_{max}	n	9	8
		Geo. Mean	0.267	0.377
		Geo. CV (%)	108	43.5
	MPR $AUC_{0\text{-}inf}$	n	9	7
		Geo. Mean	1.13	1.14
		Geo. CV (%)	57.2	65.1
Tauro-INT-787	$AUC_{0\text{-}inf}$ (h*ng/mL)	n	6	3
		Geo. Mean	481	562
		Geo. CV (%)	111	97.9
	C_{max} (ng/mL)	n	9	8
		Geo. Mean	8.67	6.86
		Geo. CV (%)	120	119
	MPR $AUC_{0\text{-}24h}$	n	9	8
		Geo. Mean	0.254	0.160
		Geo. CV (%)	130	208
	MPR C_{max}	n	9	8
		Geo. Mean	0.102	0.157
		Geo. CV (%)	129	93.1
	MPR $AUC_{0\text{-}inf}$	n	6	3
		Geo. Mean	1.19	0.807
		Geo. CV (%)	161	81.7

Geo. CV=geometric coefficient of variation; Geo. Mean=geometric mean; Max=maximum; Min=minimum; MPR=metabolite to parent ratio; NA=not applicable; n=number of subjects

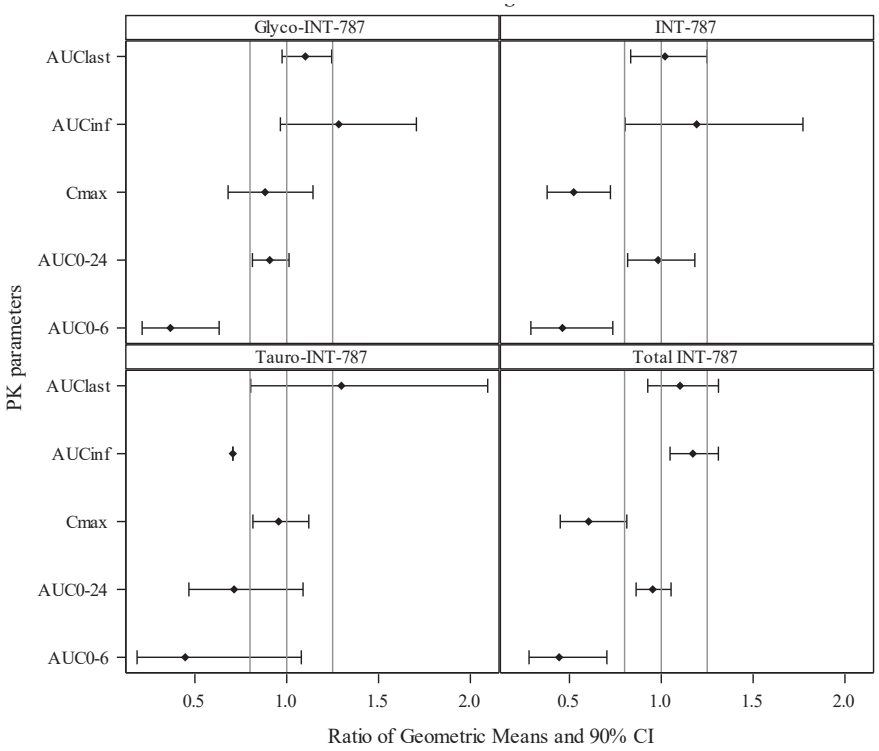

Figure S2 Forest Plot of the Effect of Food on Pharmacokinetic Parameters for INT-787 in Plasma – Part C (Food Effect)

CI=confidence interval; LSMeans=least-squares means; PK=pharmacokinetic
Note: A food effect was not rejected if the 90% CI for the ratio of geometric LSMeans was not contained within 80% and 125%.

Pharmacodynamics in Plasma

Pharmacodynamic parameters in plasma included the following FXR activation biomarkers: C4, FGF-19, and endogenous bile acids (total, unconjugated, glyco-, and tauro-conjugates of UDCA, CDCA, DCA, CA, and LCA). Only subjects who received INT-787 had plasma C4 and FGF-19 concentrations measured (ie, no placebo subjects were analyzed). Bile acids were measured in placebo subjects and those who received INT-787.

7α-Hydroxy-4-Cholesten-3-one

In Part A, no apparent changes from baseline in C4 concentrations were observed following single doses of up to 10 mg INT-787 at 24 hours postdose. For single doses of 25 mg INT-787 and higher, clear decreases in C4 concentrations were observed at 24 hours postdose. The decrease in C4 concentrations was overall more prominent and longer lasting with increasing INT-787 doses, up to mean decreases after administration of 450 mg INT-787 of 81.4%, 85.6%, 88.6%, and 86.1% at 24, 48, 72, and 96 hours postdose, respectively. The corresponding lowest mean C4 concentrations were as low as 0.9 ng/mL. Changes from baseline in C4 concentrations were similar following single doses of 100 mg INT-787 in male vs. female subjects with mean decreases of 66.4% and 65.6% at 24 hours postdose, respectively. Plasma C4 concentrations were highly variable, especially for the lower doses.

In Part B, decreases in C4 concentrations were observed during multiple dose administration of INT-787 for doses up to 15 mg, although changes were variable (for the 15-mg dose level) and/or not persistent (for the 5- and 15-mg dose levels). For multiple doses of 45 mg INT-787 and higher, clear and persistent decreases

in C4 concentrations were observed up to Day 14, with mean decreases up to 53.5%, 89.6%, and 94.2% at predose on Day 14 following multiple administration of 45, 100, and 200 mg INT-787, respectively. The corresponding lowest mean C4 concentrations were as low as 0.4 ng/mL. After dosing completion, C4 concentrations returned to baseline values and/or exceeded baseline values. Plasma C4 concentrations were highly variable, especially for the lower doses.

In Part C, changes from baseline in C4 concentrations were similar following single doses of 50 mg INT-787 under fasted vs. fed conditions with mean decreases of 71.2% and 65.5% at 24 hours postdose, respectively.

Fibroblast Growth Factor-19

In Part A, no apparent changes from baseline in FGF-19 concentrations were observed following single doses of up to 10 mg INT-787 at 24 hours postdose. For single doses of 25 mg INT-787 and higher, clear increases in FGF-19 concentrations were observed at 24 hours postdose. The increase in FGF-19 concentrations was overall more prominent and longer lasting with increasing INT-787 doses, up to mean increases after administration of 450 mg INT-787 of 566%, 442%, and 518% at 24, 48, and 72 hours postdose, respectively. Changes from baseline in FGF-19 concentrations were similar following single doses of 100 mg INT-787 in male vs. female subjects. A potential difference in mean FGF-19 increases at 24 hours postdose between males (227%) and females (99.7%) could be driven by a difference in baseline FGF-19 concentrations between males (130 ng/mL) and females (175 ng/mL) and/or a difference in group size between males (n=8) and females (n=5). Plasma FGF-19 concentrations were highly variable, especially for the higher doses.

In Part B, clear and persistent increases in FGF-19 concentrations were observed during multiple dose administration of INT-787 up to Day 14 for all doses. The increase in FGF-19 concentrations was overall more prominent with increasing INT-787 doses, with mean increases up to 187%, 230%, and 349% at predose on Day 14 following multiple administration of 45, 100, and 200 mg INT-787, respectively. After dosing completion, FGF-19 concentrations returned to baseline values after Day 16 (ie, 2 days post last dose). Plasma FGF-19 concentrations were highly variable, especially for the higher doses.

In Part C, changes from baseline in FGF-19 concentrations were similar following single doses of 50 mg INT-787 under fasted vs. fed conditions with mean increases of 184% and 166% at 24 hours postdose, respectively.

Endogenous Bile Acids

In Part A, decreases in total-CA concentrations were observed at 24 hours postdose following single dose administration of INT-787 for most doses of INT-787, with no apparent differences between INT-787 doses. No apparent changes from baseline or differences between INT-787 doses were observed for other bile acids (CDCA, DCA, LCA, and UDCA). In Part B, dose-dependent decreases in total-CA concentrations were observed on Day 16 (2 days after last dosing) following multiple dose administration of 5 to 200 mg INT-787. Changes from baseline in bile acids were similar following single doses of 100 mg INT-787 in male vs. female subjects (Part A) or following single doses of 50 mg INT-787 under fasted vs. fed conditions (Part C). Bile acid concentrations were highly variable, limiting the interpretation of these data.

Exploratory Renal Safety Biomarkers in Urine

The following exploratory renal safety biomarkers were assessed in urine: IL-18, KIM-1, L-FABP-1, and NGAL. Renal safety biomarkers were assessed as of CSP Version 7.0. Thus, only for Group SDL9 (450 mg INT-787) and the gender effect group (100 mg INT-787) in Part A and Groups MDL3 (45 mg INT-787), MDL4 (100 mg INT-787), and MDL5 (200 mg INT-787) in Part B, renal safety biomarker data are available. Of note, all subjects in the SDL groups treated with INT-787 and providing urine samples were females.

Liver-Type Fatty Acid Binding Protein-1

In Part A, excretion of L-FABP-1 in urine was higher following single dose administration of 100 mg or 450 mg INT-787 (ie, in the mean range of approximately 700-1500 µg per 24-hour collection interval) compared to placebo, where concentrations were not measurable. No apparent difference in the amount of L-FABP-1 excreted in urine was observed between the 100-mg dose group and the 450-mg dose group. In Part B, the mean amount of L-FABP-1 excreted in urine within 24 hours postdose slightly increased from Day 1 to Day 14 following multiple doses of 45, 100, and 200 mg INT-787. After dosing completion, the amount of L-FABP-1 excreted in urine decreased again. No apparent differences in the amount of L-FABP-1 excreted in urine were observed between dose groups. Considering the descriptive nature of these exploratory biomarkers and the high variability in excreted amounts of L-FABP-1, no firm conclusions on potential trends or differences between dose groups can be drawn.

Interleukin-18

In Part A, no apparent difference in the amount of IL-18 excreted in urine per 24-hour collection interval was observed following single dose administration of INT-787 between the 100-mg dose group, and the 450-mg dose group, or compared to the placebo group. In Part B, no apparent trends over time or differences between dose groups in the amount of IL-18 excreted in urine were observed following multiple doses of 45, 100, and 200 mg INT-787. Considering the descriptive nature of these exploratory biomarkers and the high variability in excreted amounts of IL 18, no firm conclusions on potential trends or differences between dose groups can be drawn.

Kidney Injury Molecule-1

In Part A, the amount of KIM-1 excreted in urine per 24-hour collection interval following single dose administration of INT-787 was 1.8 to 2.7-fold higher in the 450-mg dose group compared to the 100-mg dose group and increased compared to placebo. In Part B, no apparent trends over time or differences between dose groups in the amount of KIM-1 excreted in urine were observed following multiple doses of 45, 100, and 200 mg INT-787 although excreted amounts of KIM-1 were increased compared to placebo by approximately 2-fold. Considering the descriptive nature of these exploratory biomarkers and the high variability in excreted amounts of KIM-1, no firm conclusions on potential trends or differences between dose groups can be drawn.

Neutrophil Gelatinase-Associated Lipocalin

In Part A, the amount of NGAL excreted in urine per 24-hour collection interval following single dose administration of INT-787 was 2.0 to 2.9-fold higher in the 450-mg dose group compared to the 100-mg dose group and increased compared to placebo. In Part B, no apparent trends over time or differences between dose groups in the amount of NGAL excreted in urine were observed: following multiple doses of 45, 100, and 200 mg INT-787 although excreted amounts of NGAL were increased compared to placebo. Considering the descriptive nature of these exploratory biomarkers and the high variability in excreted amounts of NGAL, no firm conclusions on potential trends or differences between dose groups can be drawn.

Conclusions

Safety

- Single oral doses of 2.5 to 450 mg INT-787 and multiple oral doses of 5 to 200 mg INT-787 once daily for 14 days were generally well tolerated by healthy male and female subjects.
- There was no apparent relationship between the INT-787 dose and the number of TEAEs reported or the number of subjects reporting TEAEs.
- The AESI of pruritus (3 treatment-related events in 3 subjects) was not notably reported across the whole range of INT-787 doses. No events of DILI were reported.

- There were no clinically relevant findings or trends in clinical laboratory parameters, vital signs, ECG, and physical examination.

Pharmacokinetics

Pharmacokinetics of INT-787 in Plasma

- Irrespective of the administered dose levels of INT-787, and single or multiple dosing, maximum observed plasma concentrations of total and unconjugated INT-787 were overall reached between 1 and 2 hours postdose and maximum observed plasma concentrations of glyco- and tauro-INT-787 were overall reached between 6 and 10 hours postdose, consistent with bile acid metabolism.
- Following single and multiple dose administration of INT-787, C_{max} and AUCs for total, unconjugated, glyco-, and tauro-INT-787 overall increased with ascending INT-787 doses.
- The results of the SAD dose proportionality analysis suggested that the increases in AUCs and C_{max} deviated from dose proportionality, except for C_{max} of glyco-INT-787 and $AUC_{0\text{-}inf}$ of unconjugated INT-787, which showed a dose proportional increase. However, in the ad-hoc analysis, when zooming in on the presumed range of dosing for actual treatment and disregarding the lower doses which had fewer measurable concentrations, the increase of C_{max} and $AUC_{0\text{-}inf}$ for total and unconjugated INT-787 and the increase of C_{max} for glyco-INT-787 were dose proportional.
- The results of the MAD dose proportionality analysis suggested a dose proportional increase for C_{max} of total and unconjugated INT-787 on all PK days (Days 1, 7 and 14). Dose proportionality analysis on the AUC_{tau} of total and unconjugated INT-787 and on the C_{max} and AUC_{tau} of glyco- and tauro-INT-787 did not show a consistent dose proportionality result across PK days.
- Following multiple dose administration of INT-787, AUC_{tau} for total, unconjugated, glyco- and tauro-INT-787 increased from Day 1 to Day 7 by 1.2 to 5.2-fold. AUC_{tau} for total, unconjugated, glyco- and tauro-INT-787 did not further increase between Day 7 and Day 14. C_{max} remained more or less constant over 14 days per dose level for total, unconjugated, and glyco-INT-787. However, for tauro-INT-787, which generally had lower concentrations, the C_{max} increased by 2.0 to 4.7-fold from Day 1 to Day 7 across the dose range.
- Plasma exposure to total, unconjugated, glyco-, and tauro-INT-787 was not notably different between males and females, although, based on statistical analysis of a small number of subjects, a gender effect could not be fully excluded.
- A possible food effect cannot be excluded for the rate of absorption of INT-787, based on the statistical analysis of this small group where there was an approximately 2-fold higher C_{max} for unconjugated INT-787 and an approximately 2 to 3-fold higher $AUC_{0\text{-}6h}$ for total, unconjugated, and glyco-INT-787 under fasted vs. fed conditions, which seemed to disappear over time.

Pharmacokinetics of INT-787 in Urine

- Following single and multiple dose administration, the mean cumulative fraction excreted in urine of total INT-787 ranged between 1.9% and 5.1%, with glyco-INT-787 being the most prominent analyte in urine with a mean cumulative fraction excreted ranging between 1.8% and 4.6%.

Pharmacodynamics

FXR Activation Biomarkers in Plasma

- Following single dose administration of INT-787, clear decreases in C4 concentrations and clear increases in FGF-19 concentrations were observed at 24 hours postdose for doses of 25 mg and higher. These changes were more prominent and longer lasting with increasing INT-787 doses.
- During multiple dose administration of INT-787 up to Day 14, clear decreases in C4 concentrations and clear and persistent increases in FGF-19 concentrations were observed for all doses. These changes were more prominent with increasing INT-787 doses.

- No apparent changes from baseline or differences between INT-787 doses were observed in bile acids (CA, CDCA, DCA, LCA, and UDCA) following single and multiple dose administration of INT-787, except for a decrease in total-CA at 24 hours postdose following single dose administration and on Day 16 following multiple dose administration, for most doses of INT-787.
- Changes from baseline in C4, FGF-19, and endogenous bile acid concentrations were similar following single doses of 100 mg INT-787 in male vs. female subjects and following single doses of 50 mg INT-787 under fasted vs. fed conditions.
- Variability in plasma C4, FGF-19, and bile acid concentrations was high across subjects.

Exploratory Renal Safety Biomarkers in Urine

- Variability in excreted amounts of L-FABP-1, IL-18, KIM-1, and NGAL in urine was high across subjects, and the clinical significance of any increases in renal safety biomarkers remains to be determined.