Pharmacokinetics, safety, and tolerability of faldaprevir in patients with renal impairment

Running title: PK of faldaprevir in renal impairment

Authors: Fenglei Huang¹#, Viktoria Moschetti², Benjamin Lang³, Atef Halabi⁴, Marc Petersen-Sylla⁴, Chan-Loi Yong¹, and Mabrouk Elgadi⁵

¹Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; ²Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; ³Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; ⁴CRS Clinical Research Services Kiel GmbH, Kiel, Germany; ⁵Boehringer Ingelheim Ltd/Ltée, Burlington, ON, Canada

#Corresponding author:
Fenglei Huang, PhD, FCP
Clinical Pharmacokinetics & Pharmacodynamics
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
Ridgefield, CT 06877-0368
Phone: 001 203-798-4537
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ABSTRACT

Faldaprevir is a potent hepatitis C virus (HCV) NS3/4A protease inhibitor with negligible urinary excretion. We assessed the pharmacokinetics and safety of a single oral dose of faldaprevir (480 mg) in 32 HCV-negative subjects with renal impairment or normal renal function. Compared with subjects with normal renal function, the adjusted geometric mean ratios (90% confidence interval) for overall exposure AUC₀–∞ were 113.6% (41.6–310.2%), 178.3% (85.2–373.0%), and 169.2% (73.2–391.2%) for subjects with mild, moderate, or severe renal impairment, respectively. Overall, 5/8 (63%) subjects with normal renal function and 20/24 (83%) subjects with renal impairment reported adverse events, with gastrointestinal events being the most common. No severe or serious adverse events or deaths were reported. These results suggest that moderate or severe renal impairment can result in a modest increase in faldaprevir exposure. The increase in exposure may be related to decrease in the activity of the liver uptake transporter OATP1B1 as a result of renal impairment. Given this relatively slight increase in exposure, a dose adjustment in HCV patients with renal impairment is not warranted. (ClinicalTrials.gov registration number NCT01957657).
INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a cause of renal dysfunction and associated with a number of co-morbidities that can affect renal function (1,2). As impaired renal function may influence drug metabolism and pharmacokinetics (3,4), dose adjustments might be required in this patient population to avoid excess drug accumulation that can impact drug efficacy and safety. While the introduction of the NS3/4A protease inhibitors telaprevir and boceprevir represented a significant advance in the management of patients with chronic HCV genotype (GT)-1 infection, their use is associated with some disadvantages (5). In addition to being associated with a number of significant serious side effects (including rash, anemia, and gastrointestinal symptoms), these first-generation protease inhibitors require three times daily dosing due to short half-lives, they have a complex drug–drug interaction profile (limiting co-administration with other agents), and are associated with a marked decline in renal function (6–8).

In order to improve the safety, efficacy, and convenience of HCV treatments, a number of second-generation direct-acting antivirals (DAAs) for the treatment of patients infected with HCV GT-1 are in clinical development or have recently been approved (9–11). Faldaprevir is a potent HCV NS3/4A protease inhibitor (12), which, in combination with pegylated interferon α-2a and ribavirin (PR),
has been shown to be highly effective for the treatment of chronic HCV GT-1 infection (13–16). In the Phase III STARTVerso1 trial, once-daily (QD) faldaprevir 120 mg plus PR achieved sustained virologic response rates 12 weeks after completion of treatment (SVR12) of 79% in treatment-naïve patients with HCV GT-1 infection (16). Faldaprevir 120 mg QD plus PR was well tolerated, with a similar safety profile to PR alone and a low rate of adverse events (AEs) leading to discontinuations. High SVR rates have also been achieved with faldaprevir in Phase II interferon-free combinations with deleobuvir (a non-nucleoside NS5B inhibitor) and ribavirin (SOUND-C3) and with PPI-668 (an NS5A inhibitor), deleobuvir, and RBV in patients infected with GT-1a or GT-1b (17,18).

The pharmacokinetic profile of faldaprevir supports QD administration (19). Phase Ib pharmacokinetic data showed that following administration of faldaprevir (20–240 mg QD), plasma concentrations peaked at 2–6 h and increased supra-proportionally with dose (19). In addition, the half-life of faldaprevir in HCV-infected patients was approximately 20–30 h (19). Although, urinary excretion is not an important metabolic pathway for faldaprevir, with approximately 0.1% excreted through this route (20), it is currently unknown if altered renal function influences faldaprevir distribution or metabolism.
Therefore, the aim of this study was to examine the effects of mild, moderate, or severe renal impairment on the pharmacokinetics and safety of faldaprevir.

BI has recently decided not to pursue the development of faldaprevir since there was no longer deemed to be an unmet need for faldaprevir interferon-based HCV treatment. Nonetheless, this study provides important information on the potential effect of renal impairment on the activities of liver transporters, in particular, liver uptake transporters (OATP1B1) in HCV therapies, and, together with safety and efficacy data from Phase II and III studies, may help us understand the effect of renal impairment on the treatment of HCV infection.

METHODS

Study design

This study was a non-randomized, open-label, single-dose, parallel-group Phase I study, designed in accordance with the FDA guideline on pharmacokinetics in patients with reduced renal function (21). Thirty-two male and female subjects were assigned to one of four renal function groups (8 in each group), according to their estimated glomerular filtration rate (eGFR), calculated using the modification of diet in renal disease (MDRD) formula (22): normal renal function (eGFR ≥90 mL/min/1.73m²), mild renal impairment (eGFR
60–89 mL/min/1.73m²), moderate renal impairment (eGFR 30–59 mL/min/1.73m²), and severe renal impairment (eGFR 15–29 mL/min/1.73m²).

Following a 10-hour overnight fast, subjects were administered a single, 480 mg oral dose of faldaprevir (Figure 1). This is equivalent to the initial loading dose of faldaprevir given to treatment-experienced patients and twice the initial loading dose given to treatment-naïve patients in the faldaprevir Phase III clinical trials.

Subjects

This study was conducted at CRS Clinical Research Services Kiel GmbH (Kiel, Germany) following approval by the Independent Ethics Committee (IEC; Ethikkommission bei der Ärztekammer Schleswig-Holstein, Bad Segeberg, Germany). The clinical trial application was also reviewed by the German Competent Authority (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM], Bonn, Germany). The trial was carried out in compliance with the protocol and principles laid down in the Declaration of Helsinki (1996 version), and in accordance with applicable regulatory requirements. All subjects provided written informed consent prior to participation.

Non-smoking male and female subjects, 18–75 years of age (up to 79 years for subjects with severe renal impairment), with body mass index (BMI) ≥18.5–≤34.
kg/m² were eligible for inclusion. Female subjects were required not to be pregnant or nursing, and had agreed to use adequate contraception for the duration of the trial. Subjects were included if in generally good health, as judged by medical history, physical examinations, and clinical laboratory data. Subjects were excluded if they presented with clinically abnormal laboratory results or evidence of existing diseases; these included positive serology test results for human immunodeficiency virus, hepatitis B virus, or HCV. Conditions that could potentially interfere with the pharmacokinetics or tolerability of faldaprevir were also criteria for exclusion; these include histories of photosensitivity or recurrent rash, gastrointestinal surgery, smoking, consumption of alcohol, drug abuse, intake of a long half-life drug prior to administration of study drug, participation in a multiple dose trial within two months or a single dose trial within one month prior to this trial, or recent blood donation. Subjects could be withdrawn from the study at any time due to inclusion/exclusion criteria violation, failure to show for the study, AEs, withdrawal of consent, use of concomitant drugs interfering with the study medication, onset of an illness, or other medical reasons (e.g. surgery).

**Blood sample collection**

For quantification of faldaprevir plasma concentrations, blood was collected into an EDTA-anticoagulant blood drawing tube at the following time points on Day...
1: 0 h (pre-dosing), and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h post-dosing; on Days 2–7: 24, 36, 48, 72, 96, 120, and 144 h post-dosing (Figure 1).

**Bioanalytical methods**

Plasma faldaprevir concentrations were determined by a validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS; Tandem Laboratories, Salt Lake City, UT, USA) assay, with a lower limit of quantification of 10 ng/mL. LC–MS/MS used electrospray ionization and positive ion mode as the detection method. The extraction method used was solid-phase extraction method. The internal standard was [D7]-BI00201335ZW. Linear calibration curves were obtained over the range from 10 to 10,000 ng/mL. The assay accuracy precision (CV%) was in the range of 2.9–4.0%. The assay inaccuracy deviation was in the range of -1.5–0.5%.

The extent of faldaprevir protein binding was determined using equilibrium dialysis. Ten plasma samples from each of the 32 subjects were pooled, providing 32 pooled samples. Teflon dialysis cells (Spectrum) and dialysis membranes (Spectra/Por) with 12,000–14,000 molecular weight cut-off were used. After assembling the dialysis cells and membranes, the pooled plasma from each subject was adjusted to pH 7.4, and 1 mL was added to the donor side of the dialysis cell. The receiver side of each dialysis cell was filled with...
1 mL of 0.1M sodium phosphate buffer (pH 7.4). For each subject, three individual dialysis cells were prepared and rotated at 20 rpm for 4 h (equilibrium time previously determined) using a Spectrum dialysis cell rotator in a water bath maintained at approximately 37°C. At the end of the incubation period, the contents of each side were transferred to a tared scintillation vial. Volumes were determined by weighing each vial. Concentrations of faldaprevir were measured by a validated LC–MS/MS, which, qualified for the concentration range of 0.50–5,000 ng/mL, with a lower limit of quantitation of 0.50 ng/mL. Assay for buffer was qualified for the concentration range of 0.01–50.0 ng/mL, with a lower limit of quantitation of 0.01 ng/mL.

**Safety assessment**

All subjects who received at least one dose of trial medication were included in the safety evaluation. Safety was evaluated on the basis of AEs, physical (medical) examinations, and laboratory tests (serum chemistry, hematology, and urinalysis, lipid profile, drug and virus screening, and pregnancy test for female subjects). Measurement of vital signs and 12-lead electrocardiograms (ECGs) were also conducted. All safety assessments were performed at screen, before the first-dose drug administration, at follow-up visits, and at the end of the study (within 7–14 days after dosing). All clinically significant abnormal values, including laboratory parameters other than for renal function.
tests, or deviation of clinical laboratory values other than those related to renal
impairment, were followed up using the appropriate tests until a return to
baseline values or a medically acceptable level was achieved.

AEs and their severity, duration, and potential relationship to study drug were
assessed by the investigator throughout the study. AEs persisting after trial
completion were followed up until they normalized or were sufficiently
characterized.

Pharmacokinetic data analysis
Plasma concentration–time data were analyzed by a non-compartmental
approach using WinNonlin™ (version 5.2; Pharsight, Sunnyvale, CA, USA).
Maximum plasma concentration, $C_{\text{max}}$ (ng/mL) was obtained directly from the
observed data for each subject; peak time, $t_{\text{max}}$ (h), was the time at which $C_{\text{max}}$
was attained. The terminal elimination rate constant, $\lambda_z$ (h$^{-1}$), was calculated by
linear regression using the terminal log-linear portion of the plasma
concentration–time curve. The elimination half-life ($t_{1/2}$ [h]) was estimated as
$\ln 2/\lambda_z$. Area under the plasma concentration–time curve ($\text{AUC}_{0-\infty}$) was
calculated using the linear up/log down algorithm, and the last predicted
concentration was used for extrapolation of AUC. Oral clearance ($\text{CL/F}$
[mL/min]) was calculated as dose/$\text{AUC}_{0-\infty}$, and volume of distribution ($\text{Vd/F}$)
was calculated as CL/F/λz.

Statistical analysis

The sample size was not based on power calculation; however, it was considered adequate in order to obtain reliable results to meet the study objectives. Subjects in the normal renal function group were matched with subjects with renal impairment as follows: (i) age within the mean age of all renally impaired subjects ±5 years and (ii) weight within the mean weight of all renally impaired subjects ±15%.

SAS® software (SAS Institute Inc., Cary, NC, USA) was used for the statistical analyses. Faldaprevir exposure in subjects with renal impairment compared with exposure in matched normal renal function subjects was assessed using an average bioequivalence method to determine the geometric mean (gMean) ratio between subjects with renal impairment (R) versus subjects with normal renal function (N) for pharmacokinetic parameters AUC₀–∞ and Cmax (primary endpoints). Primary endpoints were log-transformed (natural logarithm) prior to fitting an ANOVA model with a fixed effect for treatment. Differences between the mean log(R)–log(N) were estimated by the differences in the corresponding adjusted means (least square means), and 2-sided 90% confidence interval (CI) based on the t-distribution were calculated. These quantities were back-
transformed to the original (linear) scale to provide a point estimate and a 90% CI for the gMeans for test (renal function deviating from normal) and reference (normal renal function). Subject data were included in the pharmacokinetic analysis if no important protocol violations, or no vomiting at or before twice the median plasma $t_{\text{max}}$ of faldaprevir occurred. Descriptive statistics were used for all other pharmacokinetic and safety assessments.

RESULTS

Demographics

Demographic data are summarized in Table 1. All 32 subjects received the single, 480 mg dose of faldaprevir. Twenty-one subjects were male (65.6%), mean age was 61.4 years (range, 42–74 years), and all were Caucasian. Overall, demographic data were similar among the four study groups.

Pharmacokinetics

Pharmacokinetic analyses were performed on 24 out of 32 subjects. Eight subjects (3, 4, and 1 subjects with normal renal function, mild, and moderate renal impairment, respectively) were excluded due to mild vomiting events occurring prior to 4 h (twice the median $t_{\text{max}}$ of faldaprevir). Plasma faldaprevir concentrations reached peak ($C_{\text{max}}$) approximately 2–6 h after dosing, with a median $t_{\text{max}}$ of 4 h for all groups (Figure 2 and Table 2). After reaching the
maximum, faldaprevir concentrations declined, first in a rapid biphasic manner, followed by a slower terminal elimination phase (Figure 2). Values of faldaprevir half-life ($t_{1/2}$) were similar between renal function groups (36.1 h for subjects with normal renal function, and 35.8 h, 33.1 h, and 31.8 h for subjects with mild, moderate, and severe renal impairment, respectively; Table 2).

The highest $\text{gMean}$ faldaprevir exposures were in subjects with moderate renal impairment (Table 2). $\text{gMean}$ values of $C_{\text{max}}$ were 3,810 ng/mL in subjects with normal renal function, and 4,080 ng/mL, 6,680 ng/mL, and 4,600 ng/mL in subjects with mild, moderate, and severe renal impairment, respectively. Similarly, $\text{gMean}$ values of $\text{AUC}_{0-\infty}$ were 76,500 ng·h/mL in subjects with normal renal function, and 86,900 ng·h/mL, 136,000 ng·h/mL, and 129,000 ng·h/mL in subjects with mild, moderate, and severe renal impairment, respectively.

However, the inter-subject variability was high for both $C_{\text{max}}$ and $\text{AUC}_{0-\infty}$, with $\% \text{geometric coefficient of variation (gCV)}$ values ranging from 63.2–144.0% for $C_{\text{max}}$ and from 67.2–98.8% for $\text{AUC}_{0-\infty}$.

Oral clearance ($\text{CL/F [mL/min]}$) was consistent with the trends observed for exposure; $\text{gMean CL/F}$ was 105 mL/min in subjects with normal renal function and 92.0 mL/min, 58.6 mL/min, and 61.8 mL/min for subjects with mild, moderate, and severe renal impairment, respectively (Table 2). The apparent
volume of distribution ($V_z F \text{[L]}$) followed a similar trend to that observed for oral clearance (Table 2).

Statistical evaluation of pharmacokinetic endpoints ($\text{AUC}_{0-\infty}$ and $C_{\text{max}}$) compared subjects with normal renal function against subjects with impaired renal function. In subjects with renal impairment, there was a general trend towards higher faldaprevir exposure, despite a broad range of 90% CI (Table 3). Compared with subjects with normal renal function, the adjusted gMean ratios (90% CI) of faldaprevir exposure were 113.6% for $\text{AUC}_{0-\infty}$ (41.6–310.2%) and 107.2% for $C_{\text{max}}$ (35.2–327.0%) for subjects with mild renal impairment; 178.3% for $\text{AUC}_{0-\infty}$ (85.2–373.0%) and 175.5% for $C_{\text{max}}$ (89.6–344.1%) for subjects with moderate renal impairment; and 169.2% for $\text{AUC}_{0-\infty}$ (73.2–391.2%) and 121.0% for $C_{\text{max}}$ (47.3–309.7%) for subjects with severe renal impairment (Table 3). A sensitivity analysis was performed in all treated subjects (N=32), and demonstrated that the gMean point estimates were not substantially different from those obtained in analysis of the pharmacokinetic data set; gMean $\text{AUC}_{0-\infty}$= 191.0% (90% CI 107.2–338.4%) and gMean $C_{\text{max}}$= 190.6% (90% CI 102.2–355.7%) for moderate renal impairment and gMean $\text{AUC}_{0-\infty}$= 185.4% (90% CI 93.7–366.8%) and gMean $C_{\text{max}}$= 136.3% (90% CI 59.9–310.2%) for severe renal impairment compared with normal renal function.
Despite the general trend toward higher faldaprevir exposure in subjects with renal impairment, there did not appear to be a correlation between faldaprevir exposure (AUC\(_{0-\infty}\) and \(C_{\text{max}}\)) and renal function as estimated by eGFR (Supplementary Figure 1).

Analysis of faldaprevir protein binding from all treated patients (N=32) indicated that there were no differences in the fraction of unbound faldaprevir between subjects with normal renal function compared with those with renal impairment. Mean (±standard deviation) unbound faldaprevir was 0.09±0.01% in subjects with normal renal function and 0.10±0.06%, 0.10±0.03%, and 0.13±0.02% in subjects with mild, moderate, and severe renal impairment, respectively.

**Safety**

AEs were reported in 62.5% of subjects with normal renal function and 83.3% of subjects with renal impairment (Table 4). The most frequent AEs across all study arms were gastrointestinal disorders, reported in 62.5% of subjects with normal renal function and 83.3% of subjects with impaired renal function (Table 4). Vomiting and diarrhea occurred in 37.5% (each) of subjects with normal renal function, and in 20.8% and 75.0% of subjects with impaired renal function, respectively (Table 4). One subject with renal impairment had a mild increase in systolic blood pressure that was reported as an AE. Three subjects had
increases in total bilirubin which were considered to be related to faldaprevir administration. These were characterized by a predominance of indirect (unconjugated) bilirubin. Increases in indirect bilirubin were not associated with changes in the levels of other markers of liver toxicity and are consistent with a known metabolic effect (inhibition of UGT1A1 and hepatic uptake transporters) of faldaprevir. There were no other relevant changes in clinical laboratory parameters or vital signs for any of the four renal function groups. There were no AEs of severe intensity, serious AEs, or deaths reported. All AEs had resolved by the end of the study.

DISCUSSION

In this study, the effect of renal impairment on the pharmacokinetics and safety of the HCV NS3/4A protease inhibitor, faldaprevir, was determined. We demonstrate that moderate or severe renal impairment results in a modest increase in exposure to faldaprevir. However, these are not considered clinically relevant as the modest increase in exposure was within the observed variability of exposure (approximately 100% in pivotal Phase III trials, BI data on file), and faldaprevir has been shown to have good tolerability and safety profiles in these studies (16,23,24). In addition, in the faldaprevir Phase III program, safety profiles of patients with mild and moderate renal impairment were generally
consistence with those of normal renal function (BI data on file), and the exposure increase of severe renal impairment was similar to those of moderate renal function; thus, dose adjustment for renal impairment was not warranted in patients with HCV infection. Similar magnitude of increase in exposure for severe renal impairment was observed in simeprevir, a NS3/4A protease inhibitor with similar pharmacokinetic profiles, no dose adjustment was recommended in its FDA approved package insert (10).

Of the 32 subjects who completed treatment, 8 (25%) were excluded from the pharmacokinetic analysis due to mild vomiting events, which may have decreased drug absorption. Sensitivity analysis showed that the results were consistent with and without the subjects with vomiting events. Following faldaprevir administration, the time to peak concentration was similar to and half-life values were slightly higher than previously reported values for faldaprevir, suggesting that renal impairment does not substantially affect these parameters (19). Assessment of pharmacokinetic data indicated that although gMean faldaprevir exposures were modestly increased in subjects with moderate and severe renal impairment compared with those with normal renal function, no correlation between exposure and renal function (eGFR) was observed. Although differences in absolute exposure were observed across study groups, the similarity in terminal elimination phase profiles between the
renal function groups suggests that observed differences in exposure were not due to altered elimination of faldaprevir.

Faldaprevir is more than 99% bound to plasma proteins (12). In this study, faldaprevir protein binding in subjects with normal renal function was consistent with previously reported values and no different from those with renal impairment.

Despite urinary excretion of unchanged drug of approximately 0.1% for faldaprevir, the effects of renal impairment upon faldaprevir exposure are important. Renal impairment may affect the non-renal clearance and distribution of therapeutic agents and it has been demonstrated that exposure to the first generation HCV protease inhibitor, telaprevir increases in patients with renal impairment (8). Metabolic enzyme (e.g. CYP enzymes) and membrane transporter protein activities are interdependent (25–27), and build-up of uremic toxins, a consequence of renal impairment, is associated with altered membrane transport protein (such as OATPs, P-gp) activity (3,4,28). Renal impairment can also directly influence the activity of certain CYP enzymes, and is associated with decreased CYP3A activity (29,30). The mechanism of observed modest effect of renal impairment on faldaprevir exposure is not fully clear at this point. However, it seems related to the reduction of liver uptake as a result of renal impairment. Faldaprevir is enriched in the liver via OATP1B1 or
Na-dependent transporters (31,32) and it has been shown that liver concentration of faldaprevir can be enriched up to 22–35-fold higher than that of plasma levels (31). The available aforementioned literature suggests that renal impairment may compromise the activity of transporters, such as OATPs, and result in less liver uptake of compounds of OATPs substrates such as faldaprevir, and as a result, the volume of distribution would be decreased and plasma levels of these compounds would be increased. This may explain the decreased CL/F observed in this study (CL/F=Dose/AUC, with increased exposure leading to a decreased CL/F). Co-administration of inhibitors of OATP1B1 with substrates of OATP1B1 such as rosuvastatin, cerivastatin, and atorvastatin led to a similar reduction of V/F and CL/F, and in most cases, it had no effect on t1/2 (33). Similar results have also been observed for simeprevir, a second-generation protease inhibitor that is also a substrate of OATP1B1/1B3 with negligible urinary excretion (34). Simeprevir showed a 1.62-fold increase in exposure (AUC) in patients with severe renal impairment and a rate of elimination that was not substantially impacted by renal impairment. In addition to the potential role of OATPs, other mechanisms such as alteration of efflux transporters or CYP3A4 (gut) may at least in part, account for the increased faldaprevir exposure in subjects with moderate or severe renal impairment.
No notable safety findings in subjects with renal impairment were observed despite a small increase in AEs in these subjects. Overall, the safety profile observed in this study was consistent with that reported in the faldaprevir clinical trial program in subjects without renal impairment (13–17). Increased levels of indirect bilirubin were not accompanied by elevations of other markers of liver toxicity and these clinically irrelevant, transient indirect bilirubin increases are a well-known effect of treatment with faldaprevir, which is an inhibitor of UGT1A1 and hepatic uptake transporters (35).

This study illustrates the potential effect of renal impairment on the activities of transporters, in particular uptake transporters in HCV therapies, and how in turn these compromised transporters may further impact the exposure of drugs (HCV therapies), even those with negligible urinary excretion. Therefore, although the development of faldaprevir has been halted, the significance of these findings may be extrapolated to other HCV therapies.

In conclusion, moderate or severe renal impairment is associated with a modest increase in faldaprevir exposure that did not negatively affect the overall tolerability of faldaprevir. Given the relatively modest increase in faldaprevir exposure, dose adjustment in HCV patients with mild to severe renal impairment is not warranted.


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experienced patients with chronic HCV genotype-1 infection. Hepatology. 58(Suppl. 1):Abstract 1100.


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Table 1. Baseline demographics

<table>
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<th>Renal function</th>
<th>Normal function (N=8)</th>
<th>Mild impairment (N=8)</th>
<th>Moderate impairment (N=8)</th>
<th>Severe impairment (N=8)</th>
<th>Total (N=32)</th>
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<td>Gender, n (%)</td>
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<tr>
<td>Male</td>
<td>6 (75.0)</td>
<td>5 (62.5)</td>
<td>5 (62.5)</td>
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<td>21 (65.6)</td>
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<tr>
<td>Female</td>
<td>2 (25.0)</td>
<td>3 (37.5)</td>
<td>3 (37.5)</td>
<td>3 (37.5)</td>
<td>11 (34.4)</td>
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<tr>
<td>Race, n (%)</td>
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<td>Caucasian</td>
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<td>8 (100)</td>
<td>8 (100)</td>
<td>8 (100)</td>
<td>32 (100)</td>
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<td>Mean age, years (range)</td>
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<td>58.8 (46–73)</td>
<td>67.1 (51–74)</td>
<td>57.6 (42–71)</td>
<td>61.4 (42–74)</td>
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<table>
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<th>Mean body mass index, kg/m² (range)</th>
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<th>26.1</th>
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<td>(24.4–30.5)</td>
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<td>(19.5–27.7)</td>
<td>(20.0–30.9)</td>
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Table 2. Summary of pharmacokinetic parameters on the basis of renal function

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<tr>
<th>Renal function</th>
<th>Normal (N=5)</th>
<th>Mild (N=4)</th>
<th>Moderate (N=7)</th>
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<tr>
<td>PK parameter</td>
<td>gMean</td>
<td>gCV, %</td>
<td>gMean</td>
<td>gCV, %</td>
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<tr>
<td>( AUC_{0-\infty} ), ng·h/mL</td>
<td>76,500</td>
<td>95.7</td>
<td>86,900</td>
<td>89.8</td>
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<td>( C_{\text{max}} ), ng/mL</td>
<td>3,810</td>
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<td>( t_{\text{max}} ), h</td>
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<td>( t_{1/2} ), h</td>
<td>36.1</td>
<td>23.5</td>
<td>35.8</td>
<td>31.0</td>
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<tr>
<td>CL/F, mL/min</td>
<td>105.0</td>
<td>95.7</td>
<td>92.0</td>
<td>89.8</td>
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<td>( V_{d}/F ), L</td>
<td>327.0</td>
<td>77.5</td>
<td>285.0</td>
<td>62.2</td>
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</table>

\( AUC_{0-\infty} \), area under the plasma concentration–time curve from time 0 to infinity; CL/F, oral clearance;
$C_{\text{max}}$, maximum concentration; gCV, geometric coefficient of variation; gMean, geometric mean; PK, pharmacokinetic; $t_{\text{max}}$, time to reach $C_{\text{max}}$; $t_{1/2}$, elimination half-life; $V_d/F$, volume of distribution.

*PK analysis excludes n=8 subjects who suffered vomiting events prior to 4 hours (twice the median $t_{\text{max}}$ of faldaprevir); $^b$Median; range.
Table 3. The relative bioavailability of faldaprevir in subjects with renal impairment compared with subjects with normal renal function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Adjusted gMean</th>
<th>Adjusted gMean</th>
<th>gMean ratio test/reference, %</th>
<th>2-sided 90% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0-\infty}), ng·h/mL</td>
<td>5</td>
<td>76,530</td>
<td>4</td>
<td>86,910</td>
<td>113.6</td>
</tr>
<tr>
<td>C(_{\text{max}}), ng/mL</td>
<td>5</td>
<td>3,806</td>
<td>4</td>
<td>4,080</td>
<td>107.2</td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0-\infty}), ng·h/mL</td>
<td>5</td>
<td>76,530</td>
<td>7</td>
<td>136,500</td>
<td>178.3</td>
</tr>
<tr>
<td>C(_{\text{max}}), ng/mL</td>
<td>5</td>
<td>3,806</td>
<td>7</td>
<td>6,680</td>
<td>175.5</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{0-\infty}), ng·h/mL</td>
<td>5</td>
<td>76,530</td>
<td>8</td>
<td>129,500</td>
<td>169.2</td>
</tr>
<tr>
<td>C(_{\text{max}}), ng/mL</td>
<td>5</td>
<td>3,806</td>
<td>8</td>
<td>4,604</td>
<td>121.0</td>
</tr>
</tbody>
</table>

AUC\(_{0-\infty}\), area under the plasma concentration–time curve from time 0 to infinity; CI, confidence interval; C\(_{\text{max}}\), maximum concentration; gMean, geometric mean.
Table 4. Frequency of subjects with adverse events (AEs) by renal function

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Normal function (N=8)</th>
<th>Mild impairment (N=8)</th>
<th>Moderate impairment (N=8)</th>
<th>Severe impairment (N=8)</th>
<th>Pooled impaired function (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE, n (%)</td>
<td>5 (62.5)</td>
<td>8 (100)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Drug-related AE, n (%)a</td>
<td>5 (62.5)</td>
<td>8 (100)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>AEs by system organ class, n (%)b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>5 (62.5)</td>
<td>8 (100)</td>
<td>5 (62.5)</td>
<td>7 (87.5)</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (37.5)</td>
<td>6 (75.0)</td>
<td>3 (62.5)</td>
<td>7 (87.5)</td>
<td>18 (75.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (37.5)</td>
<td>4 (50.0)</td>
<td>1 (12.5)</td>
<td>0</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (12.5)</td>
<td>3 (37.5)</td>
<td>1 (12.5)</td>
<td>2 (25.0)</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>0</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Disorder</td>
<td>0</td>
<td>1 (12.5)</td>
<td>0</td>
<td>1 (12.5)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
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<tr>
<td>Hyperbilirubinemia</td>
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<tr>
<td>Investigations</td>
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<tr>
<td>Blood bilirubin increased</td>
<td></td>
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<tr>
<td>Systolic blood pressure increased</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neck pain</td>
<td>1 (12.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a* Investigator-defined AEs; *b* More than one AE can occur in a single subject.
Figure 1. Study design

FDV, faldaprevir, h, hour; PK, pharmacokinetic.

Figure 2. gMean plasma concentration–time profiles of faldaprevir with or without renal impairment

FDV, faldaprevir.