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Effects of Hepatic Impairment on the Pharmacokinetics of Abrocitinib and Its Metabolites

Ellen Q. Wang, PhD[1], Vu Le, MS[2], Melissa O'Gorman, MPH[3], Sakambari Tripathy, MS[2], Martin E. Dowty, PhD[4], Lisy Wang, MD[5], and Bimal K. Malhotra, PhD[1]

Abstract

Abrocitinib, an oral once-daily Janus kinase 1 selective inhibitor, is under development for treatment of atopic dermatitis. This phase 1, nonrandomized, open-label, single-dose study (NCT03626415) investigated the effect of hepatic impairment on pharmacokinetics (PK), safety, and tolerability of abrocitinib and its metabolites after a 200-mg oral dose. Twenty-four subjects with varying degrees of hepatic function (normal, mild, and moderate impairment) were enrolled (N = 8/group). Active moiety PK parameters were calculated as the sum of unbound PK parameters for abrocitinib and its active metabolites. For abrocitinib, the ratios (percentages) of adjusted geometric means for area under the concentration-time curve from time 0 extrapolated to infinite time (AUC_{inf}) and maximum plasma concentration (C_{max}) were 133.33 (90% confidence interval [CI], 86.17-206.28) and 94.40 (90%CI, 62.96-141.55), respectively, for subjects with mild hepatic impairment vs normal hepatic function. The corresponding comparisons of ratios (percentages) for AUC_{inf} and C_{max} were 153.99 (90%CI, 99.52-238.25) and 105.53 (90%CI, 70.38-158.24), respectively, for subjects with moderate hepatic impairment. Exposures of the metabolites were generally lower in subjects with hepatic impairment. For abrocitinib active moiety, the ratios (percentages) of adjusted geometric means of unbound AUC_{inf} were 95.74 (90%CI, 72.71-126.08) and 114.82 (90%CI, 87.19-151.20) in subjects with mild and moderate impairment vs normal hepatic function, respectively. Abrocitinib was generally safe and well tolerated. Hepatic impairment had no clinically relevant effect on the PK and safety of abrocitinib and the exposure of abrocitinib active moiety. These results support the use of abrocitinib without dose adjustment in subjects with mild or moderate hepatic impairment.

Keywords

abrocitinib, active moiety, atopic dermatitis, hepatic impairment, pharmacokinetics

Atopic dermatitis is a chronic inflammatory skin disease characterized by intense itch, dry skin, and skin pain.[1–5] There are few approved systemic therapies for the treatment of moderate to severe atopic dermatitis. Systemic immunosuppressants, such as cyclosporine, methotrexate, and azathioprine, are used to treat subjects with moderate to severe atopic dermatitis who are unresponsive to topical therapy and oral antihistamines; however, these treatments are not recommended for long-term use based on adverse events.[1,6] Dupilumab is an interleukin (IL)-4 alpha receptor that targets IL-4 and IL-13 signaling that is approved for treatment of moderate to severe atopic dermatitis. Dupilumab is effective in some but not all subjects,[7] and its use is limited to subjects who are willing to receive subcutaneous injections.

Abrocitinib (PF-04965842) is a selective small-molecule Janus kinase (JAK) 1 inhibitor under development to treat moderate to severe atopic dermatitis. Its JAK1 enzyme selectivity is approximately 28-fold over JAK2, >340-fold over JAK3, and 43-fold over tyrosine kinase 2 (TYK2), and it has even higher selectivity over the broader kinome.[8] In cellular settings, where JAK isoforms signal in pairs, abrocitinib preferentially inhibits signaling by cytokine receptors utilizing JAK1 (eg, interferon [IFN]-α signaling via JAK1/TYK2 pair and IFN-γ signaling via JAK1/JAK2) and exhibits selectivity over receptors utilizing JAK2 only or JAK2/TYK2.[8] Selective inhibition of JAK1 can lead to modulation of multiple cytokine pathways involved in the pathophysiology of atopic dermatitis, such as IL-4 and IL-13, while minimizing risk for neutropenia and anemia.[9–11] Once-daily abrocitinib (100 mg or 200 mg) has been shown to be effective and well tolerated in

[1]Clinical Pharmacology, Global Product Development, Pfizer Inc., New York, New York, USA
[2]Pfizer Inc., Groton, Connecticut, USA
[3]Global Product Development, Pfizer Inc., Groton, Connecticut, USA
[4]Pharmacokinetics Dynamics and Metabolism, Medicine Design, Pfizer Inc., Cambridge, Massachusetts, USA
[5]Clinical Development and Operation, Global Product Development, Pfizer Inc., Groton, Connecticut, USA

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Corresponding Author:
Bimal K. Malhotra, PhD, Clinical Pharmacology, Global Product Development, Pfizer Inc. 235 East 42nd Street, New York, NY 10017
Email: bimal.k.malhotra@pfizer.com

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subjects with moderate to severe atopic dermatitis in one phase 2b (NCT02780167) and two phase 3 studies (NCT03349060 [JADE MONO-1] and NCT03575871 [JADE MONO-2]).[12–14]

The absolute oral bioavailability and fraction of abrocitinib absorbed is 60% and 91%, respectively (data on file). In the first-in-human study in healthy subjects, following administration of single doses and once- or twice-daily doses as a suspension, abrocitinib was rapidly absorbed, with median time to maximum plasma concentration (t_{max}) occurring in <1 hour for doses of 3 to 200 mg, and it was absorbed more slowly (median t_{max}, 1.50-4.00 hours) for 400- and 800-mg doses.[15] Over a single-dose range of 3 to 800 mg, maximum plasma concentration (C_{max}) of abrocitinib generally increased proportionally with dose, whereas at 400 and 800 mg, increases in area under the concentration-time curve (AUC) from time 0 extrapolated to infinite time (AUC_{inf}) were greater than dose proportional.[15] The terminal elimination half-life ($t_{1/2}$) of abrocitinib for the 100- and 200-mg therapeutic doses ranged from 3.59 to 3.89 hours.[15] Following multiple-dose administrations of a total daily dose of 30 mg up to 400 mg, increases in C_{max} and AUC from time 0 to time τ, the dosing interval (AUC_{τ}), were greater than proportional with increasing dose.[15] The urinary recovery of abrocitinib was low, with 1.0% to 4.4% of the dose recovered unchanged across 30- to 400-mg daily doses.[15]

In the human absorption, distribution, metabolism, and excretion study, after a single oral dose of 200-mg abrocitinib/80 μg (500 nCi) [14C], abrocitinib was the most abundant circulating species (26%), along with 3 oxidative metabolites: PF-06471658 (M1, 11%), PF-07055087 (M2, 12%), and PF-07054874 (M4, 14%) (data on file). Among the 3 metabolites, M1 (3-hydroxypropyl) and M2 (2-hydroxypropyl) are active metabolites, with JAK1 selectivity profiles consistent with abrocitinib. The JAK1 enzyme kinase selectivity of M1 was approximately 26-fold over JAK2, >230-fold over JAK3, and 74-fold over TYK2, and for M2 it was 49-fold over JAK2, >559-fold over JAK3, and 68-fold over TYK2 (data on file). Conversely, M4 (pyrrolidinone pyrimidine) is pharmacologically inactive (data on file).

In vitro cytochrome P450 (CYP) phenotyping studies in human hepatocytes indicated that CYP2C19 and CYP2C9 are the main enzymes involved in the metabolism of abrocitinib, with approximate fraction metabolized (fm) values of 0.53 and 0.30, respectively, with minor involvement of CYP3A4 (fm, 0.11) and CYP2B6 (fm, 0.07).[16] These collective results indicate that the primary clearance mechanism for abrocitinib is CYP-mediated oxidative metabolism. Therefore, impairment in hepatocellular function may alter the disposition of abrocitinib, which could potentially impact its safety and/or efficacy.

The US Food and Drug Administration recommends conducting a pharmacokinetic (PK) study in subjects with hepatic impairment when hepatic metabolism and/or excretion account for >20% of drug elimination or if the drug has a narrow therapeutic range.[17] Since subjects with hepatic impairment may potentially be exposed to a higher concentration of a drug, a PK study in this patient population can inform dosing recommendations for those with hepatic insufficiency.

The objective of this study (NCT03626415) was to estimate the effect of mild and moderate hepatic impairment on the PK of abrocitinib and its 3 major circulating metabolites as well as the active moiety, which comprises abrocitinib and active metabolites M1 and M2, following single oral administration of abrocitinib 200 mg in adult subjects with hepatic impairment relative to age- and body weight-matched subjects with normal hepatic function. The safety and tolerability of abrocitinib were also investigated.

Methods

This study was conducted across 2 centers in the United States (Prism Clinical Research, LLC, St. Paul, Minnesota; and Orlando Clinical Research Center, Orlando, Florida). The trial protocol and informed consent documentation were reviewed and approved by the institutional review boards at each of the centers participating in the study. This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular those affording greater protection to the safety of trial participants. A signed and dated informed consent was required before any study-specific activity was performed.

Study Design

This was a phase 1, nonrandomized, open-label, single-dose, parallel-cohort study. Twenty-four subjects with varying degrees of hepatic function (normal function, mild, and moderate impairment) were enrolled into 1 of the 3 hepatic function groups (N = 8/group). Child-Pugh classification score was used to assign subjects to mild (Child-Pugh Class A, 5-6 points) and moderate (Child-Pugh Class B, 7-9 points) hepatic impairment groups. Subjects with mild and moderate hepatic impairment were recruited first, followed by subjects with normal hepatic function. Subjects with normal hepatic function were enrolled after completion of final PK sampling for subjects with hepatic impairment to

match the median demographics (at a minimum, age [±10 years] and body weight [±15 kg]; sex, if possible) across the pooled hepatic impairment groups. Subjects with severe hepatic impairment (Child-Pugh Class C, >9 points) were not included in this study because the percentage of subjects with severe hepatic impairment is low for the indication under development. In addition, these subjects are already at risk of infection due to their hepatic disease, and further exposure to an immunosuppressant and trial-related procedures and restrictions could pose a risk.

Subjects received a single 200-mg dose of abrocitinib within 28 days of screening and after an overnight fast of ≥10 hours. The 200-mg dose was chosen because it is the highest dose evaluated in the phase 3 abrocitinib atopic dermatitis clinical program.[13,14] In addition, oral doses of abrocitinib as high as 800-mg single dose (≈8.2-higher AUC_{inf} than the 200-mg single dose) and repeated total daily doses as high as 400 mg were safe and well tolerated. Therefore, based on abrocitinib safety data and prior clinical experience,[15,18] the 200-mg single dose is unlikely to pose safety risks for subjects with hepatic impairment.

PK samples were collected serially up to 72 hours after dosing. Adverse events, vital signs, physical exams, 12-lead electrocardiograms (ECGs), and safety laboratory tests were also assessed up to 72 hours after dosing. Patients experiencing clinically significant abnormal laboratory tests and/or ongoing adverse events were followed up via telephone or onsite visit 28 to 35 days after abrocitinib administration.

Subjects

Eligible subjects were men or women between the ages of 18 and 70 years at the screening visit, with body mass index between 17.5 and 40 kg/m^2 and a total body weight >50 kg (110 lbs). Key exclusion criteria were clinically significant infections within 3 months; any infection within 7 days; history of disseminated herpes simplex infection or recurrent (>1 episode) or disseminated herpes zoster at screening; a history of or positive for HIV, hepatitis B, or hepatitis C; an estimated glomerular filtration rate ≤60 mL/min based on the Modification of Diet in Renal Disease equation; use of the following concomitant medications within the specified window relative to abrocitinib dosing: potent, moderate, and select weak CYP2C19 or CYP2C9 inhibitors or inducers within 14 days or 5 half-lives (whichever was longer); prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever was longer); herbal supplements and hormonal methods of contraception and hormone replacement therapy within 28 days; Depo-Provera within 6 months; investigational drug within 28 days or 5 half-lives (whichever was longer); or immunosuppressant agents within 7 days or 5 half-lives (whichever was longer). Stable concomitant medications were allowed for subjects with mild or moderate hepatic impairment if they were considered necessary for a subject's welfare, were not contraindicated with the study drug, and were unlikely to interfere with the PK of abrocitinib.

Pharmacokinetic Sample Collection and Analysis

Blood samples (10 mL), to provide approximately 5 mL of plasma were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 14, 24, 36, 48, and 72 hours after dosing. Plasma samples were stored at –80°C until analysis and assayed for abrocitinib and the 3 metabolites (M1, M2, and M4) at Syneos Health (Princeton, New Jersey) using 3 separate validated, sensitive, and specific high-performance liquid chromatography–tandem mass spectrometric (HPLC-MS/MS) bioanalytical methods.

Abrocitinib and its stable labeled internal standard PF-06651703 were extracted from human plasma using a liquid-liquid extraction procedure. Following centrifugation, the supernatant was evaporated to dryness, reconstituted, and mixed by vortexing. The separation was achieved after an injection onto an Aquasil C18 2.1×50 mm, 3 μm column (Thermo Fisher Scientific, Waltham, Massachusetts) using 0.1% formic acid and 10 mM ammonium acetate in 10/90 v/v acetonitrile/water as mobile phase A and 0.1% formic acid and 10 mM ammonium acetate in 90/10 v/v acetonitrile/water as mobile phase B. The samples were analyzed by HPLC-MS/MS using positive electrospray ionization mode. The mass spectrometer (API 5000; Sciex, Concord, Ontario) settings and acquisition parameters are listed in Table S1. The calibration range of the method was 1.00 to 2000 ng/mL, and the quality control (QC) concentrations were 3.00 ng/mL (low), 60 ng/mL (medium low), 1000 ng/mL (medium high), 1600 ng/mL (high), and 5000 ng/mL (dilution). The interday assay accuracy ranged from –9.60% to 0.00%, and the between-day precision was ≤10.9%.

M1 and M4 and their respective internal standards, PF-07222472 and PF-07222475, respectively, were extracted from human plasma using a protein precipitation extraction procedure. Following centrifugation, the supernatant was evaporated to dryness, reconstituted, and mixed by vortexing. The separation was achieved after injection onto an XBridge C18 2.1×50 mm, 3.5 μm column (Waters Corporation, Milford, Massachusetts) using 0.1% formic acid in water as mobile phase A and 0.1 % formic acid in methanol as mobile phase B. The samples were analyzed by HPLC-MS/MS using positive electrospray ionization mode. The mass spectrometer (Sciex API 5000) settings and acquisition parameters are listed in Table S1. The calibration range of the method was 1.00 to 1000 ng/mL,

and the QC concentrations were 3.00 ng/mL (low), 50 ng/mL (medium), 750 ng/mL (high), and 5000 ng/mL (dilution). The interday assay accuracy ranged from –2.93% to 3.00% for M1 and –1.40% to 1.20% for M4. The between-day assay precision was ≤5.66% for M1 and ≤5.78% for M4.

M2 and its internal standard (PF-07222473) were extracted from human plasma using a protein precipitation extraction procedure. Following centrifugation, the supernatant was evaporated to dryness, reconstituted, and mixed by vortexing. The separation was achieved after injection onto a Chiralpak AD-3, 4.6×150 mm, 3 μm column (Chiral Technologies, West Chester, Pennsylvania) using hexane as mobile phase A and ethanol as mobile phase B. The samples were analyzed by HPLC-MS/MS using positive atmospheric pressure chemical ionization mode. The mass spectrometer (Sciex API 5000) settings and acquisition parameters are listed in Table S1. The calibration range of the method was 5.00 to 5000 ng/mL, and the QC concentrations were 15.0 ng/mL (low), 75 ng/mL (mid-low), 250 ng/mL (mid-high), and 3750 ng/mL (high). The interday assay accuracy ranged from –2.40% to 3.60%, and the between-day assay precision was ≤6.31%.

Pharmacokinetic Data Analysis

Plasma samples with concentrations below the lower limit of quantification were set to 0 for summary statistics and PK analysis. PK parameters were calculated using standard noncompartmental analysis that employed a software system internally validated by Pfizer Inc (eNCA, version 2.2.4). Actual PK sampling times were used in the derivation of PK parameters. The PK parameters calculated for abrocitinib, and the 3 metabolites include AUC_{inf}, AUC from time 0 to time of the last quantifiable concentration (AUC_{last}), C_{max}, t_{max}, and $t_{1/2}$. In addition, apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F) were calculated for abrocitinib, and the ratio of metabolite to abrocitinib for AUC_{inf} ($MRAUC_{inf}$) was calculated for M1, M2, and M4. Furthermore, unbound AUC_{inf}, AUC_{last}, and C_{max} ($AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$) for the active moiety were calculated for each subject as the sum of the respective unbound PK parameters for abrocitinib (molecular weight, 323.4 g/mol) and active metabolites, M1 (339.4 g/mol) and M2 (339.4 g/mol), each in molar units and adjusted for relative inhibition potencies of IFN-α signaling using equation 1[19]:

$$AUC_{u,AM} = AUC_{u,P} + AUC_{u,M1} \times \left(\frac{IC_{50,u,P}}{IC_{50,u,M1}}\right) + AUC_{u,M2} \times \left(\frac{IC_{50,u,P}}{IC_{50,u,M2}}\right) \quad (1)$$

where $AUC_{u,AM}$ is the unbound AUC (AUC_{inf} or AUC_{last}) of the active moiety; $AUC_{u,P}$, $AUC_{u,M1}$, and $AUC_{u,M2}$ are the unbound AUC of abrocitinib, M1, and M2, respectively. $IC_{50,u}$ is the unbound half maximal inhibitory concentration determined from in vitro whole blood inhibition potency of IFN-α signaling. $IC_{50,u,P}/IC_{50,u,M1}$ and $IC_{50,u,P}/IC_{50,u,M2}$ are the relative potencies of abrocitinib to M1 and M2, respectively. In vitro whole blood IFN-α IC_{50}, fraction unbound in plasma (f_u), and blood/plasma ratios for abrocitinib, M1, and M2 were 174, 296, and 90.5 nM; 0.36, 0.63, and 0.71; and 1.07, 1.13, and 1.27, respectively (data on file). These in vitro values were generated using methods as previously described.[20] Whole blood IFN-α IC_{50} was converted to unbound IC_{50} values (ie, $IC_{50,u}$ = IC_{50} × [f_u / (blood/plasma ratio)]) and determined as 59, 165, and 50.6 nM for abrocitinib, M1, and M2, respectively. IFN-α inhibition, which occurs through a JAK1/TYK2 kinase dimer, was chosen as representative of JAK1-dependent pharmacology of abrocitinib and its metabolites.

Statistical Analyses

The effect of hepatic impairment on PK parameters (AUC_{inf}, AUC_{last}, and C_{max}) was assessed using a 1-way analysis of variance on natural log-transformed data by constructing 90% confidence intervals (CIs) around the estimated difference between the Test (subjects with mild or moderate hepatic impairment) and the Reference (subjects with normal hepatic function) groups. Analysis of variance was performed on the exposure parameters for abrocitinib and active moiety. Estimates of the adjusted mean differences and corresponding 90%CIs were obtained from the model, and these were exponentiated to calculate the ratio of adjusted geometric means (Test/Reference) and 90%CIs for the ratios. Statistical calculations were performed using SAS (version 9.4 or above; SAS Institute Inc., Cary, North Carolina).

Based on the results of a phase 2 study,[18] total daily doses up to 400 mg were safe and well tolerated. Because 400 mg is 2-fold higher than the dose used in this study, increase in unbound abrocitinib active moiety AUC up to 2-fold was not considered clinically significant. In addition, based on statistical considerations for the size of this study (N = 8 per group), the 90%CI for a 2-fold higher geometric mean AUC due to hepatic impairment was estimated to be 133.08 to 300.57.

Safety

Safety assessments included incidence, severity, and causality of treatment-emergent adverse events; clinical laboratory tests; vital signs; physical examination; and 12-lead ECGs.

Table 1. Demographic and Baseline Characteristics[a] of Study Subjects

	Normal Hepatic Function (N = 8)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)
Age, y, mean (SD)	58.5 (5.86)	57.9 (4.19)	58.6 (8.21)
Sex, n (%)			
Male	5 (62.5)	5 (62.5)	5 (62.5)
Female	3 (37.5)	3 (37.5)	3 (37.5)
Race, n (%)			
White	7 (87.5)	4 (50.0)	7 (87.5)
Black or African American	1 (12.5)	4 (50.0)	0
American Indian or Alaska Native	0	0	1 (12.5)
Weight, kg			
Mean (SD)	83.8 (8.3)	96.8 (16.4)	87.5 (22.4)
Range, minimum-maximum	75.9-100.8	77.4-126.3	53.4-125.1
Body mass index, kg/m^2			
Mean (SD)	29.4 (1.8)	32.0 (5.3)	29.6 (5.3)
Range, minimum-maximum	27.1-31.2	24.4-39.2	20.0-37.0
Child-Pugh Score, median (range)[b]	NA	5 (5.0-6.0)	8 (7.0-9.0)

NA, not applicable; SD, standard deviation.

[a] Baseline is defined as the last measurement before receiving study treatment.

[b] If a subject had Child-Pugh scores from 2 screening visits, values from the second screening visit were used in the calculation of summary statistics.

Results

Subject Characteristics

In total, 24 subjects were enrolled, 8 with normal hepatic function, and 8 each with mild and moderate hepatic impairment. All subjects received a single dose of abrocitinib 200 mg and completed the study. Demographics and baseline characteristics were largely balanced across the groups (Table 1). The 24 treated subjects comprised 15 males (62.5%) and 9 females (37.5%), and most of the subjects (75%) were White. The mean age was 58.3 years (range, 48-69), and the mean weight was 89.36 kg (range, 53.4-126.3). Body mass index ranged from 20.0 to 39.2 kg/m^2 with a mean of 30.35 kg/m^2. Median Child-Pugh scores for subjects with mild and moderate impairment were 5 and 8, respectively.

Pharmacokinetic results

Abrocitinib PK. Following oral administration of a single 200-mg dose, abrocitinib was absorbed relatively rapidly with C_{max} achieved at median t_{max} of 1.00 to 2.00 hours across the 3 hepatic function groups (Table 2A and Figure S1A). The overall exposure of abrocitinib as reflected by AUC_{inf} and AUC_{last} was higher in subjects with hepatic impairment, whereas C_{max} values were largely similar across the 3 hepatic function groups (Figure 1A and Table 2A). The ratios (percentages) of the adjusted geometric means for AUC_{inf} and C_{max} were 133.33 (90%CI, 86.17-206.28) and 94.40 (90%CI, 62.96-141.55), respectively, for subjects with mild hepatic impairment compared with subjects with normal hepatic function (Table 2B). The corresponding comparisons for AUC_{inf} and C_{max} were 153.99 (90%CI, 99.52-238.25) and 105.53 (90%CI, 70.38-158.24), respectively, in subjects with moderate hepatic impairment (Table 2B). The CL/F of abrocitinib decreased with increasing severity of hepatic impairment, and V_z/F was slightly lower in subjects with mild hepatic impairment (Table 2A). Subjects with moderate hepatic impairment appeared to have longer $t_{1/2}$ (7.3 hours) compared to subjects with normal hepatic function (4.7 hours) and mild hepatic impairment (5.1 hours) (Table 2A).

Metabolite PK. Plasma concentrations of metabolites M1, M2, and M4 by hepatic function are shown in Figure S1B-D. Following administration of single 200-mg oral dose of abrocitinib, plasma exposures (AUC and C_{max}) of M1, M2, and M4 in subjects with mild and moderate hepatic impairment were generally lower compared to subjects with normal hepatic function, except for AUC values for M4 (Table 3, Figure 1B-D). The AUC values for M4 were largely similar across the 3 hepatic function groups with a slightly higher mean value seen in the moderate hepatic impairment group (Figure 1D). Peak plasma concentrations of M1, M2, and M4 were achieved with median t_{max} of 1.50 to 2.50 hours across the 3 hepatic function groups. For all 3 metabolites, a trend toward somewhat longer $t_{1/2}$ with increasing severity of hepatic impairment was observed, with values ranging from 5.0 to 6.8, 4.2 to 6.4, and 5.5 to 7.5 hours for M1, M2, and M4, respectively (Table 3). The plasma concentrations of all 3 metabolites were lower than abrocitinib, with the highest plasma concentrations observed for M4, and the lowest concentrations observed for M1 (Figure 2A-C). In addition, the $MRAUC_{inf}$ for all 3 metabolites

Table 2. (A) Descriptive and (B) Statistical Summaries of Plasma Abrocitinib Pharmacokinetic Parameters in Subjects With Normal Hepatic Function or Hepatic Impairment After a Single 200-mg Oral Dose of Abrocitinib

(A) Pharmacokinetic Parameter Summary

Parameter, Unit[a]	Normal Hepatic Function (N = 8)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)
AUC_{inf}, ng • h/mL	5587 (74)	7449 (29)	8603 (55)
AUC_{last}, ng • h/mL	5548 (75)	7430 (29)	8552 (55)
C_{max}, ng/mL	1352 (44)	1276 (41)	1426 (63)
t_{max}, h	2.00 (0.50-3.00)	2.00 (1.00-4.00)	1.00 (1.00-3.00)
CL/F, L/h	35.80 (74)	26.87 (29)	23.22 (55)
$t_{1/2}$, h	4.7 ± 2.7	5.1 ± 2.2	7.2 ± 2.9
V_z/F, L	211.0 (126)	183. 4 (34)	224.0 (71)

(B) Statistical Comparison	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[b]	90%CI for Ratio[b]
Mild Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)				
AUC_{inf}, ng • h/mL	7449.10	5587.15	133.33	(86.17-206.28)
AUC_{last}, ng • h/mL	7429.76	5547.88	133.92	(86.21-208.03)
C_{max}, ng/mL	1275.95	1351.64	94.40	(62.96-141.55)
Moderate Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)				
AUC_{inf}, ng • h/mL	8603.38	5587.15	153.99	(99.52-238.25)
AUC_{last}, ng • h/mL	8551.63	5547.88	154.14	(99.23-239.44)
C_{max}, ng/mL	1426.43	1351.64	105.53	(70.38-158.24)

AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from time 0 to time of last quantifiable concentration; CI, confidence interval; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

N = Total number of subjects in the treatment group in the indicated population.

[a] Geometric mean (geometric % coefficient of variation) for all except median (range) for t_{max}, arithmetic mean ± standard deviation for $t_{1/2}$.

[b] The ratios (and 90%CI) are expressed as percentages.

decreased in subjects with mild and moderate hepatic impairment compared to participants with normal hepatic function (Table 3).

Active Moiety PK. The exposure for the active moiety as measured by $AUC_{inf,u}$ was slightly higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function and mild hepatic impairment, whereas $C_{max,u}$ values were slightly lower in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function (Figure 1E and Table 4A). Compared to subjects with normal hepatic function, the adjusted geometric means for $AUC_{inf,u}$ and $C_{max,u}$ were approximately 4% and 24% lower, respectively, in subjects with mild hepatic impairment, and were approximately 15% higher and 16% lower, respectively, in subjects with moderate hepatic impairment (Table 4B).

Safety

Abrocitinib was well-tolerated in all 3 hepatic function groups. Two subjects with normal hepatic function had treatment-emergent adverse events (nausea and upper respiratory tract infection), and 3 subjects with mild hepatic impairment had treatment-emergent adverse events. Diarrhea and headache were each reported for 2 subjects (25%) with mild hepatic impairment (1 subject reported both diarrhea and headache). No subjects with moderate hepatic impairment reported adverse events. All adverse events were reported as mild in severity except diarrhea, which was reported as moderately severe in the 1 subject with mild hepatic impairment. No deaths, serious adverse events, severe adverse events, or discontinuations from the study due to adverse events were reported in any group.

The most frequently reported laboratory abnormality was leukocyte esterase (≥1), which was reported for 1 subject with normal hepatic function, 4 subjects with mild hepatic impairment, and 5 subjects with moderate hepatic impairment. Among the 5 subjects in the moderate hepatic impairment group, 3 subjects had normal results at baseline but had slightly abnormal results after baseline. No instance of leukocyte esterase ≥1 in these subjects was considered clinically significant and therefore reported as an adverse event by the investigators.

Finally, no values at baseline, increases or decreases from baseline in vital signs, ECG abnormalities, or physical examination findings were considered clinically significant and reported as adverse events by the investigators.

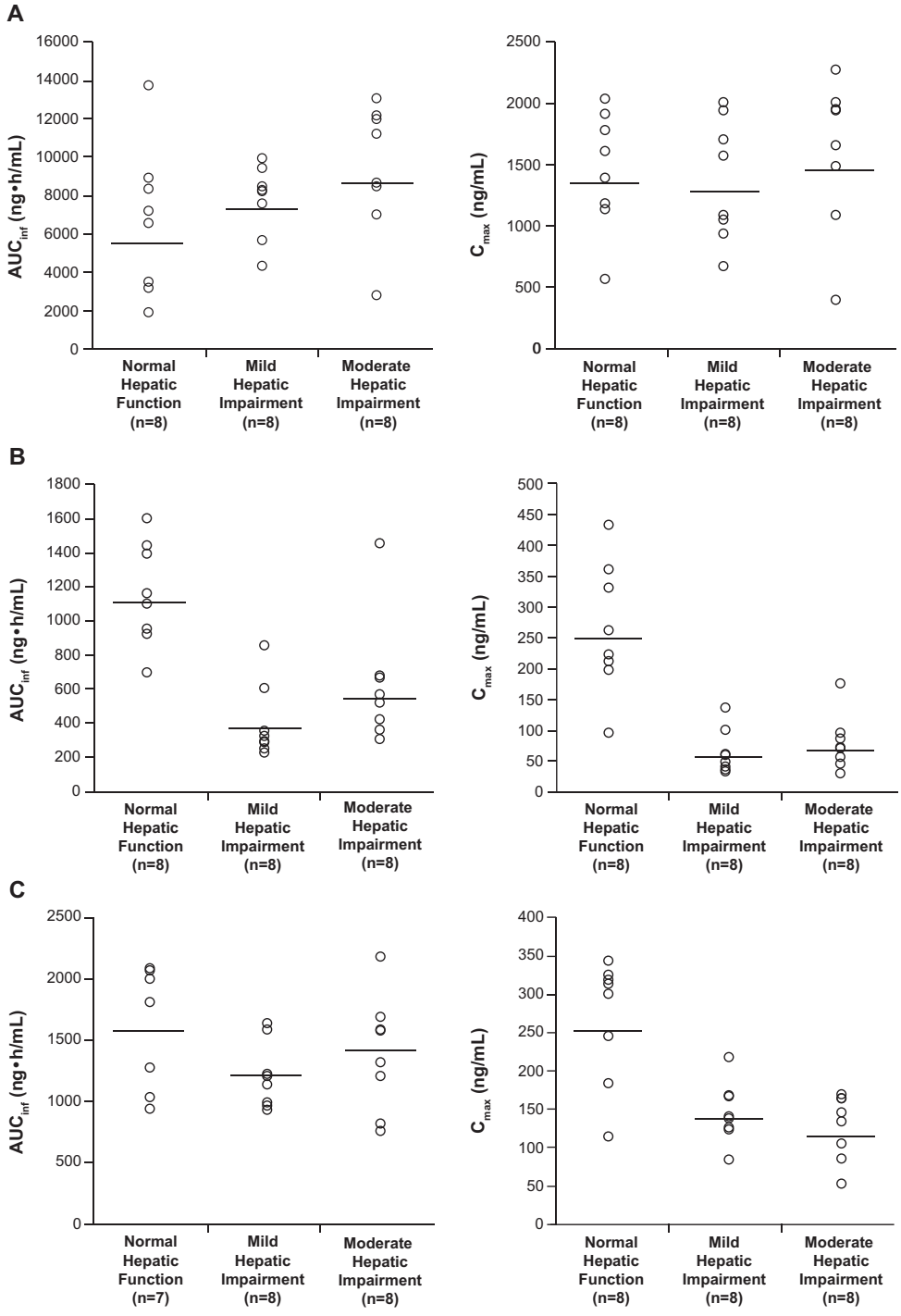

Figure 1. Scatter plots of individual (hollow dots) and geometric mean (horizontal lines) AUC_{inf} and C_{max} values for abrocitinib (A), PF-06471658 (M1) (B), PF-04965842 (M2) (C), PF-07054874 (M4) (D), and abrocitinib active moiety (E) for subjects with normal hepatic function or hepatic impairment. AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; $AUC_{inf,u}$, unbound area under the concentration-time curve from time 0 extrapolated to infinite time; C_{max}, maximum plasma concentration; $C_{max,u}$, unbound maximum plasma concentration.

Discussion

Abrocitinib, a selective JAK1 inhibitor under investigation for the treatment of atopic dermatitis, has completed 2 phase 3 monotherapy studies (JADE MONO-1 and JADE MONO-2), which demonstrate both the 100- and 200-mg once-daily doses are safe and efficacious in adult subjects with moderate to severe atopic dermatitis, as indicated by improvements in Investigator's Global Assessment and Eczema Area

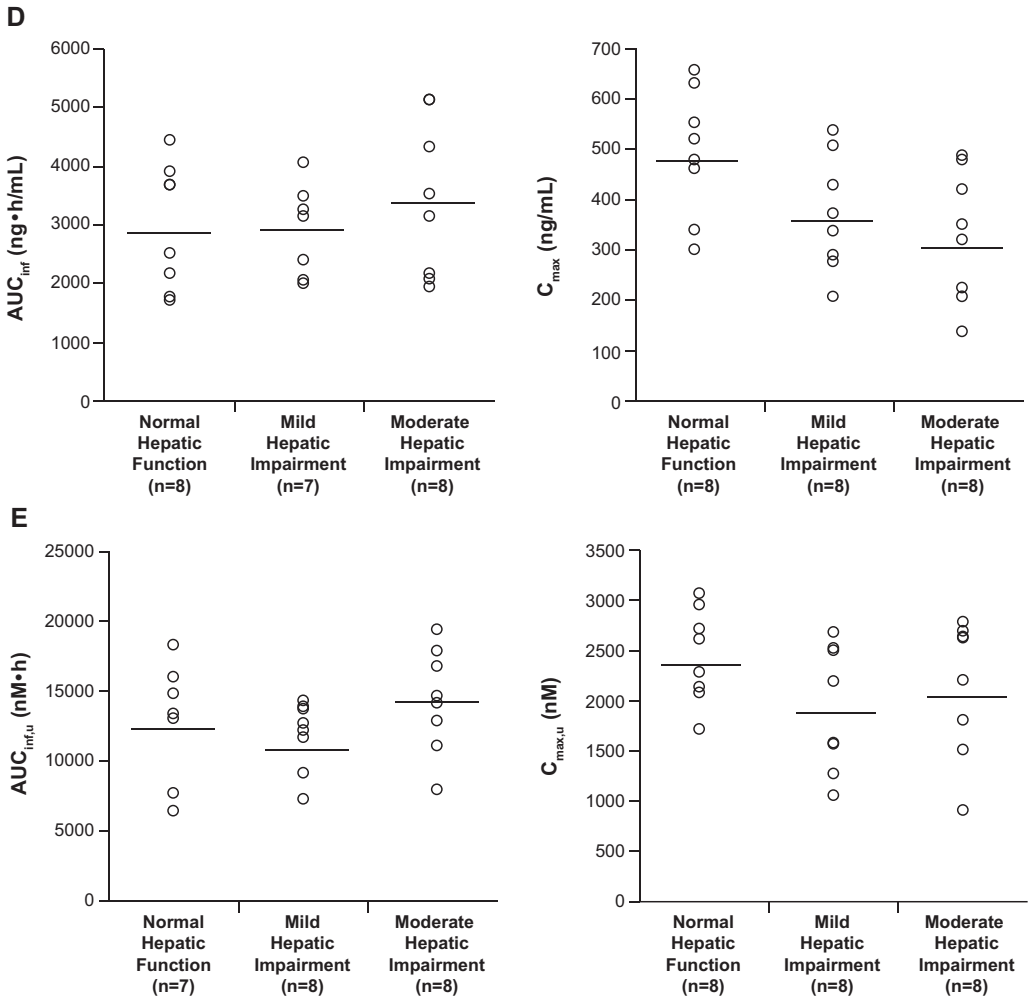

Figure 1. *Continued*

and Severity Index score.[13,14] Abrocitinib is primarily cleared through CYP-mediated oxidative metabolism[16] and has 3 metabolites in systemic circulation (data on file). Consistent with regulatory guidelines, PK of abrocitinib active moiety was compared among subjects with normal hepatic function and hepatic impairment following administration of a single oral dose of abrocitinib 200 mg to guide any potential dose adjustment recommendations in subjects with hepatic insufficiency.[17]

A single dose of abrocitinib 200 mg was examined in this study, as there was no strong evidence for time variant PK of abrocitinib. Based on the $t_{1/2}$ of abrocitinib, the accumulation ratio after once-daily dosing is predicted to be ≈1.1 following a single-dose administration.[15] A population PK model predicted that the steady-state accumulation ratio for the 200-mg once-daily regimen in patients with atopic dermatitis is 1.34, with 90% prediction intervals (PIs) of 1.05 to 1.75. The 90% PIs of the model were inclusive of the value found in healthy volunteers (accumulation ratio of ≈1.5) observed in multiple-dose studies (data on file). In addition, the PK of all 3 metabolites were linear and followed first-order kinetics between 100- and 200-mg doses (data on file). Meta-analysis of single- and multiple-dose PK data from phase 1 studies also demonstrated linearity of active moiety exposure for 100 and 200 mg doses (data on file).

This study demonstrates that mild and moderate hepatic impairment had no apparent effect on the rate of abrocitinib absorption into the systemic circulation, although a small increase in the extent of abrocitinib exposure was observed. While median t_{max} values were generally similar (1.00-2.00 hours) across the 3 hepatic function groups, abrocitinib plasma exposures increased with increasing severity of hepatic impairment. Following administration of a single 200-mg oral dose of abrocitinib, mild and moderate hepatic impairment resulted in ≈33.3% and 54.0% increases in abrocitinib AUC_{inf}, respectively, compared to normal hepatic function; however, there was a large overlap in the individual AUC_{inf} values across the 3 hepatic function groups. The small sample size may

Table 3. Descriptive Summary of Plasma PF-06471658 (M1), PF-07055087 (M2), and PF-07054874 (M4) Pharmacokinetic Parameters in Subjects With Normal Hepatic Function or Hepatic Impairment After a Single 200-mg Oral Dose of Abrocitinib

Parameter, Unit[a]	Normal Hepatic Function (N = 8)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)
AUC_{inf}, ng • h/mL			
M1	1120 (28)	357.6 (49)	552.7 (51)
M2	1519 (36)[b]	1178 (22)	1309 (38)
M4	2796 (40)	2808 (28)[b]	3188 (42)
AUC_{last}, ng • h/mL			
M1	1102 (29)	338.1 (52)	534.9 (52)
M2	1395 (35)	1081 (25)	1192 (43)
M4	2770 (40)	2882 (28)	3161 (42)
C_{max}, ng/mL			
M1	241.5 (50)	56.3 (54)	68.9 (57)
M2	253.1 (40)	139.9 (29)	119.2 (43)
M4	476.0 (28)	352.7 (33)	301.3 (48)
t_{max}, h			
M1	2.00 (1.00-3.00)	1.50 (1.00-4.00)	2.00 (1.00-3.00)
M2	2.00 (1.00-3.00)	2.50 (1.00-4.00)	2.00 (2.00-4.00)
M4	2.00 (1.00-3.00)	2.50 (1.00-4.00)	2.50 (1.00-3.00)
$t_{1/2}$, h			
M1	5.2 ± 2.8	5.0 ± 2.2	6.8 ± 2.4
M2	4.2 ± 2.6[b]	5.3 ± 2.4	6.4 ± 1.9
M4	5.5 ± 2.4	6.0 ± 2.6[b]	7.5 ± 3.1
$MRAUC_{inf}$			
M1	0.19 (100)	0.05 (54)	0.06 (111)
M2	0.22 (56)[b]	0.15 (25)	0.15 (78)
M4	0.48 (39)	0.36 (21)[b]	0.35 (59)

AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinite time; AUC_{last}, area under the concentration-time curve from time 0 to time of last quantifiable concentration; C_{max}, maximum plasma concentration; $MRAUC_{inf}$, ratio of metabolite to abrocitinib for AUC_{inf}; $t_{1/2}$, terminal elimination half-life; t_{max}, time to maximum plasma concentration.

N = Total number of subjects in the treatment group.

[a] Geometric mean (geometric % coefficient of variation) for all except median (range) for t_{max} and arithmetic mean ± standard deviation for $t_{1/2}$.

[b] N = 7.

account, at least in part, for the large CIs seen for the PK parameters. In addition, CYP2C19 and CYP2C9, the main enzymes involved in abrocitinib metabolism, are known to exhibit genetic polymorphism,[21] which may further have contributed to the variability of PK parameters in a study with parallel design. There was no apparent effect of hepatic impairment on C_{max} for either impairment group. The small increases in mean AUC_{inf} in subjects with mild and moderate impairment were associated with an ≈25% to 35% decrease in mean abrocitinib CL/F and an ≈9% to 55% longer $t_{1/2}$. The modest increase in $t_{1/2}$ in subjects with moderate hepatic impairment is unlikely to result in significantly higher drug accumulation following once-daily administration. As such, given the observed active moiety AUC and C_{max} ratios for subjects with moderate hepatic impairment vs normal hepatic function, and the 2-fold margin of safety significance, this increase in $t_{1/2}$ is not considered clinically relevant.

After a single oral administration of abrocitinib, the metabolites M1, M2, and M4 are formation-rate limited as evidenced by parallel decline in plasma concentration-time profiles for the metabolites and abrocitinib (Figure 2). The median t_{max} for M1, M2, and M4 across the 3 hepatic function groups were generally similar (1.50-2.50 hours), suggesting that the rate of metabolite formation was not impacted by hepatic impairment. However, due to hepatic impairment, there was reduced formation of the metabolites, especially for M1 and M2. Both AUC_{inf} and C_{max} values for these 2 metabolites were lower in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function, although the differences were greater for M1, with an ≈51% to 68% reduction in M1 AUC_{inf} and 71% to 77% reduction in M1 C_{max} vs 14% to 22% reduction in M2 AUC_{inf} and 45% to 53% reduction in M2 C_{max}. Although the individual AUC_{inf} values for M4 largely overlap across the 3 hepatic function groups, the mean AUC_{inf} was 14% higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function and C_{max} was 26% to 37% lower in subjects with hepatic impairment. In addition, hepatic impairment reduced the $MRAUC_{inf}$ with the greatest reduction seen for M1. The unadjusted geometric mean ratios for $MRAUC_{inf}$ for M1, M2, and M4 in subjects with

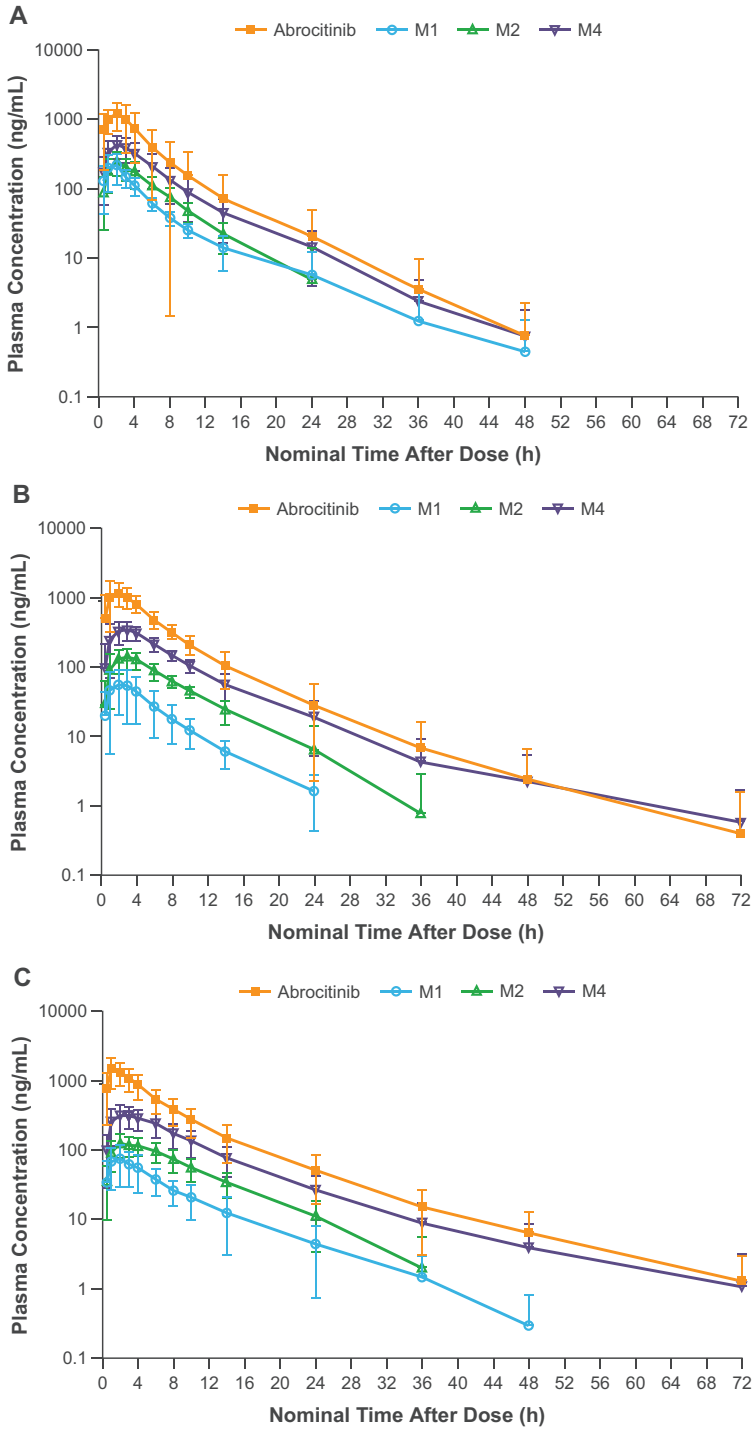

Figure 2. Mean (± standard deviation) plasma concentration-time profiles of abrocitinib, PF-06471658 (M1), PF-04965842 (M2), and PF-07054874 (M4) in subjects with (A) normal hepatic function, (B) mild hepatic impairment, and (C) moderate hepatic impairment following a single 200-mg oral dose of abrocitinib (semi-log scale).

mild hepatic impairment compared to subjects with normal hepatic function were 0.239, 0.680, and 0.764, respectively, and the corresponding ratios in subjects with moderate hepatic impairment were 0.320, 0.655, and 0.740, respectively.

In vitro data have shown that of the 3 metabolites in circulation, M1 and M2 have relative JAK1 inhibitory profiles similar to that of abrocitinib (data on file). Therefore, the total pharmacologic activity of abrocitinib is attributable to the unbound exposures

Table 4. (A) Descriptive and (B) Statistical Summaries of Plasma Abrocitinib Active Moiety Unbound Pharmacokinetic Parameters in Subjects With Normal Hepatic Function or Hepatic Impairment After a Single 200-mg Oral Dose of Abrocitinib

(A) Pharmacokinetic Parameter Summary

Parameter, Unit[a]	Normal Hepatic Function (N = 8)	Mild Hepatic Impairment (N = 8)	Moderate Hepatic Impairment (N = 8)
$AUC_{inf,u}$, nM • h	12 010 (40)[b]	11 500 (24)	13 790 (30)
$AUC_{last,u}$, nM • h	10 880 (43)	11 240 (25)	13 420 (32)
$C_{max,u}$, nM	2390 (20)	1815 (36)	2011 (41)

(B) Statistical Comparison	Adjusted (Least Squares) Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[c]	90%CI for Ratio[c]
	Test	Reference		
Mild Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)				
$AUC_{inf,u}$, nM • h	11 496.51	12 007.61	95.74	(72.71-126.08)
$AUC_{last,u}$, nM • h	11 237.74	10 883.50	103.25	(77.92-136.82)
$C_{max,u}$, nM	1815.22	2390.40	75.94	(57.39-100.47)
Moderate Hepatic Impairment (Test) vs Normal Hepatic Function (Reference)				
$AUC_{inf,u}$, nM • h	13 786.92	12 007.61	114.82	(87.19-151.20)
$AUC_{last,u}$, nM • h	13 418.06	10 883.50	123.29	(93.04-163.36)
$C_{max,u}$, nM	2011.26	2390.40	84.14	(63.59-111.33)

$AUC_{inf,u}$, unbound area under the concentration-time curve from time 0 extrapolated to infinite time; $AUC_{last,u}$, unbound area under the concentration-time curve from time 0 to time of last quantifiable concentration; CI, confidence interval; $C_{max,u}$, unbound maximum plasma concentration.
N = Total number of subjects in the treatment group in the indicated population.
[a] Geometric mean (geometric % coefficient of variation) for all.
[b] N = 7.
[c] The ratios (and 90%CI) are expressed as percentages.

of abrocitinib, M1, and M2 in circulation, and active moiety is the clinically relevant species for assessing efficacy and safety of abrocitinib. As such, abrocitinib active moiety was calculated as the best exposure parameter to guide dosing recommendations. In the calculation of active moiety exposure, the unbound exposure of abrocitinib, M1 and M2 were corrected for their relative inhibition potencies of IFN-α signaling as a surrogate for inhibition of JAK1 heterodimer signaling (eg, JAK1/JAK2, JAK1/JAK3, and JAK1/TYK2 pairs). Cytokine inhibition profiling of JAK inhibitors has shown that in general, inhibition of JAK1 heterodimer potency is similar for JAK1 selective inhibitors[20] including for abrocitinib.[8] For example, abrocitinib showed similar whole blood inhibitory potencies for IFN-α (JAK1/TYK2), IFNγ (JAK1/JAK2), and IL-21 (JAK1/JAK3), representative of 3 different JAK1 heterodimer pairs.[8] There can be numerical differences in potencies between cytokine inhibition with JAK1 inhibitors depending on their kinase selectivity profiles. However, as the application of the active moiety to dose adjustment is based on the ratio between 2 subject populations (hepatic impairment vs normal hepatic function), the choice of specific JAK1-dependent cytokine IC_{50} used is less important, as long as the same IC_{50} is consistently applied to all active drug species.

Population PK/pharmacodynamic (PD) analysis has shown that abrocitinib average exposure was able to describe the time course of Eczema Area and Severity Index scores and predicted the percentage of subjects achieving $\geq$75% improvement in Eczema Area and Severity Index at week 12.[22] Additional exposure-response analysis also showed that improvement in Investigator's Global Assessment score was well correlated with the average exposure for abrocitinib (data on file). Thus, AUC_{inf} is a clinically relevant exposure parameter for abrocitinib. Given the pharmacologic activities of M1 and M2 and their systemic exposures, active moiety is the clinically relevant species for assessing efficacy and safety of abrocitinib. Although the exposure-response analysis for the efficacy and safety end points was conducted with abrocitinib, both abrocitinib and active moiety are expected to provide similar inferences on the exposure-response relationship given the formation rate limited kinetics of the metabolites. Nevertheless, it remains important to assess the effect of intrinsic and extrinsic factors on the PK of active moiety as that is the clinically relevant species for efficacy and safety.

The $AUC_{inf,u}$ of the active moiety was $\approx$4% lower in subjects with mild hepatic impairment and 15% higher in subjects with moderate hepatic impairment, suggesting minimal to no apparent effect of hepatic

impairment on the overall activity of abrocitinib. Subjects with mild or moderate hepatic impairment had slightly lower (16%-24%) $C_{max,u}$ values compared to subjects with normal hepatic function. The small decreases in $C_{max,u}$ are unlikely to be clinically relevant for both safety and efficacy as the PK/PD analysis has shown that the effects of abrocitinib are correlated to AUC_{inf} rather than C_{max}.

Overall, this study shows that a single 200-mg oral dose of abrocitinib was generally safe and well tolerated in subjects with mild and moderate hepatic impairment and in age- and body weight-matched subjects with normal hepatic function. All treatment-emergent adverse events reported were mild in severity except for treatment-related moderate diarrhea in 1 subject with mild hepatic impairment. No treatment-emergent adverse events were reported in subjects with moderate hepatic impairment. No adverse events were considered as an event of special interest for abrocitinib. There were no deaths, serious adverse events, or clinically significant laboratory test abnormalities, including liver function tests. Finally, these safety findings reflect all exposures including abrocitinib as well as its metabolites and the active moiety.

In summary, the results from this study indicate that neither mild nor moderate hepatic impairment has a clinically relevant effect on the exposure of abrocitinib active moiety, and the safety profile of a single 200-mg oral dose of abrocitinib is similar across subjects with normal hepatic function and mild or moderate hepatic impairment. On the basis of these results, no specific dose adjustment is recommended in moderate to severe atopic dermatitis subjects with mild or moderate hepatic impairment.

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Conflicts of Interest

E.Q.W., V.L., M.O., S.T., M.E.D., L.W., and B.K.M. are employees and shareholders of Pfizer Inc. The spouse of M.E.D is an employee and shareholder of Pfizer Inc.

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Data Sharing

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Supplemental Information

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