Effect of Hepatic Impairment on the Pharmacokinetics of Nirmatrelvir/Ritonavir, the First Oral Protease Inhibitor for the Treatment of COVID-19

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Abstract

Nirmatrelvir, a novel, potent, orally bioavailable severe acute respiratory syndrome coronavirus 2 main protease inhibitor, coadministered with ritonavir for pharmacokinetic (PK) enhancement is licensed for the treatment of mild to moderate COVID-19 in individuals at increased risk of progression to severe disease. Cytochrome P450 3A4 is the primary metabolic enzyme responsible for nirmatrelvir metabolism; however, when cytochrome P450 3A4 is inhibited by ritonavir, nirmatrelvir is primarily excreted, unchanged, in urine. Because of intended use of nirmatrelvir among individuals with hepatic impairment, this Phase 1 study (NCT05005312) evaluated the effects of hepatic impairment on nirmatrelvir PK parameters to assess the potential need for any dose adjustments in this population. Participants with normal hepatic function or moderate hepatic impairment (n = 8 each) were administered a single 100-mg nirmatrelvir dose, with 100 mg of ritonavir administered 12 hours before, together with, and 12 and 24 hours after nirmatrelvir. Nirmatrelvir median plasma concentrations and systemic exposure measured by area under the plasma concentration–time curve from time zero extrapolated to infinite time and maximum observed plasma concentration values were comparable in both groups. Nirmatrelvir/ritonavir had an acceptable safety profile in both groups, and no clinically significant changes in laboratory measurements, vital signs, or electrocardiogram assessments were observed. Based on these results, no dose adjustment is deemed necessary in patients with moderate hepatic impairment and, by extension, in patients with mild hepatic impairment.

Keywords

COVID-19, hepatic impairment, nirmatrelvir, pharmacokinetics, ritonavir, safety

COVID-19 has had devastating effects on global public health, having been associated with more than 767 million confirmed cases and more than 6.9 million deaths worldwide as of early July 2023.[1] Individuals with specific underlying comorbidities or other characteristics, such as older age or smoking, are at increased risk of progression to severe disease and mortality.[2-5] In December 2021, the US Food and Drug Administration (FDA) granted emergency use authorization to nirmatrelvir (PF-07321332; Pfizer Inc.), an orally administered antiviral agent that targets the severe acute respiratory syndrome coronavirus 2 main protease enzyme, coadministered with ritonavir for the treatment of individuals with mild to moderate COVID-19 who are at risk of progression to severe disease.[6,7] Authorization and subsequent licensure were based in part on findings from the Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) Phase 2/3 study (NCT04960202) demonstrating an 88% relative risk reduction of COVID-19–associated hospitalization or death in this population when nirmatrelvir/ritonavir (Paxlovid, Pfizer Inc.) treatment was initiated within 5 days of symptom onset.[6-8]

Although individuals with hepatic impairment were excluded from the EPIC-HR trial,[8] they are at increased risk of severe COVID-19[2,5] and are therefore eligible for nirmatrelvir treatment.[7,9] Because nirmatrelvir is a cytochrome P450 (CYP) 3A4 substrate (fraction metabolized = 0.99),[10,11] it is coadministered with

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ritonavir, a potent CYP3A4 inhibitor,[12] to maintain plasma concentrations at efficacious levels.[7] When enhanced with ritonavir, the primary route of nirmatrelvir elimination becomes renal, and metabolism is limited.[13] The amount of unchanged drug excreted at steady state in multiple-ascending-dose cohorts in first-in-human studies of nirmatrelvir enhanced with ritonavir ranged from 23.4% to 63.8%.[13] In addition, absorption, distribution, metabolism, and excretion (ADME) characterization using a novel[19] F-nuclear magnetic resonance (^{19}F-NMR) technique of nirmatrelvir enhanced with ritonavir showed that 47.0% of the normalized dose was excreted in urine as total drug-related material, of which 98.5% was unchanged nirmatrelvir.[14] These observations are further corroborated by clinical data indicating the significant impact of renal impairment on the pharmacokinetics (PK) of nirmatrelvir when enhanced with ritonavir. Ritonavir, used as a PK enhancer for nirmatrelvir, is metabolized by CYP3A4; as such, ritonavir PK may be altered in patients who are hepatically impaired, in turn possibly altering nirmatrelvir PK.[7,15] Evaluations of ritonavir PK indicated that, compared with healthy participants, ritonavir exposure was approximately 40% lower in participants with moderate hepatic impairment but similar in participants with mild hepatic impairment.[15] Given the role of CYP3A4 in the metabolism of nirmatrelvir and ritonavir, an assessment of the impact of hepatic impairment on safety and PK of nirmatrelvir was conducted in accordance with FDA guidance[16] to address whether nirmatrelvir/ritonavir dosing modifications were needed for individuals with hepatic impairment.

Methods

Ethical Conduct

The study was conducted at 2 US sites (Prism Clinical Research, St. Paul, MN; and Orange County Research Center, Tustin, CA) in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council on Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. The protocol and related documents were approved by institutional review board/ethics committees for each of the sites (Advarra, Columbia, MD; and WCG Institutional Review Board, Puyallup, WA, respectively) before study commencement. All participants provided written informed consent before enrollment.

Study Description and Participants

This was a Phase 1, nonrandomized, open-label, single-dose study (NCT05005312) that evaluated the PK and safety of nirmatrelvir enhanced with ritonavir in adults with and without moderate hepatic impairment. Inclusion criteria were age 18-75 years, body mass index of 17.5-40 kg/m^2, and total body weight greater than 50 kg. For the group with moderate hepatic impairment, participants were also required to have stable hepatic impairment that met the criteria for Class B of the Child–Pugh classification (CPC) of liver dysfunction (Table S1),[16] with no clinically significant change in disease status 28 days or less before screening. For the normal hepatic function group, participants were required to be healthy as determined by medical evaluation and medical history and be within ±10 years of the mean age and within ±15 kg of the mean body weight of the hepatic impairment group; attempts were also made to ensure comparable male-to-female ratios between groups.

Key exclusion criteria for both groups included pregnancy/breastfeeding; evidence or history of clinically significant disease, including any condition possibly affecting drug absorption; HIV positivity; estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration equation and history or evidence of hepatitis (normal hepatic function group only). Participants with moderate hepatic impairment with hepatic carcinoma; hepatorenal syndrome; predicted life expectancy less than 1 year; hepatic dysfunction secondary to any acute ongoing hepatocellular process; clinically active Grade 3 or 4 hepatic encephalopathy; severe ascites or pleural effusion; and history of kidney, liver, or heart transplantation were excluded. Each group was also subject to exclusion criteria based on individually prespecified abnormalities in vital signs, electrocardiogram (ECG) measurements, or laboratory evaluations. Prohibited prior/concomitant therapies included COVID-19 vaccination (within 1 week before dosing), prescription or nonprescription drugs or supplements (7 days/5 half-lives, whichever was longer) before dosing (permitted on a case-by-case basis), strong inducers (28 days/5 half-lives) or inhibitors (7 days/5 half-lives) of CYP3A4, and substances that highly depend on CYP3A4 for clearance and for which elevated plasma concentrations may be unsafe. Participants with moderate hepatic impairment were permitted to take stable doses of concomitant medications with the sponsor's approval, if necessary, provided they were not contraindicated and were unlikely to interfere with the PK of the investigational product.

Study Procedures

Enrollment was staged such that participants in the moderate hepatic impairment group were enrolled first; participants with normal hepatic function were enrolled afterward to match average demographics (age, weight, and sex if possible) of the cohort with moderate hepatic

impairment. Following screening, enrolled participants were admitted to the clinical research unit (CRU) at Day −1 and remained there through Day 3. A single oral dose of 100-mg ritonavir was given on the evening of Day −1 (approximately 12 hours before nirmatrelvir dosing) followed by 100 mg of orally administered nirmatrelvir/100 mg of ritonavir on the morning of Day 1. Both ritonavir and nirmatrelvir were provided as 100-mg tablets. Additional 100-mg doses of ritonavir were given at 12 and 24 hours after nirmatrelvir to maintain PK boosting. This dosing schedule of nirmatrelvir enhanced with ritonavir was based on available PK data at that time, including physiologically based PK (PBPK) from a preliminary model that predicted area under the plasma concentration–time curve (AUC) and maximum observed plasma concentration (C_{max}) values.[17] At the proposed dose of 100 mg of nirmatrelvir, the PBPK model predicted AUC and C_{max} values of 23.5 μg·h/mL and 3.2 μg/mL, respectively, which are below the highest observed exposures, in healthy participants, that were considered to be safe and well tolerated. Additionally, in single-ascending-dose cohorts, pre-, co-, and postdosing of ritonavir were used to have a complete inhibitory effect of ritonavir during absorption and elimination phases of nirmatrelvir. A single codosing of ritonavir may not have provided the complete boosting effect. Such an approach has been used in previous drug–drug interaction studies to maximize the inhibitory effect.[18] Having an inhibitory effect of ritonavir through absorption and elimination phases allows reliable extrapolation to a multiple-dose scenario where codosing for 5 days is recommended. Therefore, to minimize participant burden during the trial, this strategy was employed in all studies where a single dose of nirmatrelvir was used, including the PK assessment in patients with renal impairment.[19]

Pharmacokinetics

The primary objective was to compare the PK of nirmatrelvir in participants with and without moderate hepatic impairment as measured by C_{max}, AUC from time zero to the time of last measured concentration (AUC_{last}), and AUC from time zero extrapolated to infinite time (AUC_{inf}). C_{max}, AUC_{last}, AUC_{inf}, and additional PK parameters, including time to C_{max}, apparent clearance, apparent volume of distribution, terminal elimination half-life, total amount of unchanged drug excreted in the urine over 24 hours, and renal clearance (CL_r) for nirmatrelvir, as well as C_{max}, time to C_{max}, and AUC from time zero to 12 hours (AUC_{12}) for ritonavir, were calculated by noncompartmental analysis of concentration–time data (Table S2) using an internally validated software system, openNCA Version 2.4.33. In a previous in vitro protein-binding study, nirmatrelvir was shown to have limited binding affinity for human plasma proteins (fraction unbound = 0.31); therefore, assessment of plasma protein binding was not performed.[11]

Blood samples of approximately 4 mL were collected for plasma PK analyses on Day 1 at 0 (ie, before dosing of nirmatrelvir), 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours; Day 2 at 24 and 36 hours; and Day 3 at 48 hours relative to nirmatrelvir dosing. For urine PK parameters, all urine produced during 0-24 hours after nirmatrelvir dosing was collected and thoroughly mixed before sampling for analysis. Analysis of blood and urine samples was performed using previously published, validated analytical methods in compliance with applicable standard operating procedures.[19]

PK end points were evaluated in the PK concentration analysis set, which included all participants assigned to investigational product with one or more concentrations measured, and the PK parameter analysis set, which included all participants assigned to investigational product with one or more PK parameters of primary interest measured.

Safety

Safety evaluations were considered a secondary objective and included incidence of treatment-emergent adverse events (TEAEs), abnormal electrocardiograms (ECGs), vital signs, and laboratory measurements. TEAEs were monitored during CRU confinement and additionally during a follow-up contact at Day 28-35. Other safety end points were measured at prespecified time points during CRU confinement. The safety analysis set included all participants randomly assigned to study intervention who took one or more doses of the study drug.

Statistical Analysis

The study aimed to enroll approximately 8 participants per group to ensure approximately 6 evaluable participants per group based on guidelines from the FDA.[16] This sample size was expected to provide adequate precision to estimate the effects of hepatic impairment on nirmatrelvir PK.

One-way analysis of variance was used to compare the natural log-transformed AUC_{inf}, AUC_{last}, and C_{max} in the moderate hepatic impairment group ("test") with those in the normal hepatic function group ("reference") using SAS Version 9.4 (SAS Institute). Adjusted mean differences (test−reference) and corresponding 90% confidence intervals (CIs) were obtained from a mixed-effects model, in which group was a fixed effect and variances were assumed to be unequal, and then exponentiated to provide estimates of the ratio of adjusted geometric means (test/reference) and corresponding 90% CIs. The precision needed (ie, expected 90% CI with 90% coverage probability) to estimate the effects of hepatic impairment on AUC_{inf} and C_{max} (the primary end points) is described in Table S3.

Table 1. Participant Demographics and Physical Measurements

Characteristic	Normal hepatic function (N = 8)	Moderate hepatic impairment (N = 8)
Age, years, n (%)		
<18	0	0
18-44	0	2 (25.0)
45-64	8 (100.0)	4 (50.0)
≥65	0	2 (25.0)
Mean (SD)	52.8 (6.16)	56.1 (9.33)
Median (range)	51.5 (46-64)	58.5 (42-67)
Sex, n (%)		
Male	7 (87.5)	7 (87.5)
Female	1 (12.5)	1 (12.5)
Race, n (%)		
White	6 (75.0)	7 (87.5)
Black or African American	2 (25.0)	1 (12.5)
Ethnicity, n (%)		
Hispanic or Latinx	2 (25.0)	4 (50.0)
Not Hispanic or Latinx	6 (75.0)	4 (50.0)
Height (cm)		
Mean (SD)	174.44 (10.05)	172.84 (6.67)
Median (range)	179.05 (157.5-183.0)	172.55 (165.0-184.6)
Weight (kg)		
Mean (SD)	90.88 (9.82)	89.66 (7.17)
Median (range)	87.15 (76.2-103.9)	87.55 (82.2-103.9)
Body mass index (kg/m^2)		
Mean (SD)	29.93 (2.96)	30.14 (3.34)
Median (range)	30.19 (25.74-34.75)	30.17 (24.91-35.95)

SD, standard deviation.

Results

Participants

A total of 17 participants were enrolled in the study at 2 sites (Minnesota, n = 7; California, n = 10). Both sites contributed to enrollment in both cohorts. Eight participants had normal hepatic function, and 9 had moderate hepatic impairment. Of these, 1 participant with moderate hepatic impairment discontinued because of difficulty in venous access for blood draws on Day 1 before receiving nirmatrelvir. All 16 treated participants completed the study and follow-up procedures.

Demographic characteristics were generally well balanced between groups (Table 1). Mean (SD) age among treated participants was 52.8 (6.2) and 56.1 (9.3) years for participants with normal hepatic function and moderate hepatic impairment, respectively; each group included 7 male participants and 1 female participant. Mean (SD) weight was 90.9 (9.8) and 89.7 (7.2) kg in the normal hepatic function and moderate hepatic impairment groups, respectively; mean (SD) body mass index was 29.9 (3.0) and 30.1 (3.3) kg/m^2, respectively. Table S4 describes concomitant medications that participants received across both groups.

Bioanalytical Assays

Detailed bioanalytical assay procedures, as well as the accuracy and precision of the plasma assay validation, have been previously described.[19] For plasma analysis in this study, interrun precision values (percentage coefficient of variation) across sample runs were 5.8% or less (nirmatrelvir) and 6.3% or less (ritonavir); accuracy (percentage relative error) was −1.5%-6.0% (nirmatrelvir) and 0.0%-2.0% (ritonavir). Twenty-one samples were reanalyzed for demonstration of assay reproducibility; 100% were within a difference of ±20%, with maximum differences of −16.9% (nirmatrelvir) and −9.3% (ritonavir).

For urine PK analysis, interrun precision (percentage coefficient of variation) was 5.2% or less, and accuracy (percentage relative error) ranged from −2.7% to 5.8%. Sixteen samples were reanalyzed for demonstration of assay reproducibility; 15 of these (93.8%) were within ±20% difference, with one difference of −22.2%.

Pharmacokinetics

Median plasma concentrations of nirmatrelvir through 48 hours were generally similar between groups (Figure 1a). Nirmatrelvir PK parameters for both groups are summarized in Table 2 and were generally similar across groups; for AUC_{inf}, AUC_{last}, and C_{max}, geometric mean ratios comparing moderate hepatic impairment to normal hepatic function were 98.78% (90% CI, 70.65%-138.12%), 99.29% (90% CI, 70.81%-139.21%), and 101.96% (90% CI, 74.20%-140.11%), respectively. Renal clearance was slightly higher in the moderate hepatic impairment group (mean, 3.738 L/h) compared with the normal hepatic function group (2.509 L/h), as was urinary recovery of unchanged nirmatrelvir (54.23% vs 35.66%). Individual AUC_{inf} and C_{max} values for nirmatrelvir are shown in Figure 1b, c.

For ritonavir, median plasma concentrations were higher in the moderate hepatic impairment group compared with the normal hepatic function group (Figure 2a). Geometric mean AUC_{12} and C_{max} of ritonavir were also approximately 1.68- and 1.84-fold higher, respectively, compared with those with normal hepatic function (Table 2). Individual AUC_{12} and C_{max} values for ritonavir are shown in Figure 2b, c.

Safety

Three participants (37.5%) in the normal hepatic function group each reported a single TEAE, which included injection site pruritus, dizziness, and ecchymosis; all were mild in severity and not considered related to the study treatment. Four participants (50.0%) in the moderate hepatic impairment group reported a total of 8 TEAEs, which included 2 instances of dysgeusia and one instance each of nausea, urinary tract infection, back pain, somnolence, chromaturia, and contact dermatitis. All TEAEs were mild in severity other than the reports of urinary tract infection and back pain, which

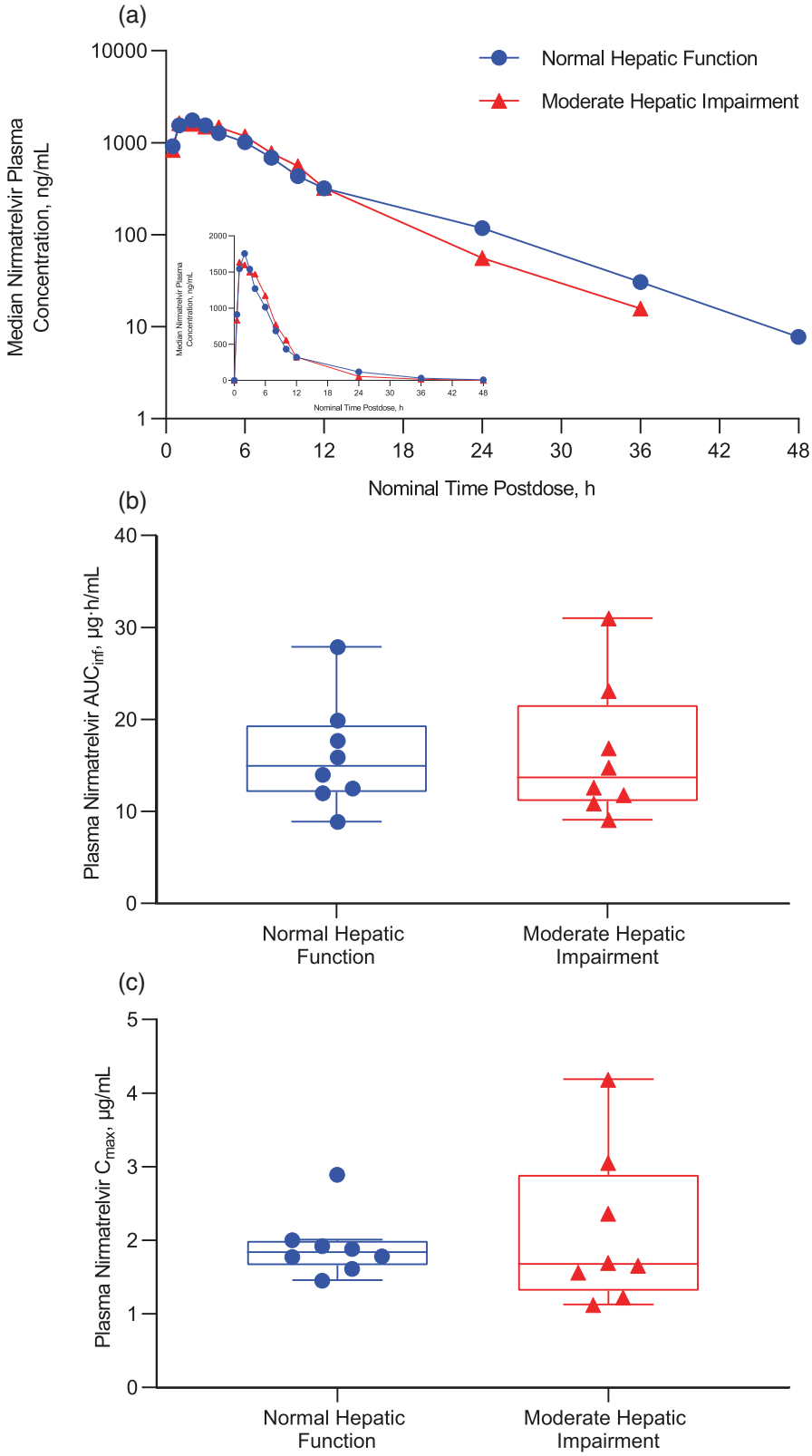

Figure 1. Nirmatrelvir PK by hepatic function group. (a) Median plasma concentrations over time; (b) geometric mean and individual plasma AUC_{inf} values; and (c) geometric mean and individual plasma C_{max} values. The inset in (a) displays data on a linear scale. Boxes in (b) and (c) show median and 25th and 75th percentiles, with whiskers extending to the last point within 1.5 times the interquartile range. AUC_{inf}, area under the plasma concentration–time curve from time zero extrapolated to infinity; C_{max}, maximum observed plasma concentration; PK, pharmacokinetics

Table 2. Summary of PK Parameters

Study intervention Parameter[a]	Normal hepatic function (N=8)	Moderate hepatic impairment (N=8)	Ratio (%) (moderate hepatic impairment/normal hepatic function) of adjusted geometric means[b]	90% CI (%) of ratio
Nirmatrelvir				
AUC_{inf} (μg·h/mL)	15.24 (36)	15.06 (43)	98.78	(70.65-138.12)
AUC_{last} (μg·h/mL)	14.97 (36)	14.86 (43)	99.29	(70.81-139.21)
CL/F (L/h)	6.560 (36)	6.650 (43)	ND	ND
C_{max} (μg/mL)	1.886 (20)	1.923 (48)	101.96	(74.20-140.11)
$t_{1/2}$ (hour)	7.209 ± 2.0990	5.448 ± 1.5743	ND	ND
t_{max} (hour)	2.000 (0.550-2.08)	1.500 (1.00-2.00)	ND	ND
V_z/F (L)	65.51 (39)	50.37 (40)	ND	ND
Ae_{24} (mg)	35.66 (31)	54.23 (23)	ND	ND
Ae_{24} (%)	35.66 (31)	54.23 (23)	ND	ND
CL_r (L/h)	2.509 (46)	3.738 (49)	ND	ND
Ritonavir				
AUC_{12} (μg·h/mL)	5.912 (57)	9.929 (36)	ND	ND
C_{max} (μg/mL)	0.8768 (50)	1.611 (42)	ND	ND
t_{max} (hour)	3.000 (2.00-4.00)	2.000 (1.00-4.00)	ND	ND

Ae_{24}, total amount of unchanged drug excreted in the urine over 24 hour; AUC_{12}, area under the plasma concentration–time profile from time zeor to 12 hour; AUC_{inf}, area under the plasma concentration–time curve from time zero extrapolated to infinity; AUC_{last}, area under the plasma concentration time curve from time zero to the time of the last measurable concentration; CL/F, apparent clearance of drug from plasma; CL_r, renal clearance of drug from plasma; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; ND, not determined; SD, standard deviation; $t_{1/2}$, terminal half-life; t_{max}, time to first occurrence of C_{max}; V_z/F, apparent volume of distribution of total drug.

[a] Geometric mean (geometric %CV) for all except median (range) for t_{max} and arithmetic mean ± SD for $t_{1/2}$.

[b] Natural log-transformed AUC_{inf}, AUC_{last}, and C_{max} for nirmatrelvir were analyzed using a mixed-effects model with group as a fixed effect and assuming unequal variances.

were reported by a single individual and were moderate in severity. Both instances of dysgeusia were considered related to ritonavir, and the instance of somnolence was considered related to nirmatrelvir. No discontinuations due to TEAEs, deaths, or serious TEAEs were reported.

In the normal hepatic function group, the following abnormal laboratory parameters were observed among 3 participants: eosinophils greater than 1.2× the upper limit of normal (ULN; 1 participant), calcium greater than 1.1 × ULN (1 participant), and abnormal urine hemoglobin and the presence of blood on microscopic exam (1 participant). All these abnormalities were present at Day −1 (ie, baseline), and none were considered clinically significant. In the moderate hepatic impairment group, abnormal laboratory parameters at Day 3 were observed for 6 participants and included eosinophils greater than 1.2 × ULN (2 participants), platelets less than 0.5 × the lower limit of normal (1 participant), monocytes greater than 1.2 × ULN (1 participant), direct bilirubin greater than 1.5 × ULN (unplanned; 1 participant); aspartate aminotransferase greater than 3.0 × ULN (1 participant), glucose greater than 1.5 × ULN (1 participant), abnormal level of urobilinogen (1 participant), and abnormal level of leukocyte esterase (1 participant). Other than urobilinogen and the unplanned direct bilirubin, all abnormalities were also present at baseline; none were considered clinically significant.

While participants were monitored throughout the study, no clinically significant changes in vital signs, including systolic and diastolic blood pressure and pulse rate, were detected during prespecified collection times on Days 1 and 3. One participant with moderate hepatic impairment had a systolic blood pressure change of 30 mm Hg or greater on Day 3, but this was not considered clinically significant because the participant had a history of hypertension. Similarly, no participants met preset categorizations of postbaseline (ie, Day 1) supine ECG changes at Day 3, and there were no clinically significant changes in any of the ECG parameters evaluated.

Discussion

Nirmatrelvir is almost exclusively metabolized (fraction metabolized = 0.99) via CYP3A4 in vitro[10,11]; however, when administered in humans with ritonavir, a CYP3A4 inhibitor,[12] the main route of elimination for nirmatrelvir switches to renal.[13] Given less than 80% recovery of unchanged nirmatrelvir in urine,[13] this PK study was conducted in accordance with FDA guidance[16] to evaluate the potential need

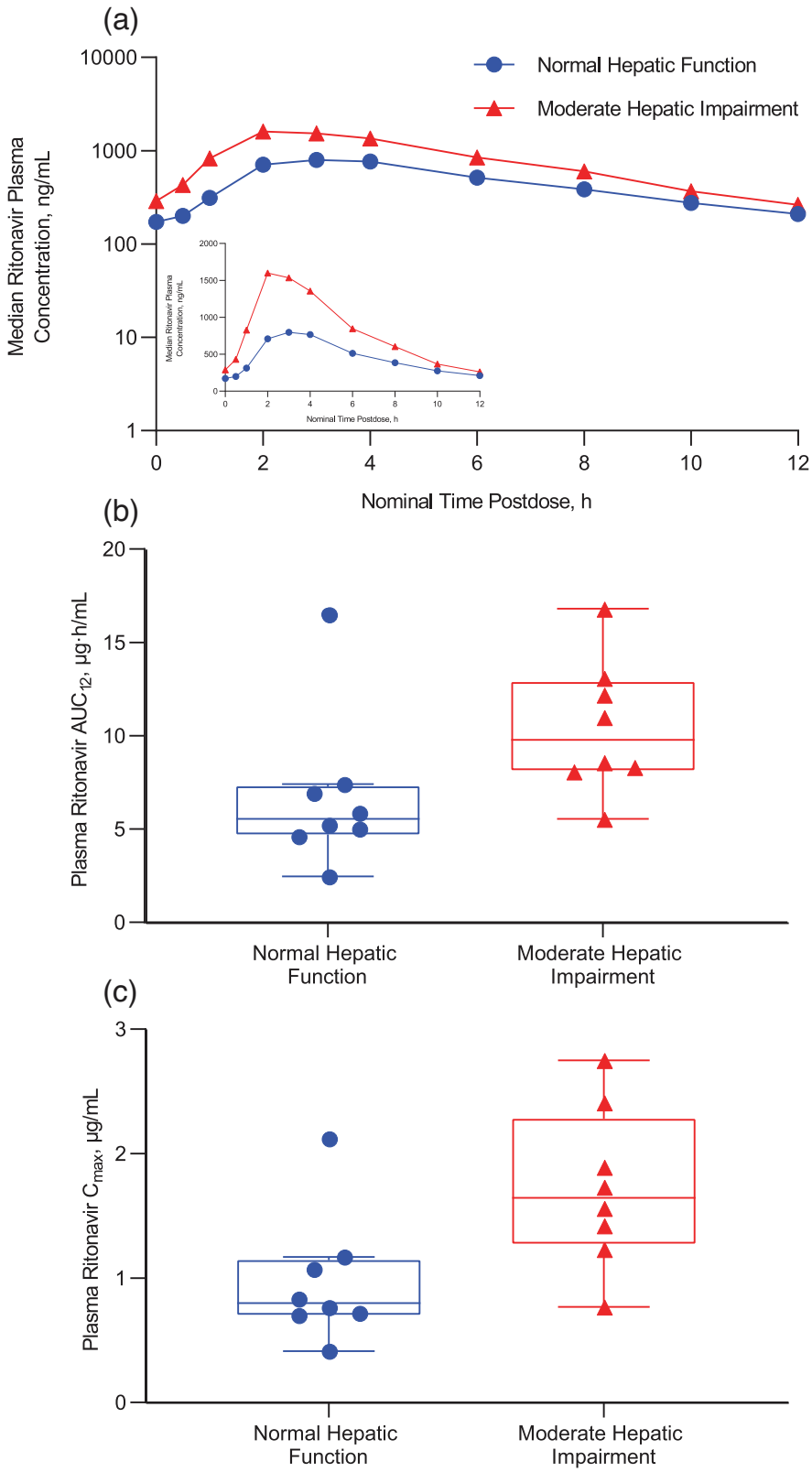

Figure 2. Ritonavir PK by hepatic function group. (a) Median plasma concentrations over time; (b) geometric mean and individual plasma AUC_{12} values; and (c) geometric mean and individual plasma C_{max} values. The inset in (a) displays data on a linear scale. Boxes in (b) and (c) show median and 25th and 75th percentiles, with whiskers extending to the last point within 1.5 times the interquartile range. AUC_{12}, area under the plasma concentration–time profile from time zero to 12 hours; C_{max}, maximum observed plasma concentration; PK, pharmacokinetics

for nirmatrelvir dose adjustment among patients with moderate hepatic impairment. Preliminary PBPK modeling showed a less than 3-fold increase in exposure (data not shown) among participants with moderate hepatic impairment (CPC Class B); therefore, the assessment of hepatic impairment was conducted first in participants with moderate hepatic impairment. To capture the moderate hepatic impairment spectrum to inform on the dosing regimen within this population, the participants with hepatic impairment with Grade 2 or less encephalopathy (CPC Class B) were permitted to participate in the study. Concerns for the potential inclusion of participants with disorientation, a symptom of encephalopathy,[16] were mitigated by excluding participants who were unable to provide their own study consent.

A single dose of nirmatrelvir was considered appropriate because a multiple-ascending-dose study did not identify any time-dependent changes in nirmatrelvir PK, with single-dose data predictive of steady-state PK.[13] To maintain adequate CYP3A inhibition at the time of nirmatrelvir dosing and throughout the duration of exposure, ritonavir 100 mg was administered 12 hours before, together with, 12 hours after, and 24 hours after nirmatrelvir dosing. To ensure that the projected nirmatrelvir exposure remained within the previously observed exposures in healthy participants, the dose selected in this study was 100 mg rather than the clinically recommended dose of 300 mg. Given that nirmatrelvir was not found to be extensively bound to human plasma proteins (fraction unbound = 0.31),[11] ex vivo protein binding analysis was not deemed necessary.

The systemic exposure to nirmatrelvir following a single oral administration of a 100-mg dose boosted with ritonavir for PK enhancement was comparable among participants with moderate hepatic impairment and age- and weight-matched participants with normal hepatic function. The adjusted geometric mean ratios of AUC_{inf} and C_{max} of adults with moderately impaired hepatic function to those with normal hepatic function were approximately 99% and 102%, respectively. This lack of observed impact of hepatic impairment on systemic exposure to nirmatrelvir is supported by the absorption, distribution, metabolism, and excretion characterization of nirmatrelvir when coadministered with ritonavir for enhancement, which demonstrated that nirmatrelvir was minimally metabolized.[14] Since systemic exposure to nirmatrelvir in individuals with moderate hepatic impairment and normal hepatic function were comparable, assessment of nirmatrelvir PK in individuals with mild hepatic impairment was not necessary.[16] Additionally, nirmatrelvir/ritonavir had an acceptable safety and tolerability profile in both groups, and no clinically significant changes in laboratory measurements, vital signs, or ECG parameters were observed. Therefore, no adjustment in nirmatrelvir dose is needed for patients with either mild (CPC Class A) or moderate (CPC Class B) hepatic impairment.[7]

Although the percentage of unchanged nirmatrelvir excreted and CL_r appeared to be higher in the moderate hepatic impairment group compared with the normal hepatic function group, the values observed in the moderate hepatic impairment group were in the range of those observed in healthy participants in the first-in-human study.[13] Given the importance of renal elimination in nirmatrelvir clearance,[13] a potential relationship between baseline estimated estimated glomerular filtration rate derived from the Chronic Kidney Disease Epidemiology Collaboration equation and CL_r was explored, but these factors did not appear to be related (Figure S1). We therefore believe that the numerical differences in CL_r observed between groups in this study are likely due to variability within the small sample size.

Systemic exposure to ritonavir was higher in the moderate hepatic impairment group compared with the normal hepatic function group, consistent with observations for ritonavir when given in combination with other protease inhibitors, such as lopinavir and darunavir.[20,21] This modest increase in ritonavir exposure during the clinically recommended 5-day treatment is unlikely to cause any safety concerns given that the recommended ritonavir dose for long-term treatment in patients with HIV infection is 600 mg twice a day.[15] Thus, no dose adjustment for ritonavir is proposed for patients with moderate hepatic impairment.[7] This recommendation is consistent with recommendations for other protease inhibitors for which exposures to coadministered ritonavir were higher among patients with moderate hepatic impairment.[20,21]

This study is subject to several limitations. Individuals with severe hepatic impairment were excluded from this study because ritonavir is contraindicated in that population.[15] No PK or safety data of nirmatrelvir/ritonavir are available in participants with severe hepatic impairment (CPC Class C); therefore, the use of nirmatrelvir/ritonavir in such patients is not recommended.[7] Additionally, because the study was not conducted in patients with COVID-19, any potential effect of COVID-19 on PK of nirmatrelvir or ritonavir remains unknown. Nirmatrelvir/ritonavir target populations are patients with mild to moderate COVID-19,[7] and in this population, interleukin-6 concentration is expected to be low.[22] Therefore, we do not expect that interleukin-6–mediated changes in CYP3A4 would impact the interpretation of the results. Another limitation is that a single dose was used, which may not reflect current practice; however, given the PK of nirmatrelvir (coadministered with ritonavir), single-dose data allow prediction of steady state.[13,19] Also,

the nirmatrelvir dose used in this study was lower than the recommended nirmatrelvir/ritonavir dose of 300/100 mg twice daily,[7] and as such, safety of the recommended dose in patients with moderate hepatic impairment could not be assessed and will instead be derived from future real-world data in the context of COVID-19 treatment. Finally, the study sample size was small; nevertheless, no differences in nirmatrelvir PK were observed between groups.

Conclusions

This study demonstrated that moderate hepatic impairment does not impact the PK or safety of nirmatrelvir enhanced with ritonavir. As such, no dose adjustment is necessary in patients with COVID-19 and mild or moderate hepatic impairment. Nirmatrelvir/ritonavir is not recommended in patients with COVID-19 who have severe hepatic impairment, as PK and safety have not been evaluated in that population.

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Conflicts of Interest

Ravi Shankar P. Singh, Robert R. LaBadie, Sima S. Toussi, Haihong Shi, and Sudeepta Aggarwal are employees of Pfizer and may hold stock or stock options. At the time of study conduct and analysis, payments were made to Nucleus Network (formerly Prism Research, LLC), which was a research site for this clinical trial; Jolene Kay Berg was an employee of Nucleus Network and received no payments related to this manuscript. Joel M. Neutel has no relevant conflicts of interest to declare.

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Data Availability Statement

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 (i.e., 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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