Pharmacokinetics of Oral Nirmatrelvir/Ritonavir, a Protease Inhibitor for Treatment of COVID-19, in Subjects With Renal Impairment

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Nirmatrelvir coadministered with ritonavir is highly efficacious in reducing the risk of coronavirus disease 2019 (COVID-19) adverse outcomes among patients at increased risk of progression to severe disease, including patients with chronic kidney disease. Because nirmatrelvir is eliminated by the kidneys when given with ritonavir, this phase I study evaluated the effects of renal impairment on pharmacokinetics, safety, and tolerability of nirmatrelvir/ritonavir. Participants with normal renal function (n = 10) or mild, moderate, or severe renal impairment (n = 8 each) were administered a single 100-mg nirmatrelvir dose with 100 mg ritonavir given 12 hours before, together with and 12 and 24 hours after the nirmatrelvir dose. Systemic nirmatrelvir exposure increased with increasing renal impairment, with mild, moderate, and severe renal impairment groups having respective adjusted geometric mean ratio areas under the plasma concentration-time profile from time 0 extrapolated to infinite time of 124%, 187%, and 304% vs. the normal renal function group. Corresponding ratios for maximum plasma concentration were 130%, 138%, and 148%. Apparent clearance was positively correlated with estimated glomerular filtration rate, and geometric mean renal clearance values were particularly lower for the moderate (47% decrease) and severe (80% decrease) renal impairment groups vs. the normal renal function group. Nirmatrelvir/ritonavir exhibited an acceptable safety profile; treatment-related adverse events were mild in severity, and there were no significant findings regarding laboratory measurements, vital signs, or electrocardiogram assessments. These findings led to a dose reduction recommendation for nirmatrelvir/ritonavir in patients with moderate renal impairment (150/100 mg nirmatrelvir/ritonavir instead of 300/100 mg twice daily for 5 days). NCT04909853.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Nirmatrelvir, a novel inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has shown high efficacy against coronavirus disease 2019 (COVID-19)–related hospitalization or all-cause death among individuals at increased risk of progression to severe disease when administered in combination with ritonavir. Preliminary data have highlighted the importance of the renal pathway in nirmatrelvir pharmacokinetics when given with ritonavir, which inhibits the metabolism of nirmatrelvir.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study evaluated whether renal impairment was associated with altered nirmatrelvir pharmacokinetics.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Increases in nirmatrelvir systemic exposure were observed with increasing renal impairment severity following a single nirmatrelvir dose enhanced with ritonavir, particularly in the moderate (approximately twofold higher than normal renal function) and severe (approximately threefold higher) renal impairment groups. Nirmatrelvir renal clearance was correspondingly lower in these groups. The safety profile of nirmatrelvir/ritonavir was acceptable in all groups.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Findings from this study were used to specify dosing recommendations for nirmatrelvir/ritonavir for patients with renal disease.

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The threat to global public health posed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting coronavirus disease 2019 (COVID-19) remains unabated nearly 2 years since the pandemic began.[1] Individuals with underlying conditions, including renal impairment, are at increased risk of developing severe COVID-19,[2–4] which may in turn be associated with hospitalization, including intensive care unit admission, mechanical ventilation, and death.[2,3] There is thus an urgent need for effective treatments for COVID-19.

Currently available treatments for nonhospitalized patients with mild to moderate COVID-19 who are at increased risk of progression to severe disease include monoclonal antibodies, which are approved under emergency use authorization (EUA) in the United States.[5–7] These treatments must be administered intravenously or subcutaneously by a healthcare provider who can also monitor and potentially treat patients for severe infusion reactions. Importantly, because monoclonal antibodies target the SARS-CoV-2 spike protein,[5–7] they may be less efficacious against emerging variants harboring spike protein mutations.[8] Molnupiravir is an oral antiviral COVID-19 treatment with EUA in the United States, achieving a 30% reduction in COVID-19–related hospitalization or death.[9]

Paxlovid (nirmatrelvir (PF-07321332)/ritonavir) is a novel, orally administered inhibitor of the 3-chymotrypsin-like cysteine protease (M^{pro}) of SARS-CoV-2.[10] In addition to exhibiting a high level of conservation across human coronaviruses, including SARS-CoV-2,[11,12] M^{pro} performs the essential role of processing viral polyproteins into functional units,[13] and inhibition is not likely to exhibit off-target activity due to the absence of known human analogs[13,14]; thus, it is an ideal target for viral inhibition. Preclinical studies found that nirmatrelvir, given alone, is primarily metabolized by cytochrome P450 3A4 (CYP3A4)[10]; nirmatrelvir is therefore administered in combination with ritonavir (Norvir; AbbVie Inc., Chicago, IL, USA), a CYP3A4 inhibitor,[15] in clinical studies to maintain effective nirmatrelvir plasma concentrations. Nirmatrelvir in combination with ritonavir exhibited overwhelming efficacy in a recent phase II/III study (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR); NCT04960202) in nonhospitalized adults with mild to moderate COVID-19 who were at increased risk of progression to severe disease due to demographic or underlying clinical characteristics, including renal impairment.[16] Among patients who initiated treatment within 3 days following symptom onset, nirmatrelvir/ritonavir was 89% efficacious at preventing COVID-19–related hospitalization and all-cause death within 28 days.[16] Nirmatrelvir/ritonavir was recently granted EUA in the United States for treatment of mild to moderate COVID-19 in patients who are ≥12 years of age (weighing ≥40 kg) with confirmed COVID-19 and at high risk for progression to severe COVID-19.[17]

Initial pharmacokinetic (PK) studies suggested that when CYP3A metabolism is inhibited by ritonavir, the main route of elimination of nirmatrelvir is by renal excretion.[18] Chronic kidney disease is a key risk factor for severe COVID-19 (refs. 19, 20); because nirmatrelvir/ritonavir is intended for use in patients at high risk for severe disease, including those with renal impairment, this study aimed to evaluate the effects of renal impairment on PK parameters of nirmatrelvir/ritonavir. Findings from this study will influence dosing recommendations for individuals with renal impairment.

METHODS

Study description and participants

This phase I, nonrandomized, open-label, two-part study (NCT04909853) investigated the effects of renal impairment on plasma and urine PK, safety, and tolerability of a single oral dose of nirmatrelvir/ritonavir. Participants were required to be 18 to 75 years of age, have a body mass index of 17.5 to 40 kg/m^2, and have a total body weight of >50 kg. Additional requirements for participants with normal renal function were absence of clinically relevant abnormalities identified by examination, detailed medical history, normal renal function (estimated glomerular filtration rate (eGFR) ≥90 mL/min based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[21]), and demographic similarity (body weight within ±15 kg and age within ±10 years of mean body weight and age of renal impairment group, as well as other demographic characteristics (i.e., sex, race, and ethnicity)) as much as possible to the groups of participants with impaired renal function. Participants categorized as having impaired renal function were required to otherwise be in good general health; other common comorbidities in this population were allowed if controlled based on the opinion of the study investigator. Mild, moderate, and severe renal impairment were defined as eGFR 60 to <90 mL/min, 30 to <60 mL/min, and <30 mL/min, respectively. Participants with severe renal impairment were not included if they required hemodialysis.

Key exclusion criteria included pregnancy/breastfeeding; positive SARS-CoV-2 test at screening or Day −1; history of or positive test for HIV, hepatitis B, or hepatitis C; renal transplant recipients; urinary incontinence without catheterization; and any condition possibly affecting drug absorption. Prohibited prior or concomitant therapies included COVID-19 vaccination within 1 week before dosing or during clinical research unit (CRU) confinement, prescription/nonprescription drugs and dietary/herbal supplements (7 days or 5 half-lives, whichever is longer, before dosing; permitted with sponsor approval if necessary, for participant welfare or on a case-by-case basis), CYP3A4 inducers (28 days before dosing), and medications highly dependent on CYP3A4 for clearance (during dosing).

Study procedures

The study was conducted at four sites according to consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonization Good Clinical Practice guidelines, and applicable laws and regulations. The protocol and related documents were reviewed and approved by an institutional review board or ethics committee before study initiation. Written informed consent was provided by all participants.

The study was conducted in two parts. Part 1 involved initial enrollment of participants with moderate renal impairment, followed by enrollment of participants with mild renal impairment, and healthy participants once preliminary safety and PK data were available in two or more participants with moderate renal impairment. Part 2 included participants with severe renal impairment following preliminary safety and PK analyses of data from Part 1, including two or more participants with moderate renal impairment. When recruiting the Part 2 participants, attempts were made to match the entire group to the participants in Part 1 with respect to age, sex, and body weight, as well as regarding race and ethnicity if possible.

Following screening, eligible participants were admitted to the CRU at Day −1 and remained there for ~3 nights and 4 days until Day 3. To ensure inhibition of CYP3A before nirmatrelvir dosing, participants received a single 100-mg oral dose of ritonavir on the evening of Day −1.

On the morning of Day 1 (i.e., 12 hours after the first dose of ritonavir), participants received 100 mg orally administered nirmatrelvir and 100 mg ritonavir. Additional doses of 100 mg ritonavir were administered 12 and 24 hours after nirmatrelvir dosing to maintain CYP3A inhibition. Both nirmatrelvir and ritonavir were provided as 100-mg tablets.

Pharmacokinetics

Primary PK parameters measured were maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}), percentage of unchanged drug excreted in the urine over 48 hours, and renal clearance (CL_r). Secondary PK measures included plasma concentrations at 12 hours, time to C_{max}, area under the plasma concentration-time profile from time 0 to the time of last measured concentration (AUC_{last}), apparent clearance (CL/F), apparent volume of distribution, and terminal elimination half-life. PK parameters were determined by noncompartmental methods using an in-house proprietary program (oNCA). Methods for population PK simulations for dosing recommendations are included in the Appendix S1.

Blood samples of ~4 mL were collected at 0 (i.e., before dosing), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours following nirmatrelvir administration for plasma PK analyses. Urine samples for additional PK analysis were collected in intervals of ≤24 hours and >24 to ≤48 hours; all urine voided during each interval was collected and mixed for analysis.

Bioanalytical assays

Specific and sensitive bioanalytical methods using liquid chromatography with tandem mass spectroscopy (LC–MS/MS) for simultaneous determination of nirmatrelvir and ritonavir in human plasma and nirmatrelvir in human urine were validated at York Bioanalytical Solutions (York, UK). The calibration curve range for the plasma method was 10.0 to 10,000 ng/mL for nirmatrelvir and 5.00 to 5,000 ng/mL for ritonavir. The calibration curve range for the urine method was 100 to 200,000 ng/mL for nirmatrelvir. The assay validations and study sample analyses were conducted at York Bioanalytical Solutions in compliance with the current US Food and Drug Administration (FDA) and European Medicines Agency Guidance requirements and met acceptance criteria.[22,23] Incurred sample reproducibility assessment was conducted and met acceptance criteria for both human plasma and urine. All clinical samples in both matrices were analyzed within the established stability interval of the analytes.

Human plasma assay methodology. Briefly, nirmatrelvir, ritonavir, and their respective internal standards, PF-07818226 and Ritonavir-d_6 (both stable isotope labeled), were isolated from 100 µL of human plasma (K_2-EDTA) by protein precipitation with acetonitrile, followed by dilution of the precipitant with 0.1% formic acid in acetonitrile:water 40:60 (v/v). The extracted samples were analyzed by turbo ion spray (TISP) ionization LC–MS/MS in positive ionization mode. Chromatographic separation was achieved using a Waters Acquity UPLC BEH column (Waters Corporation, Milford, MA) (C_{18}, 2.1 × 50 mm, 1.7 µM) and gradient elution. The respective lower and upper limits of quantification of the method are 10.0 and 10,000 ng/mL for nirmatrelvir and 5.00 and 5,000 ng/mL for ritonavir, respectively. The selectivity of each analyte at low-quality and high-quality control was demonstrated with the opposite analyte at a concentration of 10,000 ng/mL for nirmatrelvir and 3,000 ng/mL for ritonavir.

Plasma assay performance. In total, 15 analytical runs were conducted for plasma sample analysis, including 1 incurred sample reanalysis run. There were no failed runs; all runs met acceptance criteria. Assay overall (inter-run) precision (percent coefficient of variation) was <10.6% for nirmatrelvir and ≤10.9% for ritonavir, and accuracy (percent relative error) was between −1.1% and 4.7% for nirmatrelvir and between 1.2% and 2.7% for ritonavir for all sample runs. Forty-eight samples (10.9% of all study samples analyzed) were reanalyzed to demonstrate assay reproducibility; 100% were within ±20% difference, with a maximum difference of −17.6% for nirmatrelvir and −14.6% for ritonavir.

Urine assay methodology. Briefly, nirmatrelvir and its internal standard, PF-07818226 (stable isotope labeled), were isolated from 50 µL of human urine by dilution with a 0.1% formic acid in acetonitrile:water 40:60 (v/v) solution. The diluted sample was mixed and centrifuged, and the supernatant (50 µL) was further diluted with a 0.1% formic acid in acetonitrile:water 40:60 (v/v) solution. The extracted samples were analyzed by TISP ionization LC–MS/MS in positive ionization mode. Chromatographic separation was achieved using a Waters Acquity UPLC BEH column (C_{18}, 2.1 × 50 mm, 1.7 µM) and gradient elution. The lower and upper limits of quantification of the method are 100 and 200,000 ng/mL, respectively.

Urine assay performance. In total, 11 analytical runs were conducted for urine sample analysis, including 1 incurred sample reanalysis run. There were no failed runs; all runs met acceptance criteria. Assay overall (inter-run) precision (percent coefficient of variation) was ≤11.4% for sample runs, and accuracy (percent relative error) was between −7.2% and 0.7% for sample runs. Twenty-four samples (35.8% of all study samples analyzed) were reanalyzed to demonstrate assay reproducibility; 100% were within ±20% difference, with a maximum difference of −8.1%.

Safety

Safety and tolerability of nirmatrelvir/ritonavir were assessed in all participants as a secondary objective, with corresponding end points including treatment-emergent adverse events (TEAEs), clinical laboratory tests, vital signs, and electrocardiograms. TEAEs were continually monitored during the 3 days of CRU confinement and during a follow-up phone call at 28 to 35 days following the last ritonavir dose. All other safety end points were evaluated at prespecified timepoints during CRU confinement. Safety evaluations used the safety analysis set, which included all participants assigned who took ≥1 dose of nirmatrelvir.

Statistical analyses

The study aimed to enroll 8 participants into each of the renal impairment groups and 8 to 12 participants with normal renal function based on recommendations from the FDA.[24] Analysis of variance was used to compare the log-transformed AUC_{inf} and C_{max} between the normal renal function group (reference) and groups with renal impairment (test); adjusted mean differences and corresponding 90% confidence intervals were exponentiated to provide the ratios of parameters between the test and reference groups. Additionally, linear regression was used to analyze the potential relationship between PK parameters and eGFR.

RESULTS

Participants

A total of 10, 8, 9, and 8 participants were assigned to treatment within the normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment groups, respectively; 34 of these 35 participants were treated. One participant in the moderate renal impairment group received one dose of ritonavir, but was not treated further owing to an AE that occurred before nirmatrelvir treatment. One participant

Table 1 Participant demographics and physical measurements by renal function group

Characteristic	Normal renal function (*n* = 10)	Mild renal impairment (*n* = 8)	Moderate renal impairment (*n* = 8)	Severe renal impairment (*n* = 8)	Total (*n* = 34)
Age, *n* (%), y					
Mean (SD)	61.1 (3.03)	63.8 (9.07)	62.0 (8.57)	62.1 (9.46)	62.2 (7.45)
Median (range)	62.0 (55, 65)	62.0 (54, 76)	65.0 (47, 72)	62.5 (50, 75)	62.5 (47, 76)
Sex, *n* (%)					
Male	7 (70.0)	5 (62.5)	5 (62.5)	6 (75.0)	23 (67.6)
Female	3 (30.0)	3 (37.5)	3 (37.5)	2 (25.0)	11 (32.4)
Race, *n* (%)					
Black or African American	3 (30.0)	1 (12.5)	6 (75.0)	2 (25.0)	12 (35.3)
White	7 (70.0)	6 (75.0)	2 (25.0)	6 (75.0)	21 (61.8)
Ethnicity, *n* (%)					
Hispanic or Latinx	4 (40.0)	1 (12.5)	0	4 (50.0)	9 (26.5)
Not Hispanic or Latinx	6 (60.0)	7 (87.5)	8 (100.0)	4 (50.0)	25 (73.5)
Weight, kg					
Mean (SD)	90.88 (7.14)	81.23 (9.55)	88.01 (18.87)	85.85 (18.26)	86.75 (13.88)
Median (range)	93.05 (74.5, 97.4)	76.40 (73.0, 99.9)	82.80 (66.3, 113.9)	85.55 (59.1, 110.0)	87.30 (59.1, 113.9)
Body mass index, kg/m^2					
Mean (SD)	29.82 (3.16)	28.59 (5.02)	29.16 (4.66)	29.79 (3.23)	29.37 (3.89)
Median (range)	29.30 (26.5, 36.5)	27.55 (24.5, 40.3)	28.76 (22.9, 35.9)	29.57 (25.6, 35.6)	28.46 (22.9, 40.3)

SD, standard deviation.

in the severe renal impairment group discontinued the study owing to a serious AE (SAE) on Day 2; all other participants completed the study.

The mean age among the 34 treated participants was 62.2 years (SD, 7.45 years), with ~2:1 ratios for male:female sex and White:Black or African American race (**Table 1**). The overall mean weight and body mass index across all groups were 86.75 kg (SD, 13.88 kg) and 29.37 kg/m^2 (SD, 3.89 kg/m^2), respectively.

Pharmacokinetics

Median plasma nirmatrelvir concentration-time profiles for each group are shown in **Figure 1**, with PK parameters for each group summarized in **Table 2**. Compared with the normal renal function group, concentrations of nirmatrelvir were higher in the renal impairment groups, especially in the moderate and severe renal impairment groups, with higher exposures observed with increasing severity of renal impairment (**Figure S1**). When analysis of variance was used for statistical comparisons between groups, the test (i.e., varying degrees of renal function)/reference (i.e., normal renal function) ratios for systemic exposure as measured by AUC_{inf} were 123.8%, 187.4%, and 304.5% for participants with mild, moderate, and severe renal impairment, respectively (**Table 3**). Respective ratios of C_{max} were 129.8%, 138.1%, and 148.0%. CL/F was significantly correlated with eGFR (**Figure 2**), with an intercept of 1.83 ($P = 0.0009$) and slope of 0.05 ($P < 0.0001$). Mean CL/F values for the mild, moderate, and severe renal impairment groups were 5.58, 3.69, and 2.27 L/hour, respectively, compared with 6.91 L/hour for the normal renal function group. Mean terminal elimination half-life values were longer, whereas CL_r values were lower, in the moderate and severe renal impairment groups compared with the normal renal function group. Geometric mean CL_r values decreased by ~47% and 80% in the moderate and severe renal impairment groups, respectively, compared with the normal renal function group. Urinary recovery of unchanged nirmatrelvir over the collection interval of 48 hours

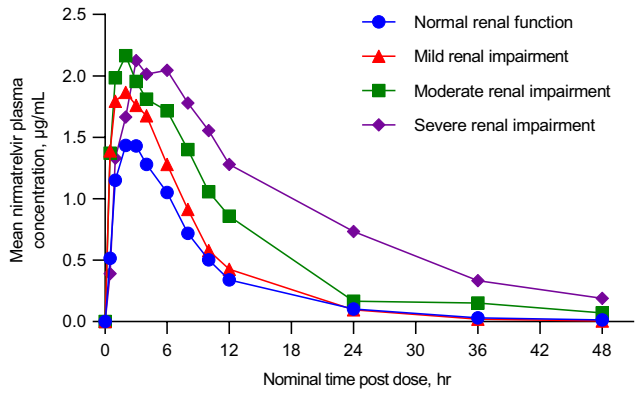

Figure 1 Median plasma nirmatrelvir concentrations over time by renal function group. Participants were given a single dose of 100 mg nirmatrelvir with 100 mg ritonavir. Ritonavir was also administered at 12 hours before dosing, and 12 and 24 hours post dosing to achieve and maintain CYP3A inhibition. CYP3A, cytochrome P450 3A.

Table 2 Descriptive summary of pharmacokinetic parameters by renal function group

Parameter[a]	Normal renal function (n^b = 10)	Mild renal impairment (n^b = 8)	Moderate renal impairment (n^b = 8)	Severe renal impairment (n^b = 8)
N1,[c] n[d]	10, 10	8, 8	8, 6	8, 7
AUC_{inf}, μg·hour/mL	14.46 (20)	17.91 (30)	27.11 (27)	44.04 (33)
AUC_{last}, μg·hour/mL	14.27 (20)	17.77 (30)	26.66 (21)	39.42 (28)
C_{12}, μg/mL	0.34 (35)	0.44 (30)	0.79 (33)	1.21 (33)
CL/F, L/hour	6.91 (20)	5.58 (30)	3.69 (27)	2.27 (33)
C_{max}, μg/mL	1.60 (31)	2.08 (29)	2.21 (17)	2.37 (38)
$t_{1/2}$, hour	7.73±1.8234	6.61±1.5344	9.95±3.4171	13.37±3.3225
T_{max}, hour	2.00 (1.00–4.00)	2.00 (1.00–3.00)	2.50 (1.00–6.00)	3.00 (1.00–6.05)
V_z/F, L	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae_{48}, %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CL_r, L/hour	2.18 (50)	2.40 (33)	1.15 (71)	0.44 (73)

Ae_{48}, amount of unchanged drug excreted in urine over the 48-hour sampling period; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration; C_{12}, plasma concentration at 12 hours post dose; 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; 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]N =total number of participants in the indicated group. [c]N1 = Number of participants contributing to the summary statistics unless n is used. [d]n =Number of participants contributing to the summary statistics for $t_{1/2}$, AUC_{inf}, CL/F, and V_z/F.

was 31.2%, 42.7%, 30.8%, and 18.5% for the normal functional group and mild, moderate, and severe renal impairment groups, respectively.

Population PK simulation for dosing recommendations

It is presumed that maintaining trough concentration (C_{trough}) values above the 90% effective concentration for SARS-CoV-2 would be necessary for therapeutic activity and hence matching C_{trough} values in renal impairment groups to reference group served as a basis for dosing recommendation. Considering the observed PK data, simulations were done using the preliminary population PK model (see Appendix S1) by reducing total body clearance by one-third and one-half in mild and moderate renal impairment groups, respectively. Since nirmatrelvir tablets are currently available in 150-mg strength, the dosing regimens simulated were either 300/100 mg or 150/100 mg nirmatrelvir/ritonavir twice daily for 5 days. Once-daily regimens were also explored but were deemed unsuitable because ritonavir needs to be administered twice daily, which complicates dosing and potentially increases the chance of noncompliance. **Figure 3** shows the Day 5 predicted C_{trough} of nirmatrelvir with reduced clearance and with doses that provided a close approximation of C_{trough} concentrations to that of the control group with no reduction in clearance. There was significant overlap in the individual predicted nirmatrelvir C_{trough} values with clearance

Table 3 Ratio of C_{max} and AUC_{inf} between test and reference groups derived using ANOVA

Parameter	Test	Reference	Adjusted geometric mean		Ratio (test/reference)[a]	90% CI
			Test	Reference		
C_{max}, μg/mL	Mild renal impairment	Normal renal function	2.08	1.60	129.78	(101.93, 165.25)
	Moderate renal impairment	Normal renal function	2.21	1.60	138.12	(113.18, 168.55)
	Severe renal impairment	Normal renal function	2.37	1.60	148.02	(111.40, 196.68)
AUC_{inf}, μg·hour/mL	Mild renal impairment	Normal renal function	17.91	14.46	123.84	(99.64, 153.91)
	Moderate renal impairment	Normal renal function	27.11	14.46	187.40	(148.52, 236.46)
	Severe renal impairment	Normal renal function	44.04	14.46	304.49	(237.60, 390.21)

ANOVA, analysis of variance; AUC_{inf}, area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration.
[a]Ratios and 90% CIs are expressed as percentages.

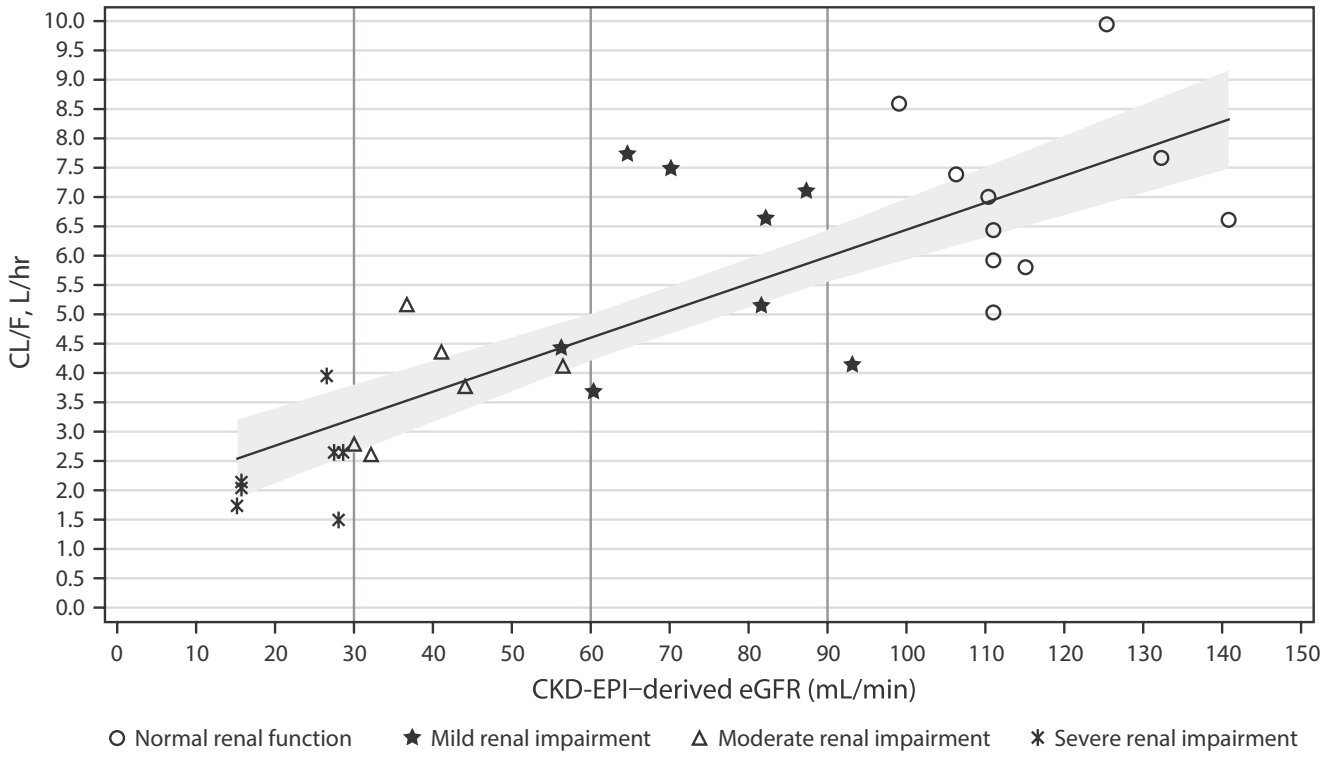

Figure 2 Linear regression plots of plasma nirmatrelvir CL/*F*. The bold line is the predicted regression line; the shaded area represents the 90% confidence region. The vertical lines represent the boundary criteria of the renal function groups. CL/*F*, apparent clearance of drug from plasma; eGFR, estimated glomerular filtration rate.

reduced by one-third (mild renal impairment) and dosing with 300/100 mg nirmatrelvir/ritonavir twice daily, and with clearance reduced by one-half (moderate renal impairment) and dosing with 150/100 mg nirmatrelvir/ritonavir twice daily. In both scenarios, the median C_{trough} values were slightly higher than the reference group, and the vast majority (>95%) of individual predicted C_{trough} values were above the *in vitro* 90% effective concentration (292 ng/mL) for SARS-CoV-2.[10] Slightly higher C_{trough} values are not expected to compromise therapeutic activity of nirmatrelvir. In contrast, significantly higher predicted C_{trough} values were noted in the severe renal impairment group for 150/100 mg nirmatrelvir/ritonavir dose per currently available formulations (data not shown).

In light of these results, no change in dose is recommended for mild renal impairment (i.e., 300/100 mg nirmatrelvir/ritonavir twice daily for 5 days).[25] A dose reduction to 150/100 mg nirmatrelvir/ritonavir twice daily for 5 days is recommended for moderate renal impairment; nirmatrelvir is not currently recommended in severe renal impairment until further PK and safety data are collected and a suitable formulation becomes available.[18]

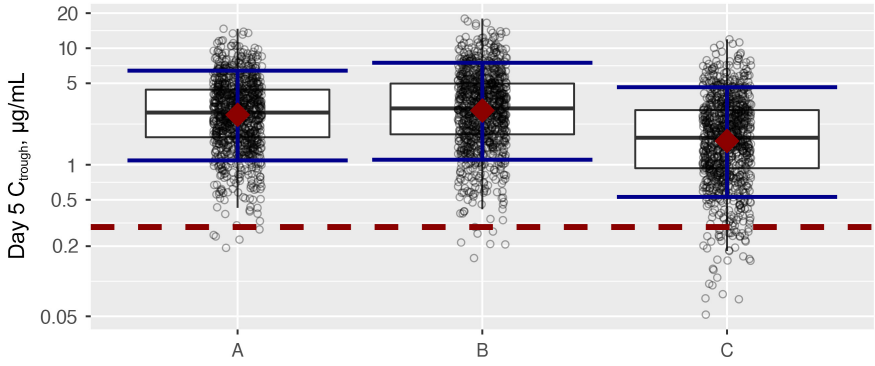

Figure 3 Predicted nirmatrelvir C_{trough} plasma concentrations by dosing regimen and clearance. Open circles represent predicted C_{trough}; red symbols represent group means; blue lines represent 10th and 90th percentiles; red dashed line is EC_{90} of 292 ng/mL for SARS-CoV-2. (**a**) 150/100 mg nirmatrelvir/ritonavir every 12 hours, with clearance reduced by one-half (i.e., moderate renal impairment); (**b**) 300/100 mg nirmatrelvir/ritonavir every 12 hours, with clearance reduced by one-third (i.e., mild renal impairment); (**c**) 300/100 mg nirmatrelvir/ritonavir every 12 hours, with no reduction in clearance (reference group). C_{trough}, trough concentration; EC_{90}, 90% effective concentration; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 4 Treatment-emergent AEs by renal function group: All causalities and treatment related[a]

	Normal renal function (*N* = 10)	Mild renal impairment (*N* = 8)	Moderate renal impairment (*N* = 8)	Severe renal impairment (*N* = 8)
All-causality AEs				
Number of AEs	3	1	1	17
Participants with AEs	2 (20.0)	1 (12.5)	1 (12.5)	5 (62.5)
Participants with SAEs	0	0	0	1 (12.5)
Participants with severe AEs	0	0	0	1 (12.5)
Discontinuations due to AEs	0	0	0	1 (12.5)
Treatment-related AEs[b]				
Participants with AEs	0	0	0	2 (25.0)
Dry mouth	0	0	0	2 (25.0)
Dysgeusia	0	0	0	2 (25.0)

AE, adverse event; SAE, serious AE.
[a]All data are *n* (%). [b]All treatment-related AEs were mild.

Safety

TEAEs are summarized by renal function group and causality in Table 4 and by system organ class, severity, and renal function group in **Table S1**. A total of 22 all-causality TEAEs were reported by 2 (20.0%), 1 (12.5%), 1 (12.5%), and 5 (62.5%) participants across the normal renal function and mild, moderate, and severe renal impairment groups, respectively. The most commonly reported TEAE was headache, which was reported by 2 participants (20.0%) with normal renal function and 1 participant (12.5%) with moderate renal impairment, followed by dry mouth, asthenia, and dysgeusia, each reported by 2 participants (25.0%) with severe renal impairment. All other TEAEs were reported by a single participant. All TEAEs reported in the normal renal function group and the mild and moderate renal impairment groups were mild in severity. In the severe renal impairment group, four of five participants had mild TEAEs. The only TEAEs considered to be treatment related during the study were the two reports each of dry mouth and dysgeusia that occurred in the severe renal impairment group; all four were mild in severity.

A 75-year-old participant with severe renal impairment discontinued the treatment phase of the study owing to acute kidney injury (AKI) and required hospitalization for management of three SAEs: AKI, pneumonia, and pulmonary edema. Other AEs reported for this participant included nonserious AEs of anemia, hyponatremia, and thrombocytopenia. None of the AEs or SAEs in this participant were considered treatment related. This participant had ongoing medical history of diabetes mellitus type 2, hypertension, chronic kidney disease stage 4, metabolic acidosis, anemia, and history of hyperkalemia, renal cell carcinoma, and left nephrectomy. Following completion of study treatment on Day 2, the participant was referred to the emergency department with AEs of AKI, hyperkalemia, and metabolic acidosis. Treatment during hospitalization included oxygen therapy, empiric vancomycin and cefepime for the pneumonia, and furosemide for the pulmonary edema. On Day 5, the pulmonary edema resolved. On Day 7, the SAEs of pneumonia and AKI resolved and the participant was discharged from the hospital. The AUC_{last} (34.3 μg·hour/mL) and C_{max} (1.88 μg/mL) values in this participant were below the median value for the severe renal impairment group.

Overall, there were no significant laboratory trends observed in the study, and no clinically significant findings in vital sign measurements or electrocardiogram assessments.

DISCUSSION

Nirmatrelvir is an antiviral agent for COVID-19 that may address a currently unmet need for effective, orally administered COVID-19 treatments. In this study, individuals with renal impairment experienced increased systemic exposure of nirmatrelvir following a single 100-mg oral dose enhanced with ritonavir compared with individuals with normal renal function. Geometric mean AUC_{inf} values in the moderate and severe renal impairment groups were approximately twofold and threefold higher, respectively, than that of the normal renal function group. Linear regression showed a significant negative correlation between AUC_{inf} and eGFR. Peak plasma concentrations of nirmatrelvir also increased with increasing severity of renal impairment. Similarly, renal clearance of nirmatrelvir was lower in the groups with moderate and severe renal impairment, with geometric mean CL_r values decreased by 47% and 80%, respectively, in these groups compared with the normal renal function group. Nirmatrelvir/ritonavir exhibited an acceptable safety profile across all study groups, with treatment-related AEs all mild in severity and no clinically significant observations in laboratory parameters, vital signs, or electrocardiogram assessments.

When nirmatrelvir is administered with ritonavir, CYP3A4-mediated metabolism is inhibited, resulting in renal elimination becoming the predominant mechanism for systemic clearance of nirmatrelvir. This is in contrast to another protease inhibitor, indinavir, in which renal clearance appears unchanged by enhancement with ritonavir.[25] In this study, the urinary recovery of nirmatrelvir over the 48-hour collection interval was 31.20%, 42.65%, 30.83%, and 18.46% in the reference (normal renal function), mild, moderate, and severe renal impairment groups, respectively. This low urinary recovery is likely due to incomplete oral absorption of the

drug. In an absorption, distribution, metabolism, and excretion study, following a single oral dose of 300/100 mg nirmatrelvir/ritonavir, the amount of drug-related material excreted in the urine and feces over 10 days was 35.3% and 49.6% respectively; this was recovered as mostly unchanged drug in both matrices.[18] The urinary excretion data for the absorption, distribution, metabolism, and excretion study suggest incomplete oral absorption of the drug, which likely explains the low urinary recovery observed in the current study. The lower urinary recovery in the severe renal impairment group compared with the other groups is probably due to the limited collection interval of urine samples for up to 48 hours in this study.

The study was conducted in a small number of participants with a 100-mg dose of nirmatrelvir/ritonavir for comparison of PK and determination of appropriate dosing in renal impairment. In the phase II/III EPIC-HR study, patients with mild renal impairment could enroll in which nirmatrelvir/ritonavir was administered at doses of 300/100 mg twice daily for 5 days.[16] Overall, ~ 16%, 3.8%, and 0.3% of subjects enrolled in EPIC-HR had mild, moderate, and severe renal impairment, respectively. Nirmatrelvir/ritonavir reduced the risk of progression to severe COVID-19 by 89% without evident safety concerns.[16] The most frequent TEAEs in nirmatrelvir/ritonavir recipients were dysgeusia and diarrhea, which occurred more frequently than in placebo recipients.[16] Safety data from EPIC-HR further substantiates dosing in patients with mild and moderate renal impairment.

In summary, this study highlights the importance of the renal pathway in nirmatrelvir clearance and provides guidance for dosing modifications among patients with impaired renal function. Such modifications will help ensure safety and efficacy of nirmatrelvir/ritonavir treatment for COVID-19 in patients with impaired renal function.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

S.S.T., M.B., H.S., O.K., P.L.S.C., N.D., R.R.L., B.C., and B.D. are employees of Pfizer and may hold stock or stock options. J.N., J.M.N. and R.P. declared no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. S.S.T., H.S., O.K., N.D., R.R.L., B.C., and B.D. designed the research. S.S.T., J.M.N., R.A.P., J.N., M.B., H.S., and O.K. performed the research. S.S.T., H.S., O.K., P.L.S.C., R.R.L., and B.D. analyzed the data.

DATA AVAILABILITY STATEMENT

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

1. World Health Organization. WHO coronavirus (COVID-19) dashboard <https://covid19.who.int/> (2021). Accessed December 9, 2021.
2. Docherty, A.B. *et al*. Features of 20,133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* **369**, m1985 (2020).
3. Kim, L. *et al*. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the US coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin. Infect. Dis.* **72**, e206–e214 (2021).
4. Thakur, B. *et al*. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. *Sci. Rep.* **11**, 8562 (2021).
5. US Food and Drug Administration. Emergency use authorization 091 (Casirivimab and Imdevimab) <https://www.fda.gov/media/145610/download> (2022). Accessed June 30, 2022.
6. US Food and Drug Administration. Emergency use authorization 094 (Bamlanivimab and Etesevimab) <https://www.fda.gov/media/145801/download> (2022). Accessed June 30, 2022.
7. US Food and Drug Administration. Emergency use authorization 100 (Sotrovimab) <https://www.fda.gov/media/149532/download> (2022). Accessed June 30, 2022.
8. Hu, B., Guo, H., Zhou, P. & Shi, Z.L. Characteristics of SARS-CoV-2 and COVID-19. *Nat. Rev. Microbiol.* **19**, 141–154 (2021).
9. Merck & Co Inc. Merck and Ridgeback Biotherapeutics provide update on results from MOVe-OUT study of molnupiravir, an investigational oral antiviral medicine, in at risk adults with mild-to-moderate COVID-19 <https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-results-from-move-out-study-of-molnupiravir-an-investigational-oral-antiviral-medicine-in-at-risk-adults-with-mild-to-moderate-covid-19/> (2021). Accessed June 30, 2022.
10. Owen, D.R. *et al*. An oral SARS-CoV-2 M^{pro} inhibitor clinical candidate for the treatment of COVID-19. *Science* **374**, 1586–1593 (2021).
11. Yang, H. *et al*. Design of wide-spectrum inhibitors targeting coronavirus main proteases. *PLoS Biol.* **3**, e324 (2005).
12. Zhang, L. *et al*. Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved alpha-ketoamide inhibitors. *Science* **368**, 409–412 (2020).
13. Hilgenfeld, R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J.* **281**, 4085–4096 (2014).
14. Anand, K., Ziebuhr, J., Wadhwani, P., Mesters, J.R. & Hilgenfeld, R. Coronavirus main proteinase ($3CL^{pro}$) structure: basis for design of anti-SARS drugs. *Science* **300**, 1763–1767 (2003).
15. US Food and Drug Administration. Highlights of prescribing information, NORVIR (ritonavir) <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209512lbl.pdf> (2017). Accessed June 30, 2022.
16. Hammond, J. *et al*. Oral Nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N. Engl. J. Med.* **386**, 1397–1408 (2022).
17. US Food and Drug Administration. FDA to hold advisory committee meeting to discuss Merck and Ridgeback's EUA application for COVID-19 oral treatment <https://www.fda.gov/news-event

s/press-announcements/fda-hold-advisory-committee-meeting-discuss-merck-and-ridgebacks-eua-application-covid-19-oral> (2021). Accessed June 30, 2022.
18. Pfizer Inc. Fact sheet for healthcare providers: emergency use authorization for Paxlovid <https://www.fda.gov/media/155050/download> (2021). Accessed February 8, 2022.
19. ERA-EDTA Council & ERACODA Working Group Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol. Dial. Transplant.* **36**, 87–94 (2021).
20. Clark, A. *et al*. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. *Lancet Glob. Health* **8**, e1003–e1017 (2020).
21. Orskov, B. *et al*. Estimating glomerular filtration rate using the new CKD-EPI equation and other equations in patients with autosomal dominant polycystic kidney disease. *Am. J. Nephrol.* **31**, 53–57 (2010).
22. US Food and Drug Administration. Guidance for industry: bioanalytical method validation <https://www.fda.gov/files/drugs/published/Bioanalytical-Method-Validation-Guidance-for-Industry.pdf> (2018). Accessed June 30, 2022.
23. European Medicines Agency. Guideline on bioanalytical method validation <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf> (2011). Accessed June 30, 2022.
24. US Food and Drug Administration Pharmacokinetics in patients with impaired renal function — study design, data analysis, and impact on dosing and labeling <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing-and> (2020). Accessed June 30, 2022.
25. Hsu, A. *et al*. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrob. Agents Chemother.* **42**, 2784–2791 (1998).