00658 Extended Nirmatrelvir/Ritonavir Treatment Durations for Immunocompromised Patients With COVID-19

Edward Weinstein,[1]* Annie Gardner,[1] Mary Almas,[1] Mary Lynn Baniecki,[2] Shunjie Guan,[2] Elena Tudone,[3] Simone Antonucci,[3] Kevin Gregg,[4] Roger Paredes,[5] Carolina Garcia-Vidal,[6] Adrian Camacho,[7] Wayne Wisemandle,[1] Steven G. Terra,[1] Jennifer Hammond,[1] James Rusnak[8]

[1]Pfizer Research & Development, Pfizer Inc, New York, NY, USA; [2]Pfizer Research & Development, Pfizer Inc, Cambridge, MA, USA; [3]Pfizer Italia srl, Milan, Italy; [4]University of Michigan Health, Ann Arbor, MI, USA; [5]Hospital Germans Trias i Pujol, Badalona, Spain; [6]Hospital Clínico de Barcelona, Barcelona, Spain; [7]Hospital Universitario Dr. José E. González, Monterrey, Mexico; [8]Pfizer Research & Development, Pfizer Inc, Pearl River, NY, USA

*Presenting Author (edward.weinstein@pfizer.com)

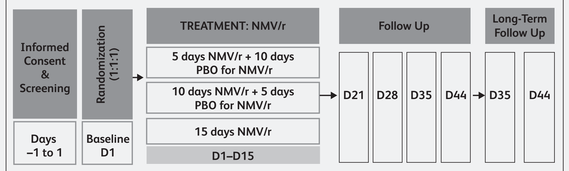
Background

- COVID-19 remains endemic in many countries and is a persistent threat to global health (accounted for >21,000 new hospitalizations/week and 2.7% of deaths in the United States alone from February 4–10, 2024).[1,2]
- Nirmatrelvir/ritonavir (NMV/r; Pfizer Inc) is a first-line oral treatment (taken twice daily for 5 days) comprising an antiviral (nirmatrelvir), which is a potent inhibitor of the SARS-CoV-2 main protease (M^{pro}), and pharmacokinetic enhancer (ritonavir) recommended for treatment of mild to moderate COVID-19 in adults at high risk of progression to severe disease.[3,4]
  - Under the Emergency Use Authorization, NMV/r has also been approved for use in adolescents ≥12 years of age weighing ≥40 kg with mild to moderate COVID-19 at high risk of progression to severe disease.[5]
- Immunocompromised (IC) individuals, who are at high risk of severe COVID-19 complications,[6] are less likely to mount a robust immune response if infected and could potentially benefit from an extended dosing regimen of NMV/r.
- This study compared efficacy and safety of the approved 5-day regimen of NMV/r with 10- and 15-day regimens in patients who are IC.

Methods

- In a multinational, randomized, double-blind, phase 2 study (NCT05438602), patients received NMV/r (300/100 mg) or placebo twice daily. Nasopharyngeal (NP) swabs for PCR assessment and rapid antigen testing (RAT) were collected or completed at baseline and on Days 5, 10, 15, 21, 28, 35, and 44 **(Figure 1)**.

Figure 1. Study Design



D, study day; NMV/r, nirmatrelvir/ritonavir; PBO, placebo.

- The study population comprised nonhospitalized IC males/females ≥12 years of age and weighing ≥40 kg who met the following eligibility criteria:
  - Confirmed SARS-CoV-2 infection within 5 days of study entry
  - ≥1 COVID-19 sign/symptom present on the day of randomization
  - Immunocompromised by ≥1 of the following:
    - Immunosuppressive drug/biologic treatment associated with receiving a solid organ transplant, chemotherapy, or immune cell-depletion therapy (eg, CAR-T)
    - Moderate to severe primary immunodeficiency
    - HIV infection with CD4 cell count <200 mm^3
    - Recent/current corticosteroid treatment
  - A subgroup of participants was considered severely IC due to receipt of CAR-T or B-cell depleting therapies, receiving a hematopoietic stem cell transplant, or having hematologic malignancies.
  - Participants who were categorized as IC based only on receiving corticosteroids or tumor necrosis factor (TNF) inhibitors were considered less severely IC, and their enrollment was capped at approximately 25%.
- The primary endpoint was the proportion of patients with NP SARS-CoV-2 RNA VL < lower limit of quantitation (LLOQ) from Days 15–44; this was evaluated in all patients receiving ≥1 treatment dose (ie, evaluable analysis set [EAS]).
- Secondary endpoints included VL rebound and changes over time, COVID-19–related hospitalizations/deaths (through Day 28), and treatment safety; RAT positivity and M^{pro} mutations were also assessed.
  - Safety analyses were performed on the safety analysis set (SAS), which included all patients receiving ≥1 treatment dose, but with some participants removed due to data quality issues.
  - Rebound was defined as a ≥0.5 log_{10} copies/mL increase relative to end of treatment with follow-up VL ≥2.5 log_{10} copies/mL.
- A post hoc analysis of the primary and secondary efficacy endpoints was also evaluated in the subset of those who were severely IC.
- SARS-CoV-2 RNA levels (VL) in all swabs were quantified by PCR at the University of Washington Retrovirology Laboratory, with an LLOQ of 2.0 log_{10} copies/mL. RAT was performed at the study visit site.
- No formal hypothesis testing was undertaken; therefore, sample size was based on the desired precision of the primary endpoint estimate.

Results

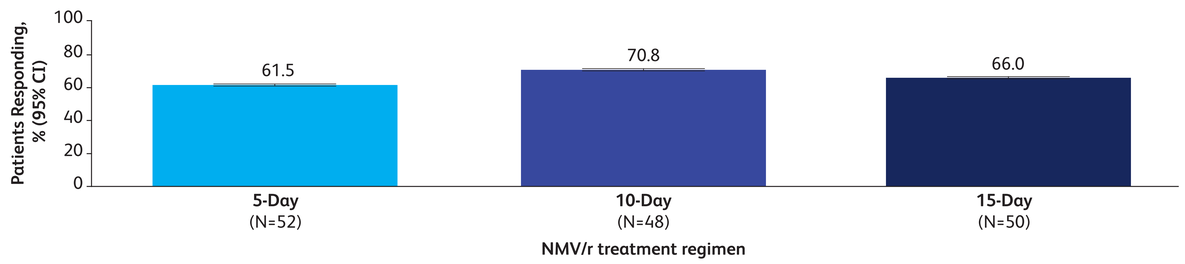
- 156 patients were enrolled (**Table 1**). The SAS comprised 155 patients, from which 5 were excluded because of quality issues; thus 150 (96.2%) patients were included in the EAS.
- Most patients were IC due to immunosuppressant drug therapy (88.5%) or hematologic malignancies (34.6%); 38.0% of patients (n=57) were identified as severely IC.
- 92.3% of patients had baseline VLs ≥2 log_{10} copies/mL.
- A numerically higher median (range) baseline VL was observed in the 15-day treatment group (7.29 [0–9]) vs the 5- and 10-day groups.

Copyright ©2024. All rights reserved.

Main Finding of Study

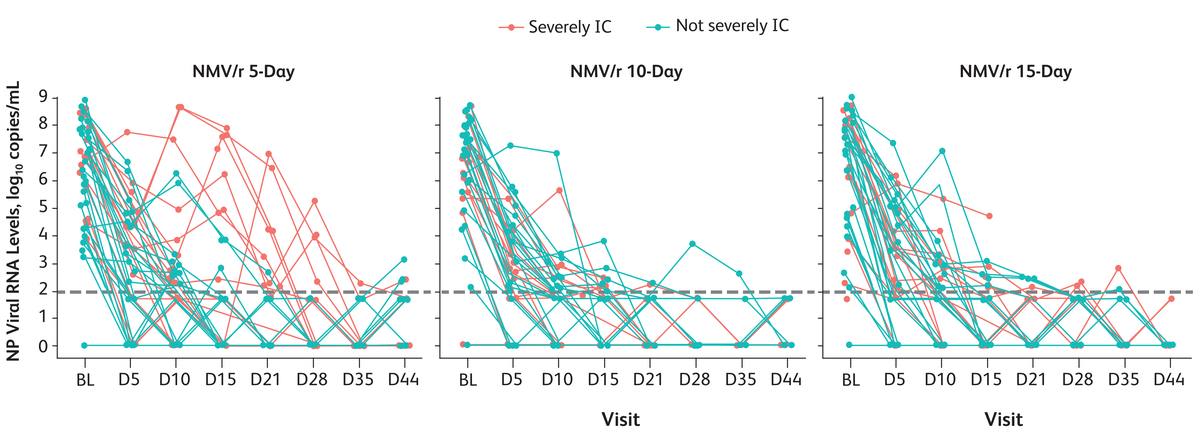
SARS-CoV-2 viral load is sufficiently controlled by the approved 5-day course of nirmatrelvir/ritonavir in patients who are mildly or moderately immunocompromised, but extending the duration of treatment may improve the control of viral load in patients who are severely immunocompromised.

Figure 2. Proportions of Patients Receiving Each NMV/r Dosing Regimen With SARS-CoV-2 RNA Levels ≤2.0 log_{10} Copies/mL From Day 15 Through Day 44 (EAS)



EAS, evaluable analysis set; NVM/r, nirmatrelvir with ritonavir.
Missing data were imputed as treatment failure.

Figure 3. Log_{10}-Nasopharyngeal SARS-CoV-2 RNA Levels Over Time by NMV/r Treatment Duration (EAS)



BL, baseline; D, day; EAS, evaluable analysis set; IC, immunocompromised; LLOQ, lower limit of quantification; NMV/r, nirmatrelvir/ritonavir; NP, nasopharyngeal; VL, viral load.
Gray dashed line represents the LLOQ (2.0 log_{10} copies/mL).

Table 1. Baseline Demographics and Clinical Characteristics of the Study Population

Characteristic	Treatment Regimen 5-Day (N=54)	10-Day (N=51)	15-Day (N=51)
Age, y, median (range)[a]	58 (19–80)	58 (16–82)	58 (28–80)
Female, n (%)	28 (51.9)	30 (58.8)	26 (51.0)
White race, n (%)	50 (92.6)	47 (92.2)	44 (86.3)
BMI, kg/m^2, median (range)	27.6 (18–45)	28.0 (17–48)	25.0 (16–46)
Not vaccinated against COVID-19 within 6 mo before randomization, n (%)	47 (87.0)	43 (84.3)	42 (82.4)
SARS-CoV-2 NP RNA ≥2 log_{10} copies/mL, n (%)	49 (90.7)	47 (92.2)	48 (94.1)
SARS-CoV-2 NP RNA ≥7 log_{10} copies/mL, n (%)	20 (37.0)	22 (43.1)	28 (54.9)
SARS-CoV-2 NP RNA, log_{10} copies/mL, median (range)	6.64 (0–9)	6.81 (0–9)	7.29 (0–9)
Severely IC, evaluable analysis set, n (%)[b,c]	20 (38.5)	17 (35.4)	20 (40.0)
Reason for IC, n (%)[d]			
Immunosuppressant drug therapy	46 (85.2)	46 (90.2)	46 (90.2)
Hematologic malignancy	19 (35.2)	15 (29.4)	20 (39.2)
Corticosteroids or TNF inhibitors	11 (20.4)	9 (17.6)	10 (19.6)

BMI, body mass index; IC, immunocompromised; NVM/r, nirmatrelvir with ritonavir; NP, nasopharyngeal; TNF, tumor necrosis factor.
[a] 69.2% of the population was <65 years of age at randomization.
[b] Number of participants for this category represent the evaluable analysis set (all randomized participants who received ≥1 dose of the study intervention): 5-day, N=52; 10-day, N=48; 15-day, N= 50.
[c] Hematologic malignancy was the most common condition (54/57 [94.7%] patients).
[d] Participants could be included in >1 category.

Results (continued)

- Overall, >60% of participants responded from Day 15 through Day 44 based on NP swab RNA levels (**Figure 2**).
- In patients who were severely IC, improved control of VL was observed with both extended treatment regimens compared to the standard 5-day treatment **(Figure 3)**.
  - VL was similarly well controlled across all treatment durations in patients who were non-severely IC.
- Improvements in VL were similar across treatment regimens among individuals who were non-severely IC.
- In patients classified as severely IC, longer treatment regimens provided better VL improvements.
- The median time to sustained NP SARS-CoV-2 RNA <LLOQ was numerically longer for patients who were severely IC in the 5-day treatment group compared with the 10-day and 15-day groups (**Table 2**).
  - Similarly, the numbers of patients with rebound and RAT positivity were numerically higher for those non-severely and severely IC in the 5-day vs 10- and 15-day groups.

Table 2. VL and RAT Positivity by Treatment Duration and Severity of IC

Post hoc assessment	5-Day		10-Day		15-Day	
	Severe N=20	Non-Severe N=32	Severe N=17	Non-Severe N=31	Severe N=20	Non-Severe N=30
Sustained NP RNA <LLOQ from Day 15 to 44, n/N (%)	7/20 (35.0)	25/32 (78.1)	11/17 (64.7)	23/31 (74.2)	8/20 (40.0)	25/30 (83.3)
Rebound, n/N (%)[a]	5/20 (25.0)	4/32 (12.5)	0/17 (0)	1/31 (3.2)	1/20 (5.0)	0/30 (0)
Any positive RAT from Day 15 to 44, n/N (%)	6/18 (33.3)	1/30 (3.3)	1/17 (5.9)	0	0	0
Any targeted symptom and positive RAT from Day 15 to 44, n/N (%)	6/18 (33.3)	1/30 (3.3)	1/16 (6.3)	0	0	0
Median time to first sustained viral RNA <LLOQ, days	28	10	13	11	15	9

IC, immunocompromised; LLOQ, lower limit of quantitation; NP, nasopharyngeal; RAT, rapid antigen test; VL, viral load.
[a] Rebound was defined as a ≥0.5 log_{10} copies/mL increase relative to end of treatment with follow-up VL ≥2.5 log_{10} copies/mL.

- No deaths occurred through Day 44; hospitalization of the 2 severely IC patients in the 5-day group due to COVID-19 occurred before Day 28.
- Currently, no M^{pro} mutations with the potential to reduce NMV susceptibility activity were identified.
- Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) with extended NMV/r treatment was within the range of results reported from previous placebo-controlled clinical trials of 5-day regimens.[7]
  - Treatment-related AEs occurred in 28 (52.8%), 34 (66.7%), and 31 (60.8%) patients in the 5-, 10-, and 15-day treatment groups, respectively.
  - There was no increase in the incidence of SAEs associated with longer treatment duration.

Conclusions

- The approved 5-day treatment course of NMV/r appears to be adequate for SARS-CoV-2 viral clearance in patients who are not severely IC.
- Extending NMV/r treatment beyond 5 days may improve SARS-CoV-2 viral clearance in patients who are severely IC.
- Extending the duration of NMV/r treatment beyond 5 days was not associated with new safety signals.

References: 1. Centers for Disease Control and Prevention. COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#datatracker-home. Accessed February 20, 2024. **2.** World Health Organization. WHO COVID-19 dashboard. Available at: https://data.who.int/dashboards/covid19/cases?n=c. Accessed February 20, 2024. **3.** Paxlovid (nirmatrelvir/ritonavir), Full Prescribing Information, Pfizer Inc, New York, NY, Revised May, 2023. **4.** COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at: https://www.covid19treatmentguidelines.nih.gov/. Accessed February 2, 2024. **5.** US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for PAXLOVID™. Available at: https://labeling.pfizer.com/ShowLabeling.aspx?id=16474. Accessed December 6, 2022. **6.** Schneider J, et al. *Expert Rev Anti Infect Ther*. 2023; doi: 10.1080/14787210.2023.2296067:1-3. **7.**Tian H, et al. *Rev Med Virol*. 2023;33(5):e2473.

Financial disclosure: EW, SA, WW, SGT, JH, and JR are employees of Pfizer and may hold stock or stock options. KG, RP, and GC-V report no conflicts of interest.

Acknowledgements: This study was sponsored by Pfizer Inc. Medical writing support was provided by Andrew Ray, PhD, of ICON (Blue Bell, PA) and was funded by Pfizer.

For more information, please contact: Edward Weinstein, MD, PhD, Global Clinical Lead, Antivirals Pfizer Inc, 66 Hudson Blvd E, New York, NY 10001, USA, (443) 766-3724, edward.weinstein@pfizer.com

Presented at the Conference on Retroviruses and Opportunistic Infections; March 3–6, 2024; Denver, CO, USA