JAMA Internal Medicine | **Original Investigation**

Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection
The STOP-PASC Randomized Clinical Trial

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➕ **Visual Abstract**

➕ **Supplemental content**

IMPORTANCE There is an urgent need to identify treatments for postacute sequelae of SARS-CoV-2 infection (PASC).

OBJECTIVE To assess the efficacy of a 15-day course of nirmatrelvir-ritonavir in reducing the severity of select PASC symptoms.

DESIGN, SETTING, AND PARTICIPANTS This was a 15-week blinded, placebo-controlled, randomized clinical trial conducted from November 2022 to September 2023 at Stanford University (California). The participants were adults with moderate to severe PASC symptoms of 3 months or longer duration.

INTERVENTIONS Participants were randomized 2:1 to treatment with oral nirmatrelvir-ritonavir (NMV/r, 300 mg and 100 mg) or with placebo-ritonavir (PBO/r) twice daily for 15 days.

MAIN OUTCOMES AND MEASURES Primary outcome was a pooled severity of 6 PASC symptoms (fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, and cardiovascular symptoms) based on a Likert scale score at 10 weeks. Secondary outcomes included symptom severity at different time points, symptom burden and relief, patient global measures, Patient-Reported Outcomes Measurement Information System (PROMIS) measures, orthostatic vital signs, and sit-to-stand test change from baseline.

RESULTS Of the 155 participants (median [IQR] age, 43 [34-54] years; 92 [59%] females), 102 were randomized to the NMV/r group and 53 to the PBO/r group. Nearly all participants (n = 153) had received the primary series for COVID-19 vaccination. Mean (SD) time between index SARS-CoV-2 infection and randomization was 17.5 (9.1) months. There was no statistically significant difference in the model-derived severity outcome pooled across the 6 core symptoms at 10 weeks between the NMV/r and PBO/r groups. No statistically significant between-group differences were found at 10 weeks in the Patient Global Impression of Severity or Patient Global Impression of Change scores, summative symptom scores, and change from baseline to 10 weeks in PROMIS fatigue, dyspnea, cognitive function, and physical function measures. Adverse event rates were similar in NMV/r and PBO/r groups and mostly of low grade.

CONCLUSIONS AND RELEVANCE The results of this randomized clinical trial showed that a 15-day course of NMV/r in a population of patients with PASC was generally safe but did not demonstrate a significant benefit for improving select PASC symptoms in a mostly vaccinated cohort with protracted symptom duration. Further studies are needed to determine the role of antivirals in the treatment of PASC.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05576662

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Postacute sequelae of SARS-CoV-2 infection (PASC), also known as *long COVID* or *post–COVID-19 condition*, has affected millions of people worldwide and encompasses a variety of conditions and symptoms that can persist months to years with impact on quality of life and function.[1-6] Evolving definitions, growing mechanistic understanding, and clinical heterogeneity present challenges to the diagnosis and treatment of PASC.[7-9] There is an urgent need for evidence-based treatments for PASC but currently a paucity of published trials testing interventions that target underlying pathophysiology.[10-13]

SARS-CoV-2 virus or viral particle persistence is one of several proposed casual mechanisms for PASC.[14-17] Prolonged SARS-CoV-2 viral RNA shedding for months in the upper respiratory tract and in the stool has been observed.[18-21] Although no reservoir of live replicating virus has been identified in individuals with PASC, SARS-CoV-2 RNA and/or protein has been found to persist in various tissues such as blood,[22-24] periodontal pockets,[25] gastrointestinal tract,[26,27] the central nervous system,[28] and other anatomic sites.[28-32] Residual viral presence may trigger ongoing inflammation and immune dysregulation, resulting in a diverse array of symptoms.[17] Thus, antiviral agents against SARS-CoV-2 present a therapeutic avenue for investigation to address a potential root cause of PASC.

Some studies suggest that antivirals such as nirmatrelvir, molnupiravir, and remdesivir taken during the acute infection period may reduce the risk of select post–COVID-19 sequelae,[33-36] while others demonstrate mixed results in different cohorts.[37-39] Nirmatrelvir is a peptidomimetic inhibitor of SARS-CoV-2 main protease (M^{pro}) preventing viral replication. Nirmatrelvir, in combination with low-dose ritonavir that slows nirmatrelvir metabolism via inhibition of *CYP3A4* (nirmatrelvir-ritonavir), was approved by the US Food and Drug Administration for the treatment of mild to moderate COVID-19 in adults at high risk for progression to severe COVID-19.[40] We and others have reported anecdotal cases of patients with PASC who noted improvement of symptoms after taking nirmatrelvir-ritonavir for SARS-CoV-2 reinfection,[41,42] but there are no published randomized clinical trials testing nirmatrelvir-ritonavir for treatment of PASC.

The landscape of PASC research is dynamic. Smaller studies that are more focused and agile can scout the terrain ahead of larger and more definitive studies. The objectives of the Selective Trial of Paxlovid for PASC (STOP-PASC) were to assess the effect of a 15-day course of NMV/r vs PBO/r in improving PASC symptoms and other patient-reported outcomes. The secondary and exploratory objectives were to explore the potential biologic and digital wearable biomarkers of PASC and to collect multidimensional data to inform future research.

Methods

This randomized clinical trial was approved by the Stanford Institutional Review Board. All participants gave written informed consent. A Community Advisory Board that included patients with PASC provided input on the study. A data and safety monitoring board provided independent oversight. The

Key Points

Question What is the efficacy of 15 days of nirmatrelvir-ritonavir for improving select symptoms of postacute sequelae of SARS-CoV-2 infection (PASC)?

Findings This randomized clinical trial including 155 participants with PASC symptoms (≥3 months' duration) found that a 15-day course of nirmatrelvir-ritonavir in a mostly vaccinated study cohort was generally safe, but did not show significant benefit in improving fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, or gastrointestinal symptoms.

Meaning These findings indicate that further studies are needed to determine the role of antivirals in the treatment of PASC.

study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Study Design

STOP-PASC was a double-blind randomized clinical trial to investigate orally administered nirmatrelvir-ritonavir (NMV/r) compared with placebo-ritonavir (PBO/r) in outpatient adult participants with PASC of 3 or more months' duration. The trial was conducted from November 8, 2022, to September 12, 2023, at Stanford University (California). The full trial protocol, statistical plan, and trial schematic are available in Supplements 1 and 2 and in eFigure 1 in Supplement 3, respectively.
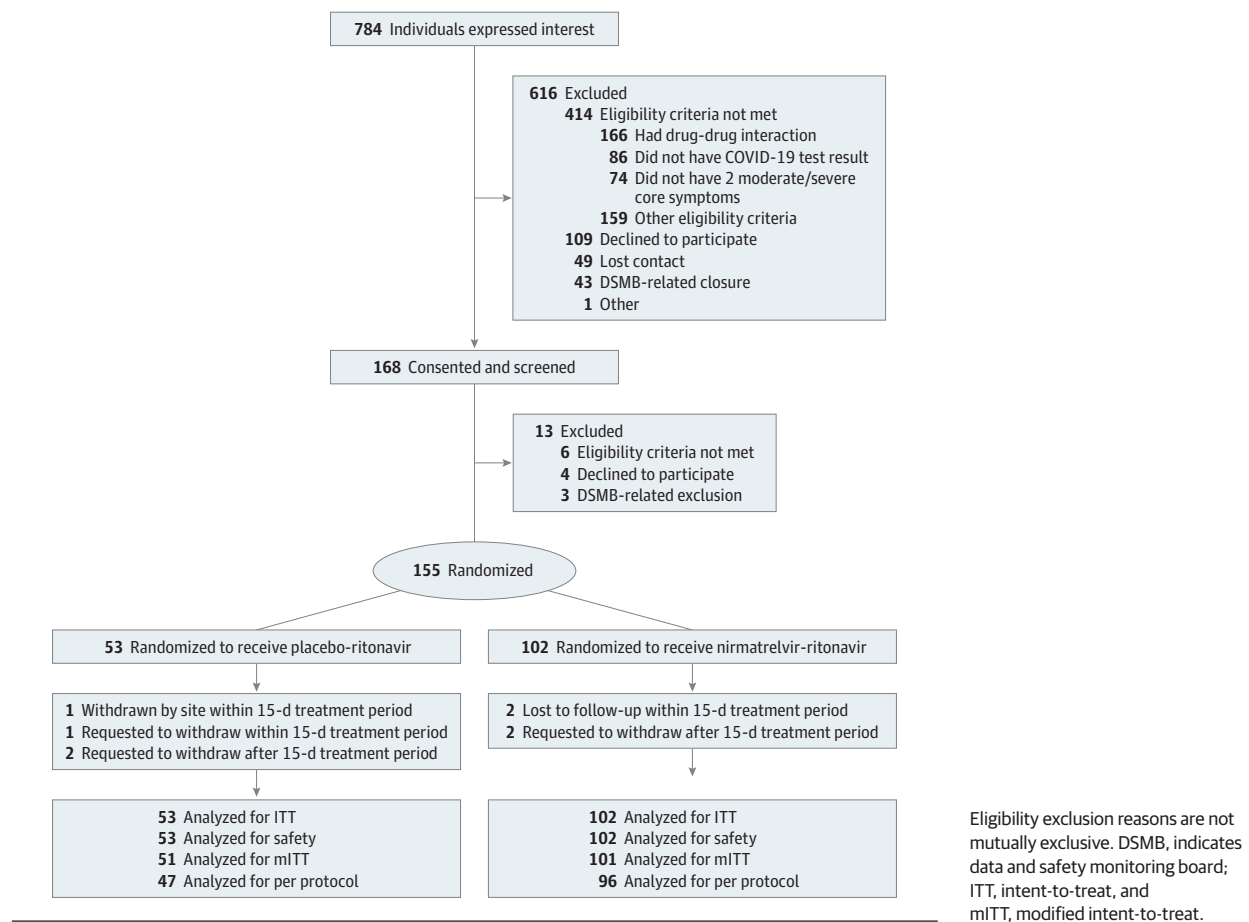
Trial Participants

Participant inclusion criteria were being 18 years or older; weight greater than 40 kg; estimated glomerular filtration rate of 60 mL/min or higher; history of confirmed COVID-19 infection from early 2020 to more than 90 days before the end of enrollment; and PASC symptoms, as determined by clinician, persisting more than 90 days after the initial (index) COVID-19 infection and with at least 2 self-reported moderate or severe core symptoms or symptom clusters defined as fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, and gastrointestinal symptoms. Key exclusion criteria included pregnancy or breastfeeding, severe liver disease, SARS-CoV-2 infection, and use of SARS-CoV-2–specific treatment within 30 days of randomization, SARS-CoV-2 vaccination within 28 days, or other vaccine within 14 days of randomization, or medications that interact with study drug. Full eligibility criteria are available in Supplement 1.

Between November 2022 and May 2023, a total of 784 individuals were prescreened of whom 168 proceeded to consent and screening (**Figure 1**). Eligible participants were randomized 2:1 to NMV/r and PBO/r and included in the intent-to-treat analyses. Enrollment was stopped early in June 2023 when the prespecified threshold for futility had been met (conditional power <10%).

Randomization and Interventions

Participants were randomized 2:1 to receive nirmatrelvir, 300 mg, with ritonavir, 100 mg, or placebo with ritonavir, 100 mg, taken orally twice daily for 15 days and followed up until

Figure 1. CONSORT Diagram

784 Individuals expressed interest

616 Excluded
414 Eligibility criteria not met
166 Had drug-drug interaction
86 Did not have COVID-19 test result
74 Did not have 2 moderate/severe core symptoms
159 Other eligibility criteria
109 Declined to participate
49 Lost contact
43 DSMB-related closure
1 Other

168 Consented and screened

13 Excluded
6 Eligibility criteria not met
4 Declined to participate
3 DSMB-related exclusion

155 Randomized

53 Randomized to receive placebo-ritonavir

1 Withdrawn by site within 15-d treatment period
1 Requested to withdraw within 15-d treatment period
2 Requested to withdraw after 15-d treatment period

53 Analyzed for ITT
53 Analyzed for safety
51 Analyzed for mITT
47 Analyzed for per protocol

102 Randomized to receive nirmatrelvir-ritonavir

2 Lost to follow-up within 15-d treatment period
2 Requested to withdraw after 15-d treatment period

102 Analyzed for ITT
102 Analyzed for safety
101 Analyzed for mITT
96 Analyzed for per protocol

Eligibility exclusion reasons are not mutually exclusive. DSMB, indicates data and safety monitoring board; ITT, intent-to-treat, and mITT, modified intent-to-treat.

15 weeks from randomization, stratified by the number of moderate or severe core symptoms (2 or 3 vs >3) and vaccination status (completed primary series vs not completed).[43] Additional details are included in the eMethods in Supplement 3. A schedule of events, including assessments and procedures, are detailed in Supplement 1 and eFigure 1 in Supplement 3.

Outcomes

The primary end point was core symptoms severity during the past 7 days based on Likert scale score (where 0 is none, 1 mild, 2 moderate, 3 severe) pooled at 10 weeks postrandomization in participants treated with NMV/r vs PBO/r (eMethods in Supplement 3). Core symptoms were selected based on mechanistic rationale, clinical experience, and reported PASC symptoms prevalence and severity.[5,44-47] A 10-week time point was chosen to assess durability of response to treatment.

Secondary end points included individual core symptom severity at 10 weeks and other time points, proportion of participants reporting relief (defined as reduction of severity from moderate to none or severe to mild or none for at least 1 core symptom) or alleviation (improvement of all core symptoms from none or mild at baseline to none or moderate to severe to none or mild) at 10 weeks, severity of most bothersome symptom, time to relief of each core symptom, change from baseline to 10 weeks in Patient-Reported Outcomes Measure-

ment Information System (PROMIS) SF v2.0 Physical Function 4a; SF v1.0 Fatigue 7a; SF v1.0 Dyspnea Severity 5a; SF v2.0 Cognitive Abilities 4a scores[48]; change in orthostatic vital signs (seated and standing blood pressure and heart rate); sit-to-stand test at 10 weeks[49]; and Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at day 15, week 5, week 10, and week 15 in NMV/r vs PBO/r groups.[50] Exploratory stool reverse transcription polymerase chain reaction was performed on all available baseline samples (eMethods in Supplement 3).

Statistical Analysis

The primary analysis followed the intent-to-treat (ITT) principle. Sensitivity analyses were conducted excluding (1) participants with no follow-up (modified ITT) and (2) participants with no follow-up and those taking more than 80% of intervention doses (per protocol).

The primary analysis involved first fitting a proportional odds logistic regression model for severity level of each core symptom at week 10. Each model was adjusted for baseline severity of the corresponding symptom and fit using only participants who experienced the corresponding symptoms at baseline. If participants missed the week-10 survey, their week 9 survey during the week-10 visit window was used for the primary analysis. A test statistic measuring the overall efficacy

was calculated as the weighted average of the regression coefficient for the treatment indicator in the proportional odds model for each core symptom with inverse variance weighting.[51,52] The P value for testing the overall efficacy was obtained by a nonparametric permutation test.

We initially determined that a sample size of 200 would provide power of at least 77% at the 2-sided significance level of P = .05 to detect an odds ratio (OR) of 1.6 for having a better Likert scale score at week 10 (NMV/r vs PBO/r) across all 6 core symptoms, assuming 10% attrition. An interim analysis for futility and safety was preplanned after 50% of participants completed week 10 with enrollment to be stopped if conditional power for concluding efficacy was less than 10% assuming that the underlying treatment effect size was the same as that observed in the interim analysis.

Proportional odds models were used to compare ordinal secondary end points. Linear regression was used to compare PGIS, PGIC, PROMIS measures, 1 minute sit-to-stand test, orthostatic vital signs, and the sum of the Likert scale scores for the core symptoms (summative score). Logistic regression was used to compare the probability of experiencing relief and the proportion of weeks with mild or no symptoms. Cox proportional hazards models were used to compare the time to relief of the most bothersome symptom and the core symptoms. Participants who did not experience any relief were right censored at the time of their last observation. We used a cumulative link mixed model with a participant-specific random intercept to compare the trajectory of symptoms between study groups in an exploratory analysis. In a post hoc analysis, we repeated selected analyses (the primary outcome, the proportion of weeks with mild or no symptoms, and PGIC) separately in patients who had their index infection before December 2021 and in patients who were infected later when the Omicron variant was dominant.

All models were adjusted for the stratification factor, ie, the number of moderate to severe core symptoms at baseline (2 or 3 vs >3), except the primary analysis and the proportion of weeks where participants had mild or no symptoms, where we adjusted for baseline severity instead. All tests were performed at the 2-sided .05 significance level. Analyses were performed in R, version 4.2.1 (The Foundation for Statistical Computing).[53]

Additional analysis information is included in Supplement 2 and the eMethods in Supplement 3. Per prespecified analysis plan, P values for secondary and exploratory analyses were not adjusted for multiple comparisons because these end points were intended to provide a global picture of the treatment effect, and therefore, individual secondary outcomes should be interpreted as exploratory given potential inflation for type I error due to multiple comparisons.

Results

Study Population

Among the 155 participants randomized (median [IQR] age, 43 [34-54] years), there were 92 (59.4%) females and 63 (40.6%) males, with 20 (12.9%) Asian, 3 (1.9%) Black, 19

(12.3%) Hispanic, 1 (1%) Native Hawaiian or other Pacific Islander, 115 (74.2%) White, and 6 (3.9%) participants of more than one race; for 10 participants' (6.5%) race was unknown. The 2 groups were similar with respect to baseline characteristics (Table 1). The mean (SD) time between index SARS-CoV-2 infection and randomization was 17.5 (9.1) months. Only 1 participant in each group had not received the initial COVID-19 vaccination series. Before enrollment, 41 participants (26.5%) had used SARS-CoV-2 acute antiviral medication including NMV/r (Table 1). The most common PASC symptoms at enrollment were fatigue, reported by all participants, and brain fog, reported by 148 (95.5%). Overall, baseline severity of symptoms similar in both groups with a slightly higher distribution of severity scores for body aches and lower for cardiovascular and gastrointestinal symptoms in NMV/r than in PBO/r groups (Table 1; Figure 2). No baseline stool specimens had detectable SARS-CoV-2 RNA (eFigure 2 in Supplement 3).

Primary Outcome

At the 10-week primary end point, 99 of 102 participants in the NMV/r group (97.1%) and 49 of 53 participants in the PBO/r group (92.5%) had primary outcome data available. Considering the 6 core symptoms together (fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, gastrointestinal symptoms), there was no statistically significant difference in the pooled symptom severity between NMV/r and PBO/r groups at 10 weeks, adjusted for baseline severity. The 6 core symptoms progressed toward lower severity in both groups (Table 2; Figure 2).

Secondary Outcomes

Evaluating individual symptoms at different time points during 15 weeks resulted in no consistent patterns to distinguish NMV/r from PBO/r groups (eFigures 3 and 4 in Supplement 3). The "most bothersome" core symptoms reported by participants most commonly were fatigue (n = 70; 45.2%) and brain fog (n =38; 24.5%), and there was no significant difference in severity of the most bothersome symptom between the 2 groups at 5 weeks but there were slightly higher odds of a more severe score for those in the NMV/r group compared with those in the PBO/r group at 10 weeks (OR, 1.99; 95% CI, 1.06-3.72; P = .03) and 15 weeks (OR, 2.42; 95% CI, 1.27-4.60; P = .01). There were no statistically significant differences in proportion of participants experiencing relief at 5, 10, and 15 weeks; alleviation at 10 weeks; or time to relief of each core symptom and the most bothersome symptom between the 2 groups (Table 2; eTable 1 in Supplement 3).

Total summative severity scores for all core symptoms at 5, 10, and 15 weeks were similar between the intervention and control groups (eFigure 5 in Supplement 3). Mean severity scores for all core symptoms in both groups generally improved (eFigure 6 in Supplement 3); the difference between groups for the change in severity scores across 15 weeks was statistically significant for brain fog only. A post hoc analysis found no statistically significant difference between the 2 groups in the proportion of total postrandomization weeks with mild or no symptoms for each core symptom when adjusted

Table 1. Baseline Characteristics of Study Participants With Postacute Sequelae of SARS-CoV-2 Infection

Characteristic	No. (%)		
	NMV/r	PBO/r	ASD[a]
Group participants, No.	102	53	NA
Age, median (IQR), y	44.5 (35.25-56)	41 (31-45)	0.34
Female	61 (59.8)	31 (58.5)	NA
Male	41 (40.2)	22 (41.5)	NA
Race			
Asian	11 (10.8)	9 (17)	
Black or African American	1 (1)	2 (3.8)	
Native Hawaiian or other Pacific Islander	1 (1)	0	0.37
White	76 (74.5)	39 (73.6)	
More than 1 race	5 (4.9)	1 (1.9)	
Unknown	8 (7.8)	2 (3.8)	
Hispanic ethnicity	12 (11.8)	7 (13.2)	0.04
Index COVID-19 infection date[b]			
Before May 2021	39 (38.2)	22 (41.5)	
May to December 2021	20 (19.6)	7 (13.2)	0.17
After December 2021	43 (42.2)	24 (45.3)	
Hospitalized for index COVID-19 infection	6 (5.9)	3 (5.7)	0.01
Time from index infection to randomization, mean (SD), mo	17.6 (9.1)	17.3 (9.1)	0.03
Total COVID-19 infections, mean (SD)[c]	1.45 (0.75)	1.34 (0.55)	0.17
Prior use of SARS-CoV-2 acute medication			
Prior use of medication[d]	27 (26.5)	14 (26.4)	<0.01
Prior use of Paxlovid	18 (17.6)	9 (17)	0.02
No prior use	75 (73.5)	39 (73.6)	NA
Vaccination status at randomization			
Initial series completed	101 (99)	52 (98.1)	0.08
Initial series not completed	1 (1)	1 (1.9)	
BMI, mean (SD)	27 (6.19)	28 (6.66)	0.18
BMI group			
Underweight (<18.5)	4 (3.9)	0	
Normal (18.5-24.9)	39 (38.2)	17 (32.1)	0.34
Overweight (25.0-29.9)	33 (32.4)	18 (34)	
Obesity (≥30.0)	26 (25.5)	18 (34)	
Comorbidities[e]			
Depression	24 (23.5)	13 (24.5)	0.02
Allergies	17 (16.7)	12 (22.6)	0.12
Asthma	15 (14.7)	13 (24.5)	0.22
Anxiety	15 (14.7)	8 (15.1)	0.02
GERD	15 (14.7)	6 (11.3)	0.13
Moderate to severe post−COVID-19 symptoms, No.			
2-3	47 (46.1)	25 (47.2)	0.02
>3	55 (53.9)	28 (52.8	
Moderate to severe symptom at baseline, % of participants			
Fatigue	95.1	96.2	NA
Brain fog	81.4	79.2	NA
Body aches	57.8	50.9	NA
Cardiovascular	49.0	60.4	NA
Shortness of breath	46.1	52.8	NA
Gastrointestinal	41.2	47.2	NA

Abbreviations: ASD, absolute standardized difference; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GERD, gastroesophageal reflux disease; NA, not applicable; NMV/r, oral nirmatrelvir-ritonavir; PBO/r, placebo-ritonavir.

[a] A larger ASD indicates a larger difference between the groups (eg, 0.2 = small difference, 0.5 = moderate difference, 0.8 = large difference).

[b] Index COVID-19 infection was defined as the initial infection associated with subsequent onset of participant's postacute sequelae of SARS-CoV-2 infection.

[c] Total COVID-19 infections was the participant-reported total number of COVID-19 infections before enrollment.

[d] Other medications for acute infection include remdesivir, molnupiravir, and bebtelovimab.

[e] Participant-reported comorbidities included onset before and after the index COVID-19 infection.

for baseline symptom severity, except for brain fog for which the NMV/r group had decreased odds of experiencing mild or no symptoms (Table 2). Heatmaps of symptom severity scores and change from baseline over time showed week-to-week variability and heterogeneity within both groups (eFigures 7 and 8 in Supplement 3).

Figure 2. Distribution of Core Symptom Severity Scores Over Time in Adults
With Postacute Sequelae of SARS-CoV-2 Infection
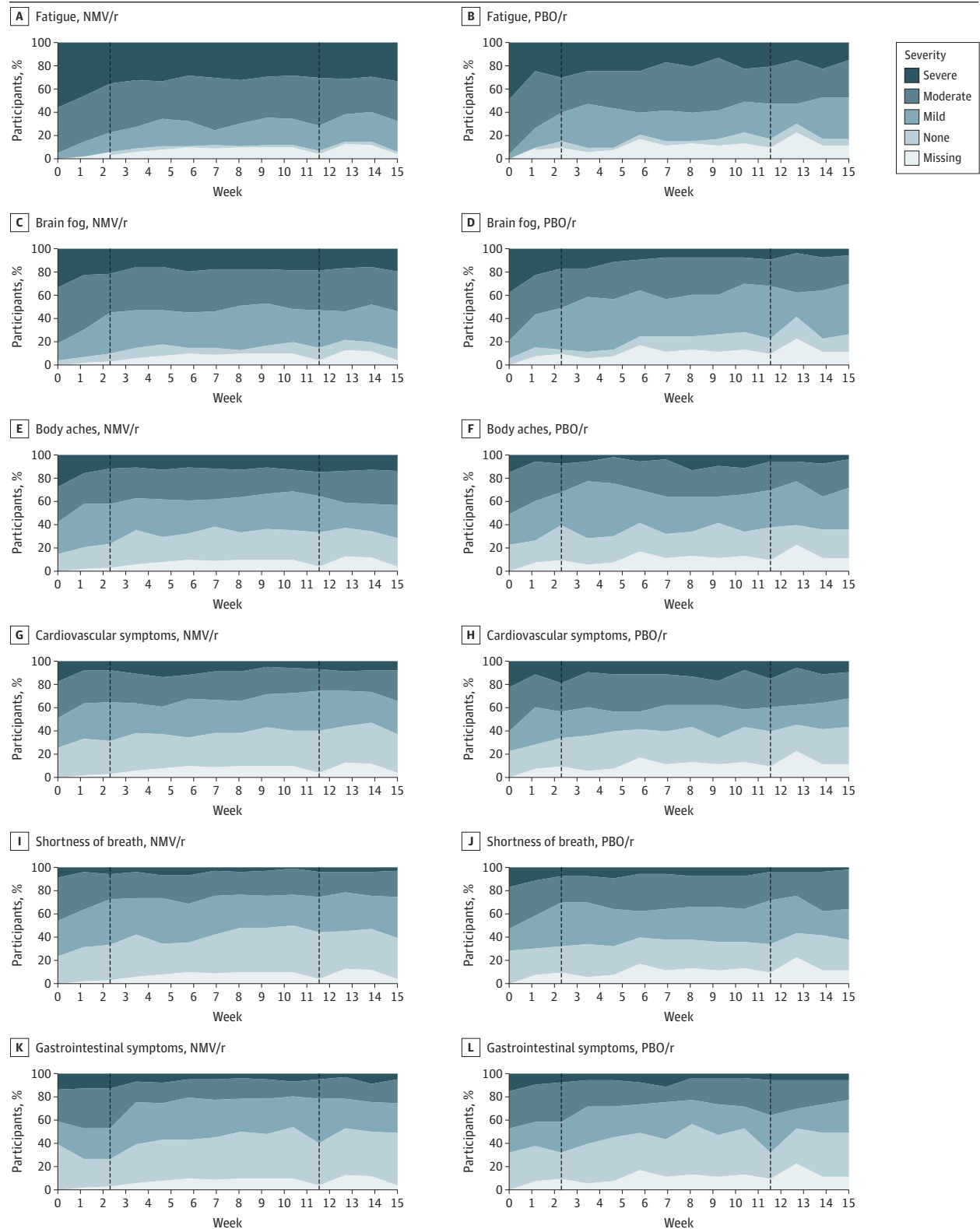
Dashed line on the left marks the end of the 15-day treatment period, and on the right, it marks the 10-week primary end point. NMV/r indicates nirmatrelvir-ritonavir, and PBO/r, placebo-ritonavir.

Table 2. Select Secondary Outcomes and Adverse Events in Nirmatrelvir-Ritonavir Use for Postacute Sequelae of SARS-CoV-2 Infection

Outcome or event	NMV/r	PBO/r		
Participants in group	102	53		
Moderate to severe symptoms, change from baseline at 10 wk, % of participants				
Fatigue	−23.5	−43.4		
Brain fog	−28.4	−47.2		
Body aches	−22.5	−20.8		
Cardiovascular	−23.5	−20.8		
Shortness of breath	−20.6	−24.5		
Gastrointestinal	−19.6	−11.3		
	Mean (SD)		**β (95% CI)[a]**	**P value**
PROMIS, change from baseline to 10 wk				
Physical function	2.73 (6.62)	1.32 (5.75)	0.57 (−1.96 to 3.10)	.66
Fatigue	−3.92 (7.88)	−4.05 (5.90)	0.38 (−2.40 to 3.15)	.79
Dyspnea	−1.96 (7.90)	−2.38 (6.13)	0.60 (−2.55 to 3.75)	.70
Cognitive function	4.84 (8.18)	5.05 (7.56)	0.03 (−3.21 to 3.28)	.98
PGIC score at 10 wk	3.38 (1.31)	3.13 (1.03)	0.10 (−0.48 to 0.67)	.74
PGIS score at 10 wk	4 (1.03)	3.79 (1.06)	0.19 (−0.25 to 0.62)	.40
Summative score at 10 wk	7.62 (3.75)	7.69 (4.09)	−0.24 (−1.46 to 0.97)	.69
			HR (95% CI)	**P value**
Time to relief of most bothersome symptom[b]			0.74 (0.40 to 1.38)	.33
	No. (%)		**OR (95% CI)**	**P value**
Experiencing relief at 10 wk[b]	33 (32.4)	22 (41.5)	0.55 (0.27 to 1.09)	.09
Experiencing alleviation at 10 wk[c]	7 (6.86)	5 (9.43)	0.72 (0.21 to 2.44)	.60
	Median (IQR)		**OR (95% CI)[d]**	**P value**
Proportion of weeks 1-15 with mild or no symptoms				
Fatigue	0.15 (0 to 0.39)	0.15 (0 to 0.77)	0.55 (0.33 to 0.92)	.02
Brain fog	0.31 (0 to 0.75)	0.56 (0.15 to 0.85)	0.50 (0.31 to 0.82)	.01
Body aches	0.54 (0.10 to 0.92)	0.64 (0.29 to 0.83)	1.32 (0.74 to 2.33)	.34
Cardiovascular symptoms	0.67 (0.19 to 0.92)	0.46 (0 to 0.92)	1.37 (0.76 to 2.48)	.29
Shortness of breath	0.769 (0.25 to 1)	0.62 (0.09 to 0.89)	1.32 (0.73 to 2.38)	.35
Gastrointestinal symptoms	0.63 (0.31 to 0.92)	0.52 (0.28 to 0.90)	1.40 (0.79 to 2.47)	.25
	No. (%)			
Participants with AEs	101 (99)	49 (92)		
No. of AEs	771	313		
Total SAE[e]	3 (2.9)	1 (1.9)		
Participants with grade 3 or 4 AEs[f]	5 (4.9)	3 (5.7)		
Fatalities	0	0		

Abbreviations: AE, adverse event; HR, hazard ratio; NA, not applicable; NMV/r, nirmatrelvir-ritonavir; OR, odds ratio; PBO/r, placebo-ritonavir; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PROMIS, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event.

[a] Estimated coefficients (βs) for PGIC or PGIS can be interpreted as differences in PGIC and PGIS score values between groups, eg, an estimate of 0.3 means that, on average, those on NMV/r reported PGIC/PGIS 0.3 points higher than those on PBO/r. However, coefficients for PROMIS measures should be interpreted as differences (in NMV/r vs PBO/r) in change scores (baseline vs wk 10). A higher score value corresponds to reduced severity for PROMIS-physical and cognitive function; greater severity for PROMIS-fatigue and dyspnea; worsening status for PGIC; and greater severity for PGIS. Therefore, improvement from baseline to week 10 corresponds to positive change scores for PROMIS-physical and cognitive function, and negative change scores for PROMIS-fatigue and dyspnea.

[b] Relief was defined as a reduction of severity from moderate to none or severe to mild or none for at least 1 core symptom; time to relief was measured in weeks.

[c] Alleviation was defined as improvement of all core symptoms from none or mild at baseline to none or moderate to severe to none or mild.

[d] An OR of 1.5 corresponds to a 50% increase in the odds of experiencing mild or no symptoms for those taking NMV/r compared to those taking PBO/r.

[e] One participant each had blood-loss anemia, forearm fracture, and melanoma in the NMV/r group (all assessed as unrelated to intervention), and 1 participant had hepatitis in the PBO/r group (assessed as possibly related).

[f] Graded per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

Changes from baseline in PGIS and PGIC scores at 2, 5, 10, and 15 weeks and PROMIS scales for physical function, fatigue, dyspnea, and cognitive abilities showed no statistically significant between-group difference at 10 weeks (Table 2; **Figure 3**). One minute sit-to-stand test and orthostatic vital signs also showed no significant between-group differences from baseline at 10 weeks (eTable 1 in Supplement 3).

Figure 3. Patient Global Impression Scores Over Time in Adults With Postacute Sequelae of SARS-CoV-2 Infection
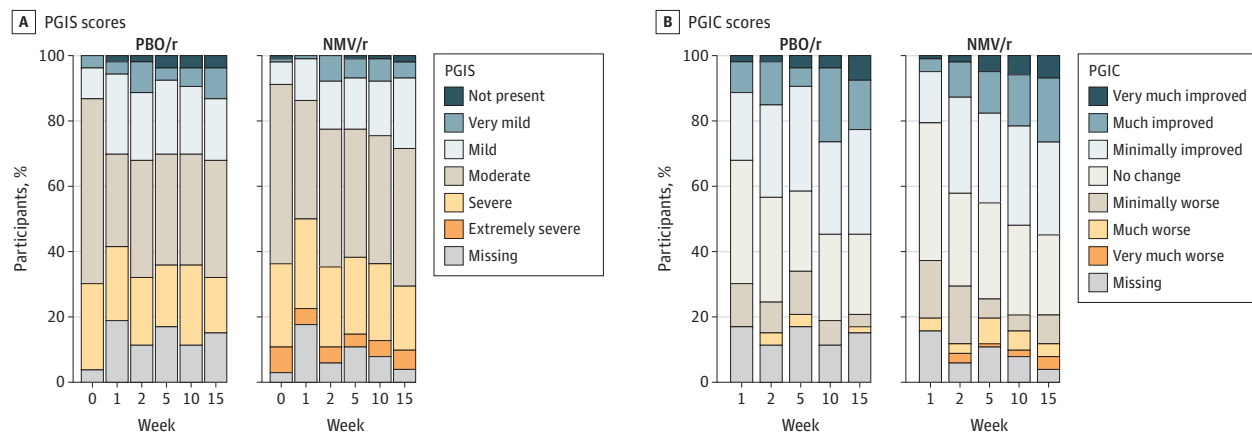
Likert plots depict the distribution of PGIS (A) and PGIC (B) scores at each week, by treatment group. NMV/r indicates nirmatrelvir-ritonavir; PBO/r, placebo-ritonavir; PGIC, Patient Global Impression of Change; and PGIS, Patient Global Impression of Severity.

Sensitivity and Subgroup Analyses

Sensitivity analyses excluding participants with no follow-up were similar to the ITT analyses. The results of the subgroup analyses of the pre- and post-Omicron subgroups were similar to the overall results (eTable 2 in Supplement 3).

Adverse Events

Throughout the 15-week study, 101 of 102 participants (99%) in the NMV/r group and 49 of 53 participants (92.5%) in the PBO/r reported at least 1 adverse event (AE), almost all of which were grade 1 or 2 (Table 2). Four serious AEs were reported: 3 in the NMV/r group (blood loss anemia, forearm fracture, and melanoma), assessed to have been unrelated to intervention; and 1 in the PBO/r group (hepatitis), assessed to have been possibly related to the intervention. The most common AEs reported during the 15-day treatment period were dysgeusia (63 [61.8%] in NMV/r group and 4 [7.5%] in the PBO/r group) and diarrhea (44 [43.1%] in NMV/r group and 19 [35.8%] in the PBO/r group). Six participants (3 [2.9%] in NMV/r group and 3 [5.7%] in PBO/r group) discontinued the intervention due to intolerability or AE. In the NMV/r group, 12 participants (11.8%) and in the PBO/r group, 5 (9.4%) reported COVID-19 reinfections during the study period. One reinfection in the PBO/r group occurred within the first 15 days; all others occurred after the 15-day treatment period. Additional information on AEs is reported in (eFigure 9 in Supplement 3).

Discussion

STOP-PASC is the first randomized clinical trial testing NMV/r for the treatment of PASC, to our knowledge. We found that a 15-day course of NMV/r had a safety profile similar to the 5-day acute treatment course and was generally tolerated; however, when compared to placebo-ritonavir, it did not improve select PASC symptoms (fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, and gastrointestinal symptoms) or other health outcomes as measured by the

PROMIS scales, global impression scales, and clinical measures of physical function and vital signs. Notably, both the intervention and control groups exhibited improvements in PASC symptoms over time. It is important to underscore that this study alone does not rule out NMV/r as a potential therapy for PASC. There are multiple reasons that would explain why this trial did not detect a benefit for the selected outcomes, and several key themes warrant further discussion to inform future trials in PASC.

PASC is likely not a single entity, and therefore, treatment will likely differ among PASC subtypes. Six core symptoms and symptom clusters were included in this exploratory study, but future trials—especially any smaller studies that are not well powered to detect subgroup differences—may benefit from targeting a specific phenotype. Our study cohort had protracted PASC illness averaging more than 16 months, and antivirals may need to be administered earlier in the illness, before downstream and possibly less reversible adverse effects occur. Our mostly vaccinated outpatient cohort likely differs from unvaccinated and previously hospitalized cohorts that often comprise older patients with multiple comorbidities, ie, risk factors for PASC.[54-56]

The natural history of PASC is varied and is still under investigation.[57] We found that many participants with PASC in the PBO/r group improved over time, as did a control group in another trial in PASC.[11] Therefore, an effective intervention needs to substantially accelerate that process to see a meaningful difference. There were week-to-week variations in symptoms severity in some participants, consistent with fluctuating patterns that have been described for PASC elsewhere.[58-60] The heterogeneity and fluctuations of symptoms severity may mask signals, especially smaller ones. Thus, global trajectory assessments should be considered in addition to individual time points.

To date, there are no validated clinical end points or biomarkers of PASC established for clinical trials, to our knowledge. The symptoms selected for this study were based on mechanistic rationale and prevalence and severity in

patients.[5,44-47] Other symptoms or clinical end points that were not captured in this study may be responsive to the intervention. The PASC symptoms survey developed and used in this study shares similarities with other patient-informed surveys used in clinical practice and by other studies,[46,61,62] and the findings in this study are consistent across a variety of different measures. With the urgent need to find therapies for PASC, exploratory studies such as ours have pushed forward to simultaneously assess efficacy and safety while investigating biomarkers. We underscore the need to establish validated clinical and biological end points for PASC.

This trial's results do not reject the hypothesis that viral persistence may lead to PASC but they will help inform further studies in this area.[63-67] None of the participant baseline stool specimens had detectable SARS-CoV-2 RNA; other tissues were not assessed. As assays to detect SARS-CoV-2 reservoirs become optimized and validated, they could help to identify individuals who may benefit from antiviral therapy.[17] Longer treatment durations, dose variations, optimal timing, and different phenotypes of PASC should be investigated in larger studies.[63] Additionally, multiple pathways may contribute to PASC pathogenesis; therefore, in addition to testing single therapies, combination therapies (eg, antivirals with immunomodulators) warrant exploration.[13,14] Adaptive platform trials would allow randomized controlled comparisons of multiple interventions simultaneously, with the flexibility to adapt key design features of the study in response to accumulating information, thereby maximizing efficiency and prioritizing more promising interventions.[68]

Strengths and Limitations

The strengths of this study include longitudinal follow-up with a high retention rate and multidimensional data collection with clinical, biospecimen, and digital wearable data that will be integrated in future analyses. The study's limitations include enrollment at a single academic center, which impacts generalizability, and a smaller sample size than originally planned due to early enrollment closure. The high rate of exclusion due to eligibility criteria, such as drug-drug interaction, also limits generalizability and potentially misses subgroups of patients who could be responders. Although PASC symptoms were assessed as not being attributable to another cause for eligibility, it is still possible that non-PASC factors impacted some participants' symptoms over the course of the study, which may bias outcomes. Co-interventions, such as concomitant medications, may also influence outcomes. Ritonavir is known to be associated with dysgeusia and was therefore part of the control intervention to minimize unmasking, but the higher rate of dysgeusia reported in the NMV/r group may have impacted self-reported outcomes if unintended unmasking occurred. Severity of the acute COVID-19 infection may impact outcomes and was not captured in depth aside from hospitalization status.

Conclusions

This randomized clinical trial demonstrated the overall safety of a 15-day course of NMV/r in patients with PASC but did not find a significant benefit of this therapy for a subset of PASC symptoms among a mostly vaccinated cohort with prolonged PASC symptoms. Ancillary analyses and evaluation for molecular and digital biomarkers from the STOP-PASC trial are forthcoming. Findings from this and other randomized clinical trials of NMV/r will collectively determine whether this antiviral is beneficial for treating PASC.

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