Nirmatrelvir–ritonavir versus placebo–ritonavir in individuals with long COVID in the USA (PAX LC): a double-blind, randomised, placebo-controlled, phase 2, decentralised trial

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Summary

Background The substantial burden of post-COVID-19 condition (also known as long COVID) underscores the need for effective pharmacological interventions. Given that viral persistence has been hypothesised as a potential cause of long COVID, antiviral therapy might offer a promising approach to alleviating long COVID symptoms. We therefore investigated the efficacy, safety, and tolerability of nirmatrelvir–ritonavir for treating long COVID.

Methods In this phase 2, decentralised, double-blind, randomised controlled trial, adults (aged ≥18 years) from the 48 states across the contiguous USA, with previous documented SARS-CoV-2 infection and long COVID symptoms starting within 4 weeks of initial infection and persisting for at least 12 weeks, were eligible for inclusion. Key exclusion criteria were use of nirmatrelvir–ritonavir within the previous 2 months, CYP3A4-dependent medications, or strong CYP3A4 inducers; acute medical illness such as SARS-CoV-2 infection within the past 2 weeks; active liver disease; renal impairment; and immunocompromise. Using software for 1:1 stratified block random assignment, participants were randomly allocated to receive either two tablets of nirmatrelvir (150 mg each) and one tablet of ritonavir (100 mg), or placebo and one tablet of ritonavir (100 mg), orally administered twice daily for 15 days, stratified by age, sex at birth, and COVID-19 vaccination status. Participants, clinicians, and the study team were masked to treatment allocation. The primary efficacy endpoint was the change in the Patient-Reported Outcomes Measurement Information System (PROMIS)-29 Physical Health Summary Score (PHSS) from baseline to day 28, analysed by intention to treat. Safety endpoints were reported from baseline to week 6 in all participants who were exposed to the study treatment. This trial is registered with ClinicalTrials.gov (NCT05668091) and is now closed to new participants.

Findings Between April 14, 2023, and Feb 26, 2024, 119 participants were screened. 100 were enrolled (66 [66%] female participants and 34 [34%] male participants), with 49 assigned to the nirmatrelvir–ritonavir group and 51 to the placebo–ritonavir group (intention-to-treat population). Three participants in the nirmatrelvir–ritonavir group and two in the placebo–ritonavir group withdrew before starting treatment and were excluded from the safety population. The mean PROMIS-29 PHSS at baseline was 39·6 (95% CI 37·4 to 41·9) in the nirmatrelvir–ritonavir group and 36·3 (34·4 to 38·2) in the placebo–ritonavir group. The adjusted change from baseline to day 28 was 0·45 (–0·93 to 1·83) in the nirmatrelvir–ritonavir group and 1·01 (–0·30 to 2·31) in the placebo–ritonavir group (adjusted mean difference –0·55 [95% CI –2·32 to 1·21; p=0·54]). No deaths or serious adverse events were recorded between baseline and week 6. Study drug-related treatment-emergent adverse events were reported in more participants in the nirmatrelvir–ritonavir group (35 [76%] of 46) compared with the placebo–ritonavir group (27 [55%] of 49), mostly driven by dysgeusia. Early treatment termination due to an adverse event occurred in two participants in the nirmatrelvir–ritonavir group and one in the placebo–ritonavir group.

Interpretation Nirmatrelvir–ritonavir administered for 15 days did not significantly improve health outcomes in participants with long COVID compared with placebo–ritonavir at day 28. However, the study showed the feasibility of large-scale, decentralised trials in long COVID.

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Introduction

Post-COVID-19 condition, also known as long COVID or post-acute sequelae of SARS-CoV-2 infection, affects approximately 7–10% of patients with SARS-CoV-2 infection.[1] Long COVID affects multiple organ systems and substantially impairs quality of life by diminishing individuals' abilities to perform daily activities and leading to physical, emotional, and financial stress.[2] Given the

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Research in context

Evidence before this study

We searched ClinicalTrials.gov on Oct 18, 2024, for studies using the search term "long COVID". Of the 538 results, 339 were classified as interventional studies, with only 92 trials testing pharmacological interventions. Among them, 42 trials included a placebo comparator group. The recruitment statuses of these trials were: 12 not yet recruiting, eight terminated, 35 actively recruiting, one enrolling by invitation, 11 active but not recruiting, and 19 completed. Of these trials, five focused on changes in fatigue, three on cognitive function, one on respiratory function, one on pain, one on postural orthostatic tachycardia syndrome, and two on general health (both of which tested a 15-day regimen of nirmatrelvir–ritonavir as the active intervention). Before the PAX LC trial, the STOP-PASC trial (NCT05576662) at Stanford University (CA, USA) enrolled 155 participants to evaluate a 15-day course of nirmatrelvir–ritonavir for long COVID. Enrolment was stopped early in June, 2023, when the prespecified threshold for futility had been met. The trial found no significant improvement in core symptoms, which included fatigue, brain fog, shortness of breath, body aches, and gastrointestinal and cardiovascular symptoms, based on a Likert scale explicitly developed for the study, compared with placebo at 10 weeks. No additional safety concerns were noted, and secondary outcomes, such as symptom burden and patient-reported measures, also showed no significant differences.

Added value of this study

The PAX LC trial adds evidence about the safety and efficacy of nirmatrelvir–ritonavir compared with placebo–ritonavir for the treatment of people with long COVID, using the Patient-Reported Outcomes Measurement Information System-29 Physical Health Summary Score for consistent assessment of health outcomes. The trial's decentralised design enabled recruitment from 28 of the 48 contiguous US states, offering broad geographical diversity within the USA and reaching individuals with severe long COVID symptoms, who are often under-represented in traditional studies. Although no significant differences were observed in primary and secondary endpoints, the trial showed the feasibility of a fully decentralised model, providing a safe, accessible option with high participant satisfaction.

Implications of all the available evidence

Both our PAX LC trial and the previous STOP-PASC trial showed that treating people with long COVID with a 15-day regimen of nirmatrelvir–ritonavir was not beneficial, with no significant short-term improvement in symptoms found on the basis of different metrics. These findings highlight the need for future research to explore longer treatment regimens, alternative antivirals or combinations of antivirals, and interventions targeting multiple pathological mechanisms of long COVID. Furthermore, decentralised trials such as PAX LC might offer an effective framework for improving accessibility, reaching under-represented populations, and enhancing the diversity of participants in future studies; however, improvements to digital recruitment strategies are needed to fully achieve these goals in long COVID and potentially other chronic illnesses.

substantial global burden of long COVID and its effect on health-care systems and economies worldwide, identifying priority areas for research and intervention is crucial to effectively mitigate its long-term effects.

Several mechanisms, including immune dysregulation, microbiota disruption, autoimmunity, clotting, and endothelial abnormalities, have been hypothesised as potential causes of long COVID.[3–5] The biological mechanisms of long COVID are incompletely understood, but one hypothesis suggests a link with viral persistence after initial SARS-CoV-2 infection. This persistence might result in ongoing immune stimulation and long COVID symptoms.[6] Previous studies examining the association between antiviral therapy during acute SARS-CoV-2 infection and the prevalence of post-infection symptoms yielded mixed results.[7–10] Hence, efforts are being directed towards deciphering whether existing antivirals can be repurposed to treat symptoms of long COVID. One antiviral being investigated is nirmatrelvir, a potent, selective SARS-CoV-2 protease inhibitor, in combination with ritonavir, which the US Food and Drug Administration (FDA) approved for the treatment of mild-to-moderate COVID-19 in adults at high risk for COVID-19 complications including hospitalisation or death.[11] Three ongoing trials and one completed trial are investigating whether nirmatrelvir–ritonavir can alleviate long-term COVID symptoms.[12] The recently published STOP-PASC (Selective Trial of Paxlovid-Post-Acute Sequelae of SARS-CoV-2) trial, which compared a 15-day course of nirmatrelvir–ritonavir with placebo–ritonavir, did not show significant improvement in symptom scores or other patient-reported outcomes.[12] STOP-PASC was conducted at a single site in the USA, used a symptom score explicitly developed for the study, and was stopped early when a prespecified threshold for futility was met.

In the PAX LC trial, we aimed to investigate the efficacy, safety, and tolerability of a 15-day nirmatrelvir–ritonavir regimen in individuals with long COVID compared with placebo–ritonavir using a decentralised design to reach participants across the USA.

Methods

Study design

The PAX LC study was a decentralised, phase 2, randomised, double-blind, placebo-controlled clinical

trial to investigate the efficacy and safety of a 15-day regimen of orally administered nirmatrelvir–ritonavir compared with placebo–ritonavir in participants with long COVID. Details of the study design have been previously published.[13] We used a decentralised design across the contiguous USA to address logistical barriers typical of site-based trials and reduce the need for participant travel. This approach also aimed to improve population diversity, promote trial efficiency, and simplify site contracting and regulatory processes. Blood tests to assess eligibility and post-intervention safety assessments were conducted at 16 Quest Diagnostics laboratories near participants' homes. Biospecimens were collected at participants' homes or another convenient location using ExamOne, a mobile phlebotomy and health assessment services company owned by Quest Diagnostics. Participants local to New Haven, CT, USA also had the option to visit Yale New Haven Hospital for blood work for eligibility assessments, biospecimen collection, or follow-up. The trial protocol, statistical analysis plan, and schematic are available in the appendix (pp 49–143). The Yale University Institutional Review Board approved this randomised clinical trial, which was conducted under a US FDA investigational new drug application held by HMK; the US FDA approved the use of the 15-day nirmatrelvir–ritonavir regimen as an investigational new drug. A group of individuals with long COVID provided input on the study design. A data monitoring committee, including a member with long COVID, provided independent oversight. This study adheres to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and followed CONSORT guidelines. This trial is registered with ClinicalTrials.gov (NCT05668091).

Participants

Individuals from the 48 contiguous states in the USA learned about joining the study through various channels, including the study website, social media posts, podcasts, webinars, Yale press releases, the Yale Help Us Discover volunteer database, and Yale Cultural Ambassadors. Interested individuals completed the prescreening questions and shared their electronic health records via Hugo Health with the Yale investigator team. Qualified Yale personnel, as defined by clinical expertise and ability to identify patient criteria (and authorised by the Yale Institutional Review Board), reviewed the information to assess initial eligibility. Key inclusion criteria were being 18 years or older and having documented previous SARS-CoV-2 infection confirmed by a positive PCR test or medical records with a long COVID diagnosis. Participants needed to have symptoms consistent with long COVID starting within 4 weeks of the initial infection and persisting for at least 12 weeks. Key exclusion criteria were acute medical illness such as SARS-CoV-2 infection within the past 2 weeks, active liver disease, renal impairment, or immunocompromise as defined by the US Centers for Disease Control and Prevention standards. We also excluded individuals using medications highly dependent on CYP3A4 for clearance or strong CYP3A4 inducers, and those treated with nirmatrelvir–ritonavir within the previous 2 months or having more than 5 days of use for a single episode of acute COVID-19. Full eligibility criteria are available in the study protocol (appendix pp 49–113).

The study participants self-reported their sex assigned at birth (male or female), race, and ethnicity. After initial eligibility clearance, clinical research coordinators contacted participants via video conference to obtain electronic informed consent using software compliant with the Code of Federal Regulations and to schedule Clinical Laboratory Improvement Amendments-certified screening laboratory tests at a local Quest Diagnostics centre. During consent, participants were informed that both nirmatrelvir–ritonavir and placebo–ritonavir could potentially affect taste. Exclusion criteria at this stage included laboratory results showing aspartate transaminase or alanine transaminase concentration of 2·5 times the upper limit of normal (ULN) or more, total bilirubin concentration of 2 times the ULN or more (or 3 times the ULN or more for Gilbert's syndrome), estimated glomerular filtration rate of less than 60 mL/min per 1·73 m² (using the updated Chronic Kidney Disease Epidemiology Collaboration equation without race), neutrophil count of less than 1000/μL, infection with HIV, and pregnancy. Participants' medical care providers were notified of study participation to promote safety and effective communication regarding the investigational drug.

For the **Code of Federal Regulations** see https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11?

See **Online** for appendix

Randomisation and masking

Eligible participants were randomly assigned 1:1 to receive a 15-day supply of either nirmatrelvir–ritonavir or placebo–ritonavir. Randomisation was performed centrally using Stata, version 16, with stratified block randomisation (block size of 2) across eight strata based on age (<50 years or ≥50 years), sex at birth (male or female), and COVID-19 vaccination status (vaccinated or unvaccinated). Ritonavir was included with the placebo to aid in masking, as it was expected to cause taste abnormalities similar to those of nirmatrelvir without activity against SARS-CoV-2.[14] Ritonavir was administered in labelled tablet bottles and both nirmatrelvir and placebo were provided in blister wallets with masked labels. The trial was conducted as a double-blind study, ensuring that participants, clinicians, and the study team remained unaware of treatment allocations. Randomisation was implemented through an electronic data capture system, with coded lot numbers used for drug allocation. Permissions within the system were configured to prevent unintentional unmasking. A dedicated team of unmasked investigators managed tasks that required access to treatment

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assignments, including data analysis and reporting to the data monitoring committee, with all relevant documents stored on a secured server inaccessible to masked personnel. To assess the integrity of masking, participants completed an electronic survey on day 28, answering the question, "If you had to guess, do you think you received Paxlovid (the real medication) or the placebo (pills with no medication)?" Additional details regarding the administration of drugs or placebo and masking procedures are summarised in the study protocol (appendix pp 49–113).

Procedures

Medications, which were paid for by Pfizer, were prescribed for each participant through a partnership with Trusted Medical and shipped to participants' homes by Almac. Participants were given clear dosing instructions to take either 300 mg nirmatrelvir (administered as two 150 mg tablets) with 100 mg ritonavir, or placebo with 100 mg ritonavir (also administered as two tablets), orally every 12 h for 15 days. The doses of ritonavir and either nirmatrelvir or placebo were instructed to be taken at the same time and no more than 10 min apart. The first dose of the trial intervention was taken as soon as possible according to the dosing schedule after the participant received the drug supply.

During the 15-day treatment period, participants completed daily electronic diaries to record drug compliance, new or worsening symptoms, concomitant medication changes, and unscheduled medical visits to monitor for potential adverse events. Additional safety assessments on day 28 and week 6 were conducted remotely through our dedicated online software, in which participants completed an assessment diary indicating any new or worsening symptoms, medication changes, or unscheduled medical visits, with positive responses triggering follow-up by the masked study team via phone or email to gather more information. Although medical records were not reviewed in real time, medical record transmissions via the Hugo Health platform were reviewed weekly until the end of week 6.

To assess compliance via pill counts, participants were asked to return unused study medication to Almac, the vendor responsible for shipment and collection, for reconciliation on day 28; if participants did not return unused medication, the daily diary responses were used as the primary source for calculating compliance.

Blood samples for pharmacokinetic analysis were taken at baseline and once more between day 7 and day 14 as part of participants' at-home biospecimen collection. All the plasma samples for the pharmacokinetic analysis assays were stored in 80°C freezers until the collections were completed. The samples were all run together to ascertain concentrations of nirmatrelvir in the blood.

Participants completed an online exit survey at day 28 that asked them which medication they thought they had taken and about their overall experience in the trial (appendix pp 145–146). The schedule for surveys, biospecimen collection for immunophenotyping, and taking of pharmacokinetic blood samples is included in the study protocol (appendix pp 49–113).

Outcomes

The primary efficacy endpoint was the change in the Patient-Reported Outcomes Measurement Information System (PROMIS)-29 v2.1 Physical Health Summary Score (PHSS) between the two groups from baseline to day 28. PROMIS-29 v2.1, a well validated general health assessment tool for medical conditions beyond long COVID, was chosen to assess changes in symptoms and function over time at baseline, day 15, day 28, and week 6 post randomisation.[15] PROMIS-29 measures are scored on the T-score metric, so that scores have a normal distribution with a population mean T score of 50 and SD of 10.

Key secondary endpoints were changes from baseline for scores and answers from the PROMIS-29 v2.1 Mental Health Summary Score (MHSS), PROMIS-Preference (PROPr) Score, PROMIS v2.0 Cognitive Function Short Form 6a, Modified General Symptom Questionnaire (GSQ)-30,[16] additional long COVID symptom reporting, COVID Core Outcome Measures for Recovery,[17] EuroQol EQ-5D-5L (comprising the EQ-5D descriptive system and the EQ Visual Analogue Scale [EQ-VAS]),[18] Functional Assessment of Chronic Illness Therapy Item GP5,[19] and the Patient Global Impression of Severity and Patient Global Impression of Change scales.[20] The additional long COVID symptom questions were developed by the study team to capture the 26 symptoms that were not covered by the other patient-reported outcome tools of the 96 unique symptoms frequently reported in a previous study conducted in collaboration with patients.[2,21] Details can be found in the study protocol (appendix pp 49–113).

Safety endpoints as secondary endpoints were the incidence of adverse events during the trial period, serious adverse events, including death and hospitalisation, and adverse events that led to discontinuation of nirmatrelvir–ritonavir or placebo–ritonavir until the end of week 6. This Article is a full report of the primary endpoint and a preliminary report of the full study, which will be available once all participants have completed week 24.

Statistical analysis

We determined that a sample size of 100, with a treatment-to-placebo ratio of 1:1, would provide 80% power at the two-sided significance of p=0·05 to detect a 5-point or greater improvement in the PROMIS-29 PHSS at day 28, assuming an effect size in mean difference of 5 absolute points, a standard deviation of 8, a baseline score of 42, and a 15% trial discontinuation rate.[15] All tests were two-sided with a p=0·05 significance. Analyses were conducted in SAS 9.4.

The primary analysis was done in the intention-to-treat (ITT) population. Sensitivity analyses for the primary endpoint were conducted using modified ITT and per-protocol populations. The modified ITT analysis included all randomly assigned participants who adhered to at least 80% of the prescribed intervention and were analysed according to their assigned treatment. The per-protocol analysis included participants who had completed the trial without major protocol deviations (ie, failure to obtain informed consent before study procedures, enrolment before completing screening procedures, and inclusion of participants taking medications that could interact with the interventional drug) and analysed participants according to the treatment they received. A safety analysis was also done, including all participants who were randomly assigned to the trial intervention and had taken at least one dose.

The primary and secondary analyses were conducted using mixed models for repeated measures,[22,23] with change from baseline as the dependent variable; treatment, time, and treatment-by-time interaction terms as fixed effects; participant as a random effect; and age, sex at birth, and baseline value as fixed covariates. The time variable was categorical and corresponded to planned study visits, such as day 15, day 28, and week 6. For missing data, the fully conditional specification multiple imputation technique was used to impute both primary and secondary survey endpoints. The multiple imputation was stratified by treatment group and used additional covariates, including compliance status, baseline demographics, clinical status, and clinical symptoms. We imputed data up to 6 weeks for the primary and secondary efficacy survey outcomes. We used data up to 28 days for primary endpoint analyses and used data up to 6 weeks for secondary endpoint analyses. We did not prespecify or perform formal assessments of model assumptions because the primary dependent variable is normally distributed by design, the covariates are categorical, and the small sample size was underpowered for distributional tests.

Unadjusted mean PROMIS PHSS and MHSS were calculated for each timepoint (day 15, day 28, and week 6) across the two treatment groups, stratified by prespecified subgroups of age, sex at birth, race, COVID-19 vaccination status, and US census region. Subgroup analyses were descriptive and did not include statistical testing. We used complete data for the unadjusted scores and did not impute for subgroup analyses. Additional details regarding the statistical analysis can be found in the appendix (pp 49–113).

Role of the funding source

The funder of the study (Pfizer) was involved in study design, data interpretation, and the writing of the report but had no role in data collection or data analysis.

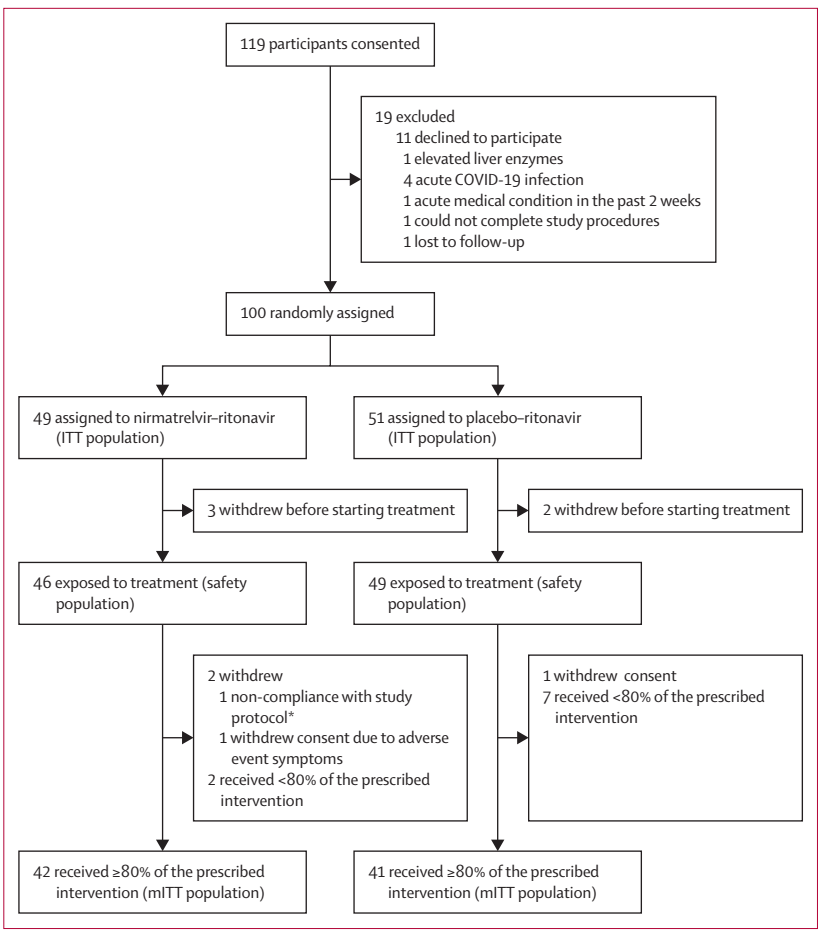

Figure 1: **CONSORT diagram**
The per-protocol population (38 in the nirmatrelvir–ritonavir group and 41 in the placebo–ritonavir group) includes all participants who had not withdrawn from the study by week 24, regardless of their adherence to the investigational drug or completion of the required patient-reported outcomes. The numbers shown in the diagram reflect data from the dataset as of July, 2024, at which point some participants had completed week 6 but had not yet reached week 24. ITT=intention to treat. mITT=modified intention to treat. *Non-compliance with the study protocol primarily includes failure to complete baseline or day 28 questionnaires, or both.

Results

From April 14, 2023, to Feb 26, 2024, 119 participants consented, with 19 excluded, resulting in 100 eligible participants randomly assigned (ITT population; figure 1). 49 participants were assigned to the nirmatrelvir–ritonavir group and 51 were assigned to the placebo–ritonavir group. Three participants in the nirmatrelvir–ritonavir group and two in the placebo–ritonavir group withdrew from the study before starting treatment; the safety population therefore comprised 46 participants in the nirmatrelvir–ritonavir group and 49 in the placebo–ritonavir group.

For the ITT population, the mean age at consent was 42·3 years (SD 12·1); 66 (66%) of 100 participants were assigned female at birth (of whom 53 [80%] were of childbearing potential [ie, were not in menopause, were maintaining adequate reproductive health, had not undergone a hysterectomy, and were aged ~18–45 years]

	Nirmatrelvir–ritonavir (n=49)	Placebo–ritonavir (n=51)
Age, years	42·0 (12·3)	43·1 (11·8)
Sex at birth		
Male	17 (35%)	17 (33%)
Female	32 (65%)	34 (67%)
Child-bearing potential	24 (49%)	29 (57%)
Race		
White	46 (94%)	45 (88%)
Black or African American	0	2 (4%)
Asian	2 (4%)	3 (6%)
Native Hawaiian or other Pacific Islander	0	0
American Indian or Alaskan Native	0	0
More than one race	0	1 (2%)
Other	1 (2%)	0 (0%)
Hispanic or Latino	4 (8%)	1 (2%)
US census region		
Northeast	27 (55%)	24 (47%)
Midwest	7 (14%)	12 (24%)
South	7 (14%)	4 (8%)
West	8 (16%)	11 (22%)
COVID-19 history		
Days from acute SARS-CoV-2 infection*	511 (362–777)	722 (433–1159)
Days from long COVID diagnosis or onset*	442 (282–645)	561 (362–1058)
Received at least 1 dose of COVID-19 vaccine	48 (98%)	49 (96%)
Received vaccine later than Sept 11, 2023, and before consent	6 (12%)	8 (16%)
Days from latest COVID-19 vaccination*	303 (92–588)	302 (37–483)

Data are mean (SD), n (%), or median (IQR). *All durations were calculated as the number of days between the date of the event, as documented in electronic health records, and the date of study consent.

Table 1: **Patient characteristics at time of enrolment (intention-to-treat population)**

and 34 (34%) were assigned male at birth. 91 (91%) participants self-identified as White, five (5%) as Asian, two (2%) as Black or African American, one (1%) as more than one race, and one (1%) identified their race as other. Five (5%) identified as Hispanic or Latino and 95 (95%) as non-Hispanic or Latino. Each of the US census regions was represented, with participants recruited from 28 (58%) of the 48 contiguous states. The baseline characteristics were similar across the randomised groups (table 1).

At baseline, participants in the nirmatrelvir–ritonavir group reported slightly better health status according to unadjusted mean scores compared with the placebo–ritonavir group across various patient-reported outcomes: PROMIS-29 PHSS (39·6 [95% CI 37·4–41·9] *vs* 36·3 [34·4–38·2]), PROMIS-29 MHSS (39·8 [38·1–41·6] *vs* 37·1 [35·6–38·6]), PROPr Score (0·203 [0·161–0·244] *vs* 0·147 [0·114–0·181]), GSQ-30 (40·3 [34·5–46·1] *vs* 51·1 [45·6–56·6]), COVID Core Outcome Measures for Recovery (2·7 [2·5–3·0] *vs* 2·9 [2·7–3·1]), EQ-5D-5L (10·7 [9·9–11·5] *vs* 11·9 [11·1–12·8]), and EQ-VAS (53·8 [49·0–58·6] *vs* 49·4 [44·0–54·8]; appendix pp 4–14). According to the GSQ-30 taken at baseline, 76 (76%) of 100 participants reported moderate-to-severe fatigue, 64 (64%) reported feeling worse after exertion, and 63 (63%) reported not feeling rested on awakening (appendix pp 15–25). 12 of the 30 baseline symptoms in the GSQ-30 were at least 10 or more percentage points lower in the nirmatrelvir–ritonavir group compared with the placebo–ritonavir group: not feeling rested on awakening (26 [53%] of 49 *vs* 37 [73%] of 51); headaches (six [12%] *vs* 16 [31%]); discomfort with normal light (three [6%] *vs* 12 [24%]); feeling fatigued (33 [67%] *vs* 43 [84%]); trouble falling or staying asleep (15 [31%] *vs* 24 [47%]); change in visual clarity (four [8%] *vs* 12 [24%]); trouble with memory (14 [29%] *vs* 22 [43%]); trouble finding words (19 [39%] *vs* 27 [53%]); hot or cold sensations in extremities (four [8%] *vs* 11 [22%]); needing more sleep than usual (18 [37%] *vs* 25 [49%]); stiff or painful neck (seven [14%] *vs* 13 [25%]); and feeling irritable (11 [22%] *vs* 17 [33%]). Additional baseline characteristics and medical history are provided in the appendix (pp 15–25).

The ITT analysis evaluating the primary efficacy endpoint, change in PROMIS-29 PHSS from baseline to day 28, did not show a significant difference between the nirmatrelvir–ritonavir group and the placebo–ritonavir group (mean difference –0·55 [95% CI –2·32 to 1·21], p=0·54) after adjustment (table 2). This effect estimate should be compared with a 5-point difference, which is considered clinically meaningful and for which the study was powered. On day 28, the mean PHSS was 40·0 (37·9 to 42·1) for the nirmatrelvir–ritonavir group and 37·8 (35·7 to 39·8) for the placebo–ritonavir group. Ten (10%) of 100 participants were missing data on the primary outcome and had their data imputed (six [12%] of 49 in the nirmatrelvir–ritonavir group and four [8%] of 51 in the placebo–ritonavir group). PROMIS-29 PHSSs from all timepoints can be found in figure 2 and the appendix (pp 4–13).

The modified ITT analysis and the per-protocol population analysis (appendix pp 4–13) did not show statistically significant differences between groups in the primary endpoint. Furthermore, no statistically significant differences were found for the PROMIS-29 MHSS, the PROPr Score, individual PROMIS-29 domain scores, or PROMIS-29 Cognitive Function score in any of the ITT, modified ITT, and per-protocol analyses (table 2).

An analysis of unadjusted scores at each timepoint suggested no differences in changes from baseline in PROMIS PHSS or MHSS between the two treatment groups across prespecified subgroups, including age, sex at birth, race, vaccination status, and US census region (appendix pp 4–13). Similarly, all other secondary endpoints including scores from the modified GSQ-30, COVID Core Outcome Measures for Recovery, EuroQol EQ-5D-5L, EQ-VAS, Patient Global Impression of Severity, Patient Global Impression of Change, and PROPr did not show statistically significant differences (table 3; appendix pp 31–48). Unadjusted scores from each timepoint can be found in the appendix (p 14).

From baseline to week 6, no deaths or serious adverse events were recorded in the safety population. Two (4%) SARS-CoV-2 reinfections occurred among the 49 participants exposed to treatment in the placebo–ritonavir group, and none occurred among the 46 participants exposed to treatment in the nirmatrelvir–ritonavir group. In total, 412 treatment-emergent adverse events were reported among 95 participants (table 4). 79 (83%) of these 95 participants had one or more treatment-emergent adverse events, with 12 (13%) having a severe event (six in each group; table 4). The most common treatment-emergent adverse events were dysgeusia (22 [48%] of 46 in the nirmatrelvir–ritonavir group *vs* three [6%] of 49 in the placebo–ritonavir group), headache (15 [33%] *vs* 19 [39%]), diarrhoea (14 [30%] *vs* 14 [29%]), and nausea (six [13%] *vs* 11 [22%]; appendix pp 26–29). Study-drug-related treatment-emergent adverse events were reported by 62 (65%) of 95 participants, with a higher incidence in the nirmatrelvir–ritonavir group compared with the placebo–ritonavir group (appendix pp 24–29). Early treatment termination due to an adverse event occurred in two participants in the nirmatrelvir–ritonavir group and one participant in the placebo–ritonavir group (table 4). There were no deaths in the study. The mean Functional Assessment of Chronic Illness Therapy Item GP5 scores were 1·4 (SD 1·0) on day 7 and 1·5 (1·1) on day 15 in the nirmatrelvir–ritonavir group, compared with 0·8 (0·8) on day 7 and 0·8 (1·1) on day 15 in the placebo–ritonavir group.

At day 28, while still masked, participants were asked whether they thought they had received nirmatrelvir–ritonavir or placebo–ritonavir. In the nirmatrelvir–ritonavir group, 19 (41%) of 46 participants correctly guessed their treatment, with 23 (50%) mistakenly believing they were taking a placebo (table 4). Conversely, 33 (67%) of 49 participants in the placebo–ritonavir group correctly identified their treatment and 15 (31%) incorrectly thought they were receiving nirmatrelvir–ritonavir (table 4).

	Nirmatrelvir–ritonavir (n=49)	Placebo–ritonavir (n=51)	Difference	p value
Primary endpoint, change from baseline*				
PROMIS-29 Physical Health Summary Score, day 28	0·45 (–0·93 to 1·83)	1·01 (–0·30 to 2·31)	–0·55 (–2·32 to 1·21)	0·54
Secondary endpoints, change from baseline*				
PROMIS-29 Physical Health Summary Score				
Day 15	0·84 (–0·67 to 2·35)	0·54 (–0·87 to 1·95)	0·30 (–1·60 to 2·20)	0·76
Day 28	0·41 (–1·10 to 1·91)	0·93 (–0·49 to 2·36)	–0·53 (–2·46 to 1·40)	0·59
Week 6	0·47 (–1·05 to 1·98)	1·62 (0·21 to 3·02)	–1·15 (–3·06 to 0·76)	0·24
PROMIS-29 Mental Health Summary Score				
Day 15	1·87 (0·09 to 3·65)	1·64 (0·01 to 3·27)	0·23 (–2·00 to 2·46)	0·84
Day 28	2·27 (0·52 to 4·01)	1·84 (0·20 to 3·48)	0·42 (–1·81 to 2·65)	0·71
Week 6	1·82 (0·07 to 3·57)	1·60 (–0·02 to 3·23)	0·22 (–2·01 to 2·44)	0·85
PROMIS-Preference Score				
Day 15	0·03 (–0·01 to 0·07)	0·03 (–0·01 to 0·06)	0·01 (–0·04 to 0·06)	0·79
Day 28	0·03 (–0·01 to 0·07)	0·03 (–0·01 to 0·07)	0·00 (–0·05 to 0·05)	0·96
Week 6	0·03 (–0·01 to 0·07)	0·04 (0·00 to 0·08)	–0·01 (–0·06 to 0·04)	0·75
PROMIS-29 domains				
Physical function†				
Day 15	0·63 (–0·87 to 2·12)	0·32 (–1·04 to 1·69)	0·30 (–1·57 to 2·18)	0·75
Day 28	0·07 (–1·41 to 1·56)	0·75 (–0·66 to 2·15)	–0·67 (–2·57 to 1·22)	0·49
Week 6	0·13 (–1·35 to 1·60)	1·48 (0·11 to 2·86)	–1·36 (–3·22 to 0·51)	0·15
Anxiety†				
Day 15	–2·50 (–4·63 to –0·37)	–1·24 (–3·18 to 0·69)	–1·26 (–3·95 to 1·43)	0·36
Day 28	–2·30 (–4·35 to –0·24)	–3·16 (–5·14 to –1·19)	0·87 (–1·78 to 3·51)	0·52
Week 6	–1·66 (–3·73 to 0·40)	–1·34 (–3·29 to 0·61)	–0·32 (–2·96 to 2·31)	0·81
Depression†				
Day 15	–1·10 (–3·16 to 0·97)	–1·62 (–3·57 to 0·33)	0·52 (–2·10 to 3·14)	0·70
Day 28	–2·11 (–4·11 to –0·12)	–1·82 (–3·79 to 0·15)	–0·29 (–2·90 to 2·31)	0·83
Week 6	–0·56 (–2·56 to 1·43)	–1·14 (–3·07 to 0·79)	0·58 (–1·99 to 3·14)	0·66
Fatigue†				
Day 15	–2·87 (–5·31 to –0·43)	–1·75 (–3·98 to 0·48)	–1·11 (–4·12 to 1·89)	0·47
Day 28	–2·98 (–5·36 to –0·59)	–1·78 (–4·03 to 0·46)	–1·19 (–4·20 to 1·81)	0·44
Week 6	–2·08 (–4·44 to 0·29)	–1·56 (–3·80 to 0·68)	–0·51 (–3·51 to 2·49)	0·74

(Table 2 continues on next page)

	Nirmatrelvir–ritonavir (n=49)	Placebo–ritonavir (n=51)	Difference	p value
(Continued from previous page)				
Sleep disturbance†				
Day 15	−0·93 (−2·67 to 0·81)	−1·21 (−2·87 to 0·46)	0·28 (−2·02 to 2·58)	0·81
Day 28	−1·88 (−3·63 to −0·13)	−0·09 (−1·75 to 1·58)	−1·79 (−4·08 to 0·50)	0·13
Week 6	−1·88 (−3·63 to −0·14)	−1·03 (−2·68 to 0·62)	−0·85 (−3·10 to 1·41)	0·46
Ability to participate in social roles and activities†				
Day 15	0·35 (−1·61 to 2·30)	1·00 (−0·80 to 2·80)	−0·66 (−3·12 to 1·81)	0·60
Day 28	0·76 (−1·19 to 2·70)	1·61 (−0·24 to 3·45)	−0·85 (−3·32 to 1·62)	0·50
Week 6	1·07 (−0·87 to 3·00)	1·29 (−0·53 to 3·10)	−0·22 (−2·67 to 2·22)	0·86
Pain—interference†				
Day 15	−2·14 (−4·33 to 0·05)	−0·88 (−2·96 to 1·20)	−1·26 (−4·04 to 1·52)	0·37
Day 28	−0·85 (−3·01 to 1·30)	−0·32 (−2·41 to 1·77)	−0·53 (−3·32 to 2·26)	0·71
Week 6	−1·74–3·89 to 0·41)	−0·67 (−2·73 to 1·39)	−1·07 (−3·84 to 1·69)	0·45
Pain—intensity†				
Day 15	−0·27 (−0·75 to 0·21)	−0·29 (−0·76 to 0·17)	0·02 (−0·59 to 0·64)	0·94
Day 28	−0·13 (−0·62 to 0·36)	−0·17 (−0·64 to 0·29)	0·04 (−0·58 to 0·66)	0·90
Week 6	−0·24 (−0·72 to 0·24)	−0·51 (−0·97 to −0·04)	0·27 (−0·35 to 0·89)	0·39
PROMIS version 2.0 Cognitive Function Short Form 6a				
Day 15	3·08 (1·05 to 5·12)	2·66 (0·75 to 4·56)	0·43 (−2·10 to 2·96)	0·74
Day 28	2·72 (0·66 to 4·77)	3·44 (1·52 to 5·36)	−0·73 (−3·28 to 1·82)	0·58

Data are mean (95% CI) change from baseline unless otherwise stated. Mean difference estimates with 95% CIs were obtained from a mixed models for repeated measures analysis fitted to assess the change from baseline in each PROMIS-29 Score, including treatment, time, and treatment-by-time interaction as fixed effects; age, sex, and baseline as covariates; and participant as a random effect. PROMIS=Patient-Reported Outcomes Measurement Information System. *The primary endpoint used only data up to 28 days for analysis. The secondary endpoints used data up to 6 weeks for analysis. †Mean T score.

***Table 2*: Primary and secondary endpoints (changes from baseline, intention-to-treat analysis with imputation)**

Upon reaching day 28, participants were asked to rate their overall experience in the trial. The mean overall satisfaction was 7·9 (SD 1·8) of 10, with a median of 8·0 (IQR 7·0–9·0); the mean rating for the participant experience with the PAX LC team was 8·6 (SD 1·7), with a median of 8·0 (IQR 7·0–10·0); and the mean score for likelihood of referring someone to the PAX LC trial or another similar trial was 8·3 (SD 2·1), with a median of 9·0 (IQR 7·0–10·0). Ratings for other sections of the exit interview are available in the appendix (pp 30–31).

Discussion

We found that a 15-day course of nirmatrelvir–ritonavir did not significantly improve the mean PROMIS-29 PHSS at day 28 compared with placebo–ritonavir in individuals with long COVID. Additionally, no significant differences were observed in our secondary endpoints. Despite these disappointing findings, the trial was successful in establishing an innovative approach to clinical research in patients with long COVID by implementing a fully decentralised design across the contiguous USA, with high participant-reported satisfaction.

The trial results align with the recently published STOP-PASC trial, which also found that nirmatrelvir–ritonavir was associated with no significant improvement in long COVID symptoms.[12] Our study is an advancement due to its decentralised approach, which enabled broader geographical participation within the USA, and use of validated outcome measures, albeit not specifically validated for long COVID. The consistency of results across both studies suggests that 15-day treatment with this antiviral is insufficient to treat long COVID.[4] Additional studies, such as the PROLIFIC trial (NCT05823896), which is testing the same 15-day treatment, and the RECOVER-VITAL trial (NCT05595369), which is testing the efficacy of a 25-day nirmatrelvir–ritonavir regimen in reducing three distinct long COVID symptoms, are expected to provide insight into whether treatment duration is the key issue. Future research might need to explore other agents or combinations of agents and focus on specific subgroups of individuals with long COVID to better address their unique needs.

Our findings do not overturn the viral persistence hypothesis.[24–26] The viral reservoirs might have been inaccessible to nirmatrelvir–ritonavir, or the drug dose might not have been high enough or of sufficient duration to eliminate the virus. Ample evidence suggests that these reservoirs exist, and they could be related to the underlying mechanisms of long COVID.[6,26] The PAX LC participants had biospecimens collected at baseline and day 28, and we have plans to conduct deep immune phenotyping of these specimens to seek biomarkers of disease activity and response to nirmatrelvir–ritonavir. Additionally, therapeutic agents that target various

proposed mechanisms, including neuroinflammation, excessive blood clotting, and autoimmunity, are urgently needed.[4,6]

The PAX LC trial, approved by a single institutional review board, established an innovative approach to clinical research and achieved a fully decentralised design that reduced the need for participants to visit research sites.[27] The participant experience scores suggest the trial fostered a culture of treating participants as partners, encouraging active, meaningful, and collaborative interaction between participants and the research team throughout the research process. Individuals with long COVID provided feedback about the study in the design phase, and an individual with long COVID participated in the data monitoring committee and is an author. This decentralised approach allowed the trial to leverage digital tools, such as electronic medical record access and online questionnaires, direct shipment of study drugs, home-based biospecimen collection, and local commercial laboratories for baseline and post-intervention blood samples. These efforts enhanced accessibility, broadened geographical diversity, and prioritised generating evidence that aligns with patient needs and priorities.

This study has several limitations. Given the digital nature of the trial and the requirement for a medical record and physician-confirmed diagnosis of long COVID, recruitment might have been skewed towards individuals with good access to digital infrastructure and health-care services, which could have resulted in a convenience sample rather than a fully representative trial population. Specifically, despite multiple campaigns through social media, podcasts, and webinars to target participant recruitment, we did not reach our pre-set diversity goal of recruiting 20% of participants from under-represented populations. The inability to meet this goal could be attributed to the higher prevalence of long COVID among young White female individuals compared with other sex, age, race, or ethnic groups, which in turn could be a result of differential disease recognition.[2,28,29] Digital recruitment strategies need to be improved to ensure broader participation. Another important limitation is the absence of a validated tool to assess treatment efficacy for long COVID. Although PROMIS-29 is a well validated instrument to assess functioning and wellbeing in physical, mental, and social health domains for various medical conditions and has been used in other long COVID research, the instrument has not been validated as a long COVID-specific instrument. As of writing, the symptom burden questionnaire for long COVID developed in the UK is the only instrument developed through rigorous, psychometric methods, but unfortunately it has not yet been validated in the USA.[30] Additionally, although we captured a range of symptoms through multiple patient-reported outcomes, treatment could have affected a specific symptom that we did not detect given the number of participants in our trial, which was not powered to assess individual symptoms. Although we added ritonavir to the placebo to mimic the dysgeusia of the active drug, the notable difference between groups in the frequency of dysgeusia reported as a treatment-emergent adverse event suggests that this approach might not have been entirely effective in masking

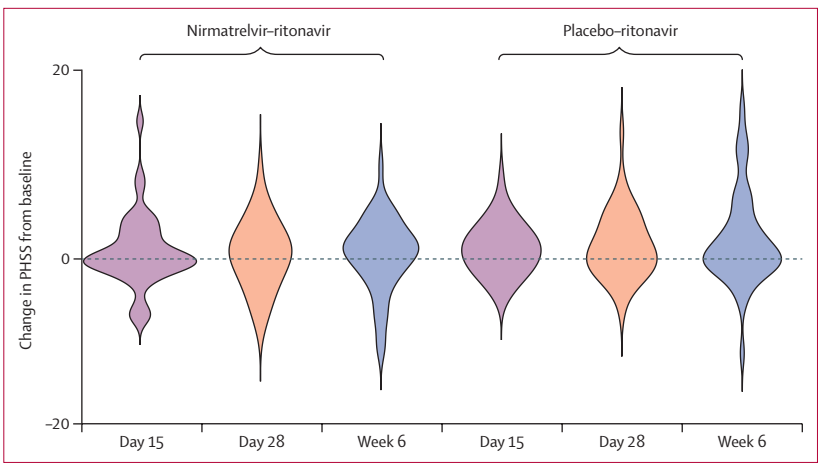

Figure 2: **Change in PHSS by timepoint (intention-to-treat population)**
The violin plot illustrates the change from baseline in the PHSS at each timepoint for participants in the nirmatrelvir–ritonavir group and placebo–ritonavir group. Positive values on the y-axis indicate improvement. The width of each violin represents the distribution and density of score changes, with wider sections showing a higher concentration of participants with that score. PHSS=Physical Health Summary Score.

	Nirmatrelvir–ritonavir (n=49)	Placebo–ritonavir (n=51)	Difference	p value
Modified GSQ-30 score				
Day 15	–9·72 (–14·52 to –4·92)	–7·98 (–12·40 to –3·57)	–1·74 (–7·82 to 4·34)	0·57
Day 28	–12·62 (–17·31 to –7·93)	–9·19 (–13·59 to –4·79)	–3·43 (–9·37 to 2·50)	0·26
COVID Core Outcome Measures for Recovery score				
Day 15	–0·10 (–0·36 to 0·15)	–0·10 (–0·34 to 0·14)	–0·01 (–0·33 to 0·32)	0·97
Day 28	–0·15 (–0·40 to 0·11)	–0·08 (–0·32 to 0·16)	–0·07 (–0·39 to 0·26)	0·68
EuroQol EQ-5D-5L				
Day 15	–0·41 (–1·11 to 0·30)	–0·48 (–1·14 to 0·17)	0·07 (–0·82 to 0·97)	0·87
Day 28	–0·57 (–1·25 to 0·12)	–0·54 (–1·20 to 0·11)	–0·02 (–0·89 to 0·85)	0·96
EuroQol Visual Analogue Scale score				
Day 15	5·79 (1·28 to 10·30)	1·23 (–2·97 to 5·43)	4·57 (–1·00 to 10·14)	0·11
Day 28	7·81 (3·32 to 12·30)	4·05 (–0·22 to 8·31)	3·76 (–1·91 to 9·44)	0·19
Patient Global Impression of Severity score				
Day 15	3·96 (3·62 to 4·30)	3·88 (3·56 to 4·20)	0·08 (–0·34 to 0·50)	0·71
Day 28	3·97 (3·63 to 4·31)	3·97 (3·65 to 4·29)	–0·00 (–0·42 to 0·42)	1·00
Week 6	3·98 (3·65 to 4·32)	3·86 (3·54 to 4·18)	0·12 (–0·30 to 0·54)	0·56
Patient Global Impression of Change overall health score				
Day 15	4·04 (3·69 to 4·38)	4·03 (3·70 to 4·35)	0·01 (–0·42 to 0·44)	0·97
Day 28	4·06 (3·71 to 4·40)	3·96 (3·64 to 4·29)	0·09 (–0·34 to 0·53)	0·67
Week 6	4·05 (3·71 to 4·39)	3·90 (3·58 to 4·23)	0·15 (–0·28 to 0·58)	0·49

Data are mean (95% CI) change from baseline unless otherwise indicated. Mean difference estimates with 95% CIs were obtained from a mixed models for repeated measures analysis fitted to assess the change from baseline in each secondary endpoint, including treatment, time, and treatment-by-time interaction as fixed effects; age, sex, and baseline as covariates; and participant as a random effect. GSQ=General Symptom Questionnaire. ITT=intention to treat.

Table 3: **Secondary endpoints (change from baseline, ITT with imputation)**

	Nirmatrelvir–ritonavir (n=46)	Placebo–ritonavir (n=49)
TEAEs		
Total number of TEAEs	199	213
Participants with one or more TEAEs	37 (80%)	42 (86%)
Maximum severity of TEAE*		
Mild	19 (41%)	21 (43%)
Moderate	12 (26%)	15 (31%)
Severe	6 (13%)	6 (12%)
Participants with one or more study drug-related TEAEs	35 (76%)	27 (55%)
Participants with one or more serious TEAEs	0	0
Participants with one or more study drug-related serious TEAEs	0	0
Participants with TEAEs resulting in termination of treatment	2 (4%)	1 (2%)
Deaths	0	0
Mean FACIT-Item GP5 score, difference from baseline		
n	43	48
Day 7	1·4 (1·0)	0·8 (0·8)
Day 15	1·5 (1·1)	0·8 (1·1)
Treatment compliance		
≥80%	42 (91·3)	41 (83·7)
<80%	4 (8·7)	8 (16·3)
Pharmacokinetic analysis†		
n	42	45
Days 7–14	42 (100%)	0
Missing	4 (9%)	4 (8%)
Response to survey question: "If you had to guess, do you think you received Paxlovid (the real medication) or the placebo (pills with no medication)?"		
n	46	49
Paxlovid	19 (41%)	15 (31%)
Placebo	23 (50%)	33 (67%)
Missing	4 (9%)	1 (2%)

Data are n (%) or mean (SD), unless otherwise stated. FACIT=Functional Assessment of Chronic Illness Therapy. TEAE=treatment-emergent adverse event. *Severity was determined subjectively by physician-study investigators by reviewing contents from the e-diaries and notes from conversations that occurred between patient and study coordinator. In general, mild was used for symptoms that did not necessitate any intervention and did not result in significant reduction in quality of life; moderate was used for symptoms that necessitated some symptom-alleviating medication or other measures that resulted in moderate reduction in quality of life with possibly a visit to the health-care provider office (but not emergency department visit or hospitalisation); and severe was used for symptoms that resulted in an emergency department visit or hospitalisation. †Nirmatrelvir concentrations were measured once in both groups between day 7 and day 14 as part of the at-home biospecimen collection. A few samples were not analysable due to poor sample condition (nirmatrelvir–ritonavir n=7; placebo–ritonavir n=6). All 45 placebo group samples included had values <10 ng/mL, which is the lower limit of quantification of the assay, and among the 42 analysed from the nirmatrelvir–ritonavir group, the range varied between 158 ng/mL and 7520 ng/mL.

Table 4: **Safety and tolerability (baseline to week 6, safety population)**

participants to their treatment allocation. Furthermore, the results observed in the exit survey might have been influenced by participants being informed during the consent process that the treatment could potentially affect taste, which might have shaped their perceptions and responses. One limitation related to our small sample size is that we randomly assigned participants in blocks of 2. We chose to use blocks of this size because of the large number of strata relative to the sample size but recognise that this meant that in some situations the next treatment assignment could have been predicted. However, the risk of bias was minimal given the decentralised design, and we consider it a reasonable trade-off against the risk of imbalance from using larger blocks. Finally, even with randomisation, ITT, modified ITT, and per-protocol analyses can be prone to bias; however, methods such as instrumental variable analysis, which could have addressed residual confounding and provided more robust causal inferences regarding the efficacy of the treatment for long COVID, were not prespecified in our analytical plan. Although our study population underwent block randomisation, baseline differences existed between the groups, such as in time since infection and long COVID diagnosis.

In conclusion, although our study did not show a significant benefit for a 15-day regimen of nirmatrelvir–ritonavir for long COVID symptoms, it contributes important data to the field and highlights the complexity of this condition. The decentralised trial design proved feasible and could serve as a model for future studies in this population. As the burden of long COVID continues to grow, ongoing research efforts remain crucial to develop effective treatments and improve outcomes for affected individuals.

Contributors

AI, HMK, and RK conceptualised the study. AC, YH, S-XL, and FW curated the data. DC, JHe, and S-XL did the formal analysis. LC, MDJ, AI, HMK, and DN were responsible for funding acquisition. MAM, BB, AI, RK, HMK, and MS were responsible for carrying out the investigation and managing individuals during the study. MAM, CC, HMK, S-XL, and JAS formulated the statistical analysis plan. MAM, BB, LC, MDJ, YH, JHo, ACH, AI, MAJ, HMK, DN, ER, and MS were responsible for project administration. KDC, AI, and HMK were responsible for contracting with various vendors involved and providing necessary environment and tools to preserve and process the biospecimens collected. AC and FW operated the software. BB, YH, JHo, ACH, AI, RK, HMK, S-XL, TBG, MS, and FWZ supervised the individuals who were conducting the patient enrolment, eligibility determination, and biospecimen analysis, and supervised all related activities. DC, YH, JHe, S-XL, and MS accessed and verified the data. WBH and S-XL visualised the figures. BB, YH, JHo, ACH, HMK, S-XL, and MS wrote the original draft. PA, BB, CC, KDC, LC, AC, MDJ, YH, JHe, JHo, ACH, AI, MAJ, RK, HMK, S-XL, DN, DFP, ER, MS, JAS, and FWZ reviewed and edited the Article. All authors had full access to all the data in the study and had final responsibility for the decision to submit the work for publication. The final decision about the content of the manuscript was solely made by HMK and AI.

Declaration of interests

MS was partly supported by Polybio. BB (in part) and CC (in full) were supported by a grant from the Yale-Mayo Clinic Center of Excellence in Regulatory Science and Innovation (U01FD005938). RK is an Associate Editor of *JAMA*. He receives support from the National Institutes of Health (NIH; awards R01HL167858, R01AG089981, and K23HL153775), the Doris Duke Charitable Foundation (award 2022060), and the Blavatnik Family Foundation. He also receives research support, through

Yale, from Bristol Myers Squibb, Novo Nordisk, and BridgeBio. He is a co-inventor of US Pending Patent Applications WO2023230345A1, US20220336048A1, 63/346,610, 63/484,426, 63/508,315, 63/580,137, 63/606,203, 63/619,241, 63/562,335 and 18/813,882. He is a co-founder of Ensight-AI and Evidence2Health, which are health platforms to improve cardiovascular diagnosis and evidence-based cardiovascular care. JAS has provided consultative services on patient-reported outcomes and evidence evaluation to Alnylam, AstraZeneca, Bayer, Janssen, Bristol Myers Squibb, Terumo, Cytokinetics, and Imbria. He holds research grants from the NIH, the Patient-Centered Outcomes Research Institute, the American College of Cardiology Foundation, BridgeBio, Bristol Myers Squibb, Cytokinetics, Imbria, and Janssen. He owns the copyright to the Seattle Angina Questionnaire, Kansas City Cardiomyopathy Questionnaire, and Peripheral Artery Questionnaire and serves on the board of directors for Blue Cross Blue Shield of Kansas City, MO, USA. AI co-founded RIGImmune, Xanadu Bio, and PanV, and is a member of the Board of Directors of Roche Holding and Genentech. In the past 3 years, HMK received stock options for Element Science and Identifeye and payments from F-Prime for advisory roles. He was a co-founder of and held equity in Hugo Health. He is a co-founder of and holds equity in Refactor Health and Ensight-AI. He is associated with research contracts through Yale University from Janssen, Kenvue, Novartis, and Pfizer. All other authors declare no competing interests.

Data sharing

Anonymised individual participant data can be requested from the corresponding author. These data and documents will be made available subject to approval by the trial steering committee and securing funding for data anonymisation.

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