Extended nirmatrelvir–ritonavir treatment durations for immunocompromised patients with COVID-19 (EPIC-IC): a placebo-controlled, randomised, double-blind, phase 2 trial

Edward Weinstein, Roger Paredes, Annie Gardner, Mary Almas, Mary Lynn Baniecki, Shunjie Guan, Elena Tudone, Simone Antonucci, Kevin Gregg, Carolina Garcia-Vidal, Adrian Camacho-Ortiz, Wayne Wisemandle, Steven G Terra, Sean Liu, Judith A Aberg, Meenakshi M Rana, Lawrence Corey, Emily S Ford, Jennifer Hammond, James Rusnak

Summary

Background Nirmatrelvir–ritonavir is approved for adults with mild-to-moderate COVID-19 who are at risk of severe disease. There are little clinical data to guide the duration of therapy in patients who are immunocompromised. We aimed to compare the approved 5-day regimen of nirmatrelvir–ritonavir with 10-day and 15-day regimens.

Methods This placebo-controlled, randomised, double-blind, phase 2 trial enrolled non-hospitalised, immunocompromised individuals aged 12 years or older with symptomatic COVID-19 from 73 sites across nine countries. Participants were randomly assigned (1:1:1) to receive 300 mg nirmatrelvir and 100 mg ritonavir orally twice per day for 5, 10, or 15 days. Randomisation was stratified according to whether participants were considered immunocompromised due to use of corticosteroids or tumour necrosis factor blockers. Investigators, participants, and caregivers were masked to the assigned study group. The primary endpoint was proportion of randomly assigned and dosed participants with sustained nasopharyngeal SARS-CoV-2 RNA concentrations below the lower limit of quantification (2·0 $\log_{10}$ copies per mL) from days 15 to 44. Secondary endpoints included the incidence of viral rebound after the end of treatment up to day 44. Safety, a secondary endpoint, was assessed in all randomly assigned participants who received at least one dose of nirmatrelvir–ritonavir. This trial was registered with ClinicalTrials.gov (NCT05438602) and is completed.

Findings Among 156 participants (84 female, 72 male) randomly assigned from Aug 3, 2022 to July 17, 2023, 150 comprised the analysis population. The primary endpoint was reached in 32 (61·5%, 95% CI 48·3–74·8) of 52 participants in the 5-day treatment group, 34 (70·8%, 58·0–83·7) of 48 participants in the 10-day treatment group, and 33 (66·0%, 52·9–79·1) of 50 participants in the 15-day treatment group. Viral rebound occurred in 17·3% (95% CI 8·2–30·3) of participants in the 5-day group, 2·1% (0·1–11·1) in the 10-day group, and 2·0% (0·1–10·6) in the 15-day group. Adverse events occurred in 28 (52·8%) of 53, 34 (66·7%) of 51, and 31 (60·8%) of 51 participants across the 5-day, 10-day, and 15-day groups, respectively. Two COVID-19-related hospitalisations were reported, both in the 5-day treatment group.

Interpretation No difference was observed between the three treatment durations in the primary endpoint. Extending nirmatrelvir–ritonavir treatment beyond 5 days resulted in a nominal improvement in the frequency of viral rebound and was generally well tolerated.

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Antivirals, Global Product Development, Pfizer, New York, NY, USA (E Weinstein MD, M Almas MS); **Hospital Germans Trias i Pujol, Badalona, Spain** (R Paredes MD); **Center for Global Health and Diseases, Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, OH, USA** (R Paredes); **Pfizer, Cambridge, MA, USA** (A Gardner MS, M L Baniecki PhD, S Guan PhD, S G Terra PharmD); **Pfizer, Milan, Italy** (E Tudone MA, S Antonucci MD); **Division of Infectious Diseases, University of Michigan Medical School, University of Michigan, Ann Arbor, MI, USA** (Prof K Gregg MD); **Hospital Clinic of Barcelona-IDIBAPS, Barcelona, Spain** (C Garcia-Vidal PhD); **Hospital Universitario Dr José Eleuterio González, Monterrey, Mexico** (Prof A Camacho-Ortiz PhD); **Pfizer, Lake Forest, IL, USA** (W Wisemandle MA); **Icahn School of Medicine at Mt Sinai, New York, NY, USA** (S Liu MD, Prof J A Aberg MD, M M Rana MD); **Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA** (Prof L Corey MD, E S Ford MD); **Pfizer, Collegeville, PA, USA** (J Hammond PhD); **Pfizer, Tampa, FL, USA** (J Rusnak MD)

Correspondence to: Dr Edward Weinstein, Antivirals, Global Product Development, Pfizer, New York, NY 10001, USA **edward.weinstein@pfizer.com**

Introduction

More than 5 years since the start of the pandemic, COVID-19 continues to threaten public health and health-care systems worldwide.[1] Older individuals and people with comorbidities remain at greatest risk of progression to severe disease.[2] COVID-19 poses a particular threat to people who are immunocompromised, who have impaired immune responses to promote viral clearance, leading to prolonged infection and an increased potential for both viral resistance and severe disease.[3–6] Although COVID-19 vaccines have drastically reduced the risk of severe disease, hospitalisation, and death for most individuals, patients who are moderately to severely immunocompromised often have suboptimal immune response after vaccination.[7–11] Current treatment guidelines from the Infectious Diseases Society of America (IDSA) recommend that individuals with mild-to-moderate COVID-19 at high risk for progression to severe disease, which includes people with immunocompromising conditions, receive prompt treatment with the antivirals nirmatrelvir–ritonavir (Paxlovid, Pfizer, New York, NY, USA) or remdesivir, or with anti-SARS-CoV-2 monoclonal antibodies if circulating variants are susceptible.[12] If these options are unavailable, the IDSA recommends consideration of molnupiravir or, particularly in individuals who are immunocompromised, high-titre convalescent plasma with activity against circulating variants.

Research in context

Evidence before this study

Nirmatrelvir–ritonavir (Paxlovid, Pfizer, New York, NY, USA) is a SARS-CoV-2 main protease inhibitor approved in more than 70 countries worldwide to treat COVID-19 among adults who are at high risk of progression to severe disease. Numerous clinical and real-world studies have shown efficacy and effectiveness of nirmatrelvir–ritonavir at the approved dosage of 300 mg nirmatrelvir and 100 mg ritonavir twice per day for 5 days in reducing risk of hospitalisation and death. However, among immunocompromised patients, SARS-CoV-2 RNA and clinical progression often persist after completion of the approved 5-day treatment course. This issue is of particular concern because the impaired immune responses of these patients can lead to reduced viral clearance, prolonged infection, viral resistance, and severe clinical outcomes. A PubMed search of randomised clinical trials up to March 15, 2025, with no language restrictions and with the terms "persistent COVID-19" and "immunocompromise" did not yield any studies. No clear guidelines are available regarding how to treat immunocompromised patients, for whom the standard of care might be insufficient. However, one small retrospective, observational study by Götz and colleagues suggested that symptoms and radiological changes associated with persistent viral replication in severely immunocompromised patients were at least partially reversible by prolonging the treatment course. We conducted a randomised controlled trial to investigate whether 10-day or 15-day treatment with nirmatrelvir–ritonavir can improve sustained viral clearance compared with 5-day treatment among immunocompromised adolescents and adults with mild-to-moderate COVID-19.

Added value of this study

Among the 150 immunocompromised participants in the analysis population, similar percentages across the 5-day, 10-day, and 15-day treatment groups had concentrations of SARS-CoV-2 RNA (viral load) sustained below the lower limit of quantification from the end of treatment (day 15) up to 44 days. A shorter time to viral clearance was observed with longer treatment duration (median 15, 11, and 10 days in the 5-day, 10-day, and 15-day treatment groups, respectively). Viral RNA rebound after the end of treatment also occurred more frequently among participants treated for 5 days compared with those treated for 10 or 15 days. In a subset of 57 participants who were considered severely immunocompromised (due to receipt of chimeric antigen receptor T-cell therapy, B-cell-depleting therapies, haematopoietic stem-cell transplantation, or haematological malignancy), post-hoc analyses suggested that extending nirmatrelvir–ritonavir treatment beyond 5 days might improve time to SARS-CoV-2 viral clearance. Safety profiles were consistent across the three treatment duration groups, and no new safety signals were identified.

Implications of all the available evidence

For most immunocompromised patients, the approved 5-day course of nirmatrelvir–ritonavir treatment is likely to promote sustained viral clearance and sufficiently control disease progression. Additional studies are needed to confirm whether extended nirmatrelvir–ritonavir treatment durations might better control viral load and rebound risk compared with the standard 5-day treatment course among severely immunocompromised patients.

Nirmatrelvir–ritonavir is a SARS-CoV-2 M^{pro} inhibitor approved in more than 70 countries worldwide for the treatment of mild-to-moderate COVID-19 among adults at high risk of severe disease progression.[13,14] Nirmatrelvir–ritonavir has shown robust antiviral activity and efficacy across clinical and real-world studies for the prevention of hospitalisation and death.[14–20]

The approved dosage of nirmatrelvir–ritonavir is 300 mg nirmatrelvir and 100 mg ritonavir orally twice per day for 5 days (if estimated glomerular filtration rate is ≥60 mL/min).[14] However, both SARS-CoV-2 positivity and symptoms often persist after 5 days of treatment in people who are immunocompromised.[21–23] The optimal treatment strategy for COVID-19 is particularly uncertain in the subset of patients who are severely immunocompromised due to impaired humoral immunity, with some guidelines recommending combination or extended durations of antiviral therapy, or both.[24] In one small study[25] in patients who were severely immunocompromised, symptoms and radiological changes associated with persistent viral replication were partially or completely reversed with prolonged antiviral treatment, suggesting that this population might benefit from longer treatment durations. In our study, we aimed to evaluate the efficacy and safety of 5-day, 10-day, and 15-day nirmatrelvir–ritonavir regimens among people who are immunocompromised to determine whether they might benefit from durations of therapy longer than the approved 5-day treatment course.

See Online for appendix

For the **protocol and statistical analysis plan** see https://www.clinicaltrials.gov/study/NCT05438602

Methods

Study design

This phase 2, randomised, double-blind, placebo-controlled study was conducted at 73 outpatient clinics, including hospital-based, community, or dedicated research facilities, across nine countries (Spain, the USA, Slovakia, Mexico, Canada, Australia, Brazil, Hungary, and Bulgaria; appendix pp 2–3). The trial protocol and statistical analysis plan are available online. Ethics approval was provided by central or local independent review boards (listed in the appendix p 4). The trial is registered with ClinicalTrials.gov, NCT05438602.

Participants

Participants were recruited through internal sources (eg, site internal databases and referrals), external sources (eg, advertisements and external referrals), patient-facing

and site-facing materials, and media campaigns through recruitment vendors. Eligible participants were non-hospitalised, immunocompromised adults and adolescents (aged ≥12 years and weighing ≥40 kg) with confirmed, symptomatic COVID-19 who tested positive within 5 days before randomisation. Immunocompromised status was consistent with the US Centers for Disease Control and Prevention's (CDC's) categorisation of moderate-to-severe immunocompromising conditions (appendix p 5).[26] A post-hoc subpopulation of participants who were severely immunocompromised was defined as individuals with haematological malignancy or who had received chimeric antigen receptor T-cell therapy, B-cell-depleting therapies, or haematopoietic stem-cell transplantation. Key exclusion criteria included a current or anticipated need for hospitalisation within 24 h of randomisation, medical history of active liver or kidney disease, systemic infection other than COVID-19, any life-threatening comorbidity or comorbidity requiring hospitalisation or surgery within 7 days before randomisation, dialysis, or early pregnancy. See the appendix (p 5) for a full list of inclusion and exclusion criteria. All participants provided written informed consent. The biological sex of participants was determined by study site investigators from the participant's medical history and physical examination. Race and ethnicity information was collected from the participants by the investigator at screening.

Randomisation and masking

Participants were randomly assigned (1:1:1) to receive nirmatrelvir–ritonavir for 5, 10, or 15 days. Participants in the 5-day treatment group received placebo for the last 10 days of treatment and participants in the 10-day treatment group received placebo for the last 5 days of treatment.

The randomisation sequence was developed centrally by Pfizer, and randomisation was conducted with the use of interactive response technology, whereby the site study coordinator or specified designee entered user identification and password, protocol number, and participant number to be provided with a randomisation number corresponding to assigned treatment group (5-day, 10-day, or 15-day treatment). A confirmation report was generated for each participant and stored in the site's files. Randomisation was stratified according to whether participants were considered immunocompromised solely due to use of corticosteroids or tumour necrosis factor blockers, and inclusion of these participants was capped at approximately 25%.

All investigators, participants, and participant caregivers were masked to the assigned study intervention. Sponsor staff were also masked, except for staff who were not directly involved with study conduct but were required to prepare documentation and analysis for use by the data monitoring committee. Participants were enrolled by the individual site investigators and their staff; investigators were involved in the collection of the study data in a masked manner. The placebo tablets had an identical appearance to the active tablet. Masking was maintained throughout the study period. See appendix (p 5) for additional details and ethics considerations.

Procedures

Participants received 300 mg nirmatrelvir and 100 mg ritonavir orally every 12 h for 5, 10, or 15 days. Each dose was administered as two tablets of nirmatrelvir or placebo and one capsule of ritonavir or placebo. Per US prescribing information for nirmatrelvir–ritonavir,[14] participants with moderate renal impairment (estimated glomerular filtration rate from 30 to <60 mL/min or estimated creatinine clearance from 30 to <60 mL/min) received a reduced dose of 150 mg nirmatrelvir and 100 mg ritonavir.

Study duration was 24 weeks, including the 15-day treatment phase, safety and efficacy assessments up to day 44, and long-term follow-up at weeks 12 and 24 (appendix p 8). Single nasopharyngeal swabs were collected at baseline (day 0); on days 5, 10, 15, 21, 28, 35, and 44; and at weeks 12 and 24 for SARS-CoV-2 detection by RT-PCR; done at the University of Washington Retrovirology Laboratory, Seattle, WA, USA) and rapid antigen testing (RAT; done at the site using study-provided kits). Viral sequencing was also performed on samples with nasopharyngeal SARS-CoV-2 RNA (viral load) of at least $3\cdot0$ $\log_{10}$ copies per mL (performed at the University of Washington Retrovirology Laboratory; appendix p 6). Serology status was assessed on days 0, 10, 15, 35, and 44 and at weeks 12 and 24. Viral load and serology status were measured as described previously (appendix p 7).[19] Presence and severity of COVID-19 signs and symptoms were reported by participants at each visit using an electronic diary up to week 24, and adverse events (AEs) were actively solicited up to day 44. AEs were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

Outcomes

The primary objective was to assess the proportion of participants who were able to maintain a low or undetectable SARS-CoV-2 viral load from days 15 to 44 of the study after nirmatrelvir–ritonavir treatment for 5, 10, or 15 days. This endpoint was defined as the percentage of participants with sustained viral load below the lower limit of quantification (LLOQ; defined as $<2\cdot0$ $\log_{10}$ copies per mL) from days 15 to 44, where sustained indicates that once the viral load was lower than the LLOQ, it was not recorded at or above the LLOQ at any subsequent visit. To meet these criteria, data had to be available on days 14 and 44 and at least one of days 21, 28, and 35; participants were otherwise considered as not meeting the primary endpoint. Prespecified secondary endpoints included time to initial and time to sustained viral load below the LLOQ up to day 44 (among participants with baseline viral load ≥LLOQ); proportion of participants with viral rebound (defined as

viral load increase of ≥0·5 log_{10} copies per mL after treatment cessation, resulting in a follow-up viral load ≥2·5 log_{10} copies per mL up to day 44); change from baseline in viral load; proportion of participants with viral load below LLOQ over time at each study visit; duration of each targeted COVID-19 sign or symptom; proportion of participants with severe signs or symptoms attributed to COVID-19 up to day 44; proportion of participants with COVID-19-related hospitalisation, admission to an intensive care unit, or death from any cause; proportion of participants requiring invasive mechanical ventilation or extracorporeal membrane oxygenation; number of COVID-19-related hospitalisation days; number of COVID-19-related medical visits; nirmatrelvir and ritonavir pharmacokinetics; and incidence of AEs, serious AEs (SAEs), and AEs leading to study discontinuations. Post-hoc endpoints included proportion of participants with any positive SARS-CoV-2 RAT from days 15 to 44 and the emergence of SARS-CoV-2 M^{pro} or cleavage site mutations in at least two participants.

Statistical analysis

EPIC-IC was a descriptive study as there was little previous knowledge of the potential treatment effect on virological endpoints to adequately power the study for inference testing. No formal hypothesis testing was done, and statistics for all endpoints were not prespecified. Baseline characteristics were summarised in all randomly assigned patients (the full analysis set [FAS]). All endpoints were descriptively analysed in the evaluable analysis set (EAS) or safety analysis set (SAS), which included all participants who were randomly assigned and dosed. Additional post-hoc analyses of the primary and secondary efficacy endpoints were conducted within the subset of participants who were severely immunocompromised. These same endpoints were also evaluated in the subset of participants who did not meet this definition and were therefore considered non-severely immunocompromised.

Details regarding oversight by a data monitoring committee are provided in the appendix (p 5). Because no formal hypothesis testing was conducted, no power calculation was done to assess the number of participants required for each treatment arm. Up to 200 participants were planned to be enrolled with approximately 50 participants randomly assigned (1:1:1) to each treatment group based on study feasibility. For the main study population, the goal of the primary analysis was to estimate the treatment effect for each duration of nirmatrelvir–ritonavir. The small numbers of participants in these groups are reflected in the precision of the estimates for the primary endpoint. The appendix (p 14) shows the precision (width of the confidence interval) for the respective proportion to be estimated with a sample size of 50 when the proportion of participants with sustained nasopharyngeal swab SARS-CoV-2 RNA below LLOQ from day 15 to day 44 ranges from 0·1 to 0·5; that is, the width of the 95% CI does not exceed 14%. Analyses were done with SAS software (version 9.4).

Role of the funding source

The funder of the study was responsible for study design and conduct, data collection, data analysis, data interpretation, manuscript writing, and the decision to submit the manuscript for publication.

Results

From Aug 3, 2022, to July 17, 2023, 156 immunocompromised participants were randomly assigned (FAS; figure 1). Of these, one was randomly assigned but not treated and five were excluded from efficacy analyses due to anomalous laboratory values at one study site. The remaining 150 (96·2%) of 156 participants were included in the EAS (5-day, n=52; 10-day, n=48; and 15-day, n=50); the 155 (99·4%) participants who received at least one dose of nirmatrelvir–ritonavir were included in the SAS. Baseline characteristics in the FAS were similar between groups (table 1). Overall, 144 (92·3%) of 156 participants had a quantifiable baseline viral load (≥2·0 log_{10} copies per mL). 84 (53·8%) participants were female, 141 (90·4%) were White, and the median age was 58 years (range 16–82). Most participants—136 (87·2%)—had been vaccinated against COVID-19; however, only 24 (15·4%) had received their last dose within 6 months before randomisation. The most common reasons for immunocompromised status were receipt of immunosuppressant drug therapy (138 [88·5%]) and haematological malignancy (54 [34·6%]). 30 (19·2%) participants were considered immunocompromised based only on the use of corticosteroids or tumour necrosis factor blockers.

Within the FAS, 57 (36·5%) participants were included in the severely immunocompromised subgroup (table 1). Within this subset, 54 (94·7%) of 57 had an underlying haematological malignancy. Baseline median titre of SARS-CoV-2 anti-spike antibodies was lower among severely immunocompromised (1378 [IQR 200–6052] U/mL) compared with non-severely immunocompromised (5008 [1882–12 378] U/mL) participants. Regarding nirmatrelvir–ritonavir drug exposure, the plasma steady-state exposures of nirmatrelvir in the presence of ritonavir were similar among the 5-day, 10-day, and 15-day treatment groups (appendix p 9).

In the overall EAS, 32 (61·5%, 95% CI 48·3–74·8) of 52 participants in the 5-day, 34 (70·8%, 58·0–83·7) of 48 in the 10-day, and 33 (66·0%, 52·9–79·1) of 50 in the 15-day treatment groups had sustained viral load below the LLOQ from days 15 to 44, with no observed differences across groups (nominal p=0·62; figure 2, appendix p 16). Median time to reach a sustained viral load below the LLOQ in the overall population was numerically longer in the 5-day group (15 days, 95% CI 9–16) compared with the 10-day group (11 days, 10–15) and 15-day group (10 days, 9–16; appendix pp 17–21).

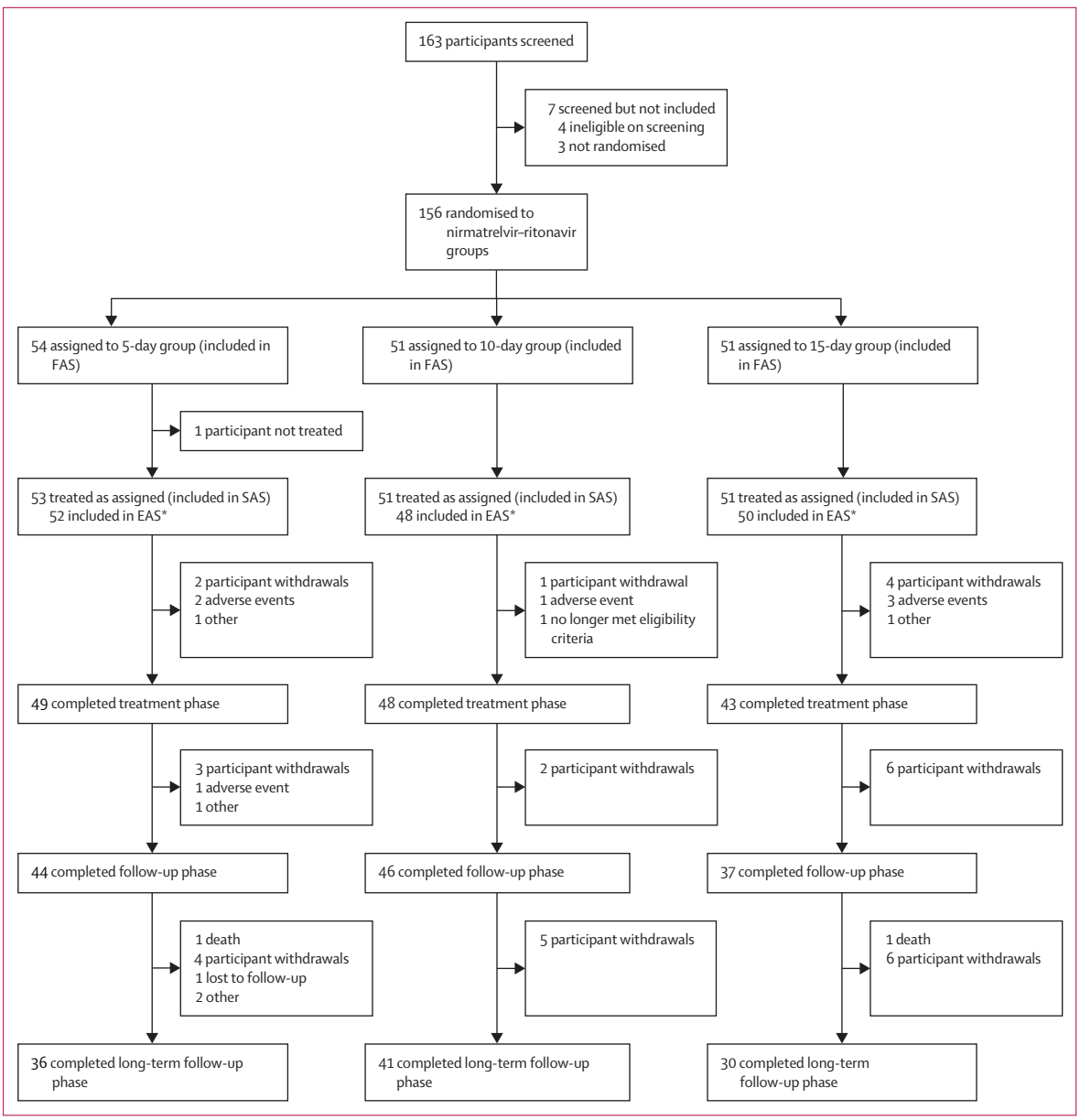

Figure 1: **Participant disposition during treatment and follow-up phases**
EAS=evaluable analysis set. FAS=full analysis set. SAS=safety analysis set. *Five participants were excluded from efficacy analysis due to anomalous laboratory values at one study site.

Within the subset of severely immunocompromised participants, viral clearance was sustained between days 15 and 44 in 11 (64·7%, 95% CI 42·0–87·4) of 17 and eight (40·0%, 18·5–61·5) of 20 participants treated for 10 days and 15 days, respectively, compared with seven (35·0%, 14·1–55·9) of 20 participants treated for 5 days (figure 2; appendix p 16). The median time to reach a sustained viral load below the LLOQ was substantially higher in the severely immunocompromised versus the non-severely immunocompromised population after 5 days of treatment (28 [range 9–33] *vs* 10 [6–15] days; difference 18 days). Differences between these subgroups were less pronounced among individuals treated for 10 days (13 [10–16] *vs* 11 [9–15] days; difference 2 days) or 15 days (15 [9–28] *vs* 9 [6–15] days; difference 6 days; appendix pp 10–12). Most participants who continued to test positive also continued to experience symptoms; severely immunocompromised participants treated for 5 days were less likely than those who received extended treatment to be symptom-free and SARS-CoV-2-negative by PCR (appendix pp 6, 13).

Numbers of participants with viral RNA rebound from days 15–44 were lower among participants in the 10-day and 15-day groups compared with the 5-day group,

	Overall population				Severely immunocompromised population				Non-severely immunocompromised population			
	5-day group (n=54)	10-day group (n=51)	15-day group (n=51)	Total (n=156)	5-day group (n=20)	10-day group (n=17)	15-day group (n=20)	Total (n=57)	5-day group (n=34)	10-day group (n=34)	15-day group (n=31)	Total (n=99)
Age, years												
Median (range)	58 (19–80)	58 (16–82)	58 (28–80)	58 (16–82)	68 (19–77)	66 (24–82)	56 (34–78)	64 (19–82)	54 (23–80)	54 (16–79)	58 (28–80)	57 (16–80)
IQR	(48–69)	(48–66)	(46–65)	(46–67)	(52–71)	(58–68)	(46–69)	(49–70)	(42–61)	(46–61)	(48–63)	(46–62)
Sex												
Female	28 (51·9%)	30 (58·8%)	26 (51·0%)	84 (53·8%)	9 (45·0%)	6 (35·3%)	6 (30·0%)	21 (36·8%)	19 (55·9%)	24 (70·6%)	20 (64·5%)	63 (63·6%)
Male	26 (48·1%)	21 (41·2%)	25 (49·0%)	72 (46·2%)	11 (55·0%)	11 (64·7%)	14 (70·0%)	36 (63·2%)	15 (44·1%)	10 (29·4%)	11 (35·5%)	36 (36·4%)
Race												
White	50 (92·6%)	47 (92·2%)	44 (86·3%)	141 (90·4%)	17 (85·0%)	16 (94·1%)	18 (90·0%)	51 (89·5%)	33 (97·1%)	31 (91·2%)	26 (83·9%)	90 (90·9%)
Black	1 (1·9%)	0	1 (2·0%)	2 (1·3%)	1 (5·0%)	0	0	1 (1·8%)	0	0	1 (3·2%)	1 (1·0%)
American Indian, or Alaskan Native	1 (1·9%)	3 (5·9%)	3 (5·9%)	7 (4·5%)	0	1 (5·9%)	1 (5·0%)	2 (3·5%)	1 (2·9%)	2 (5·9%)	2 (6·5%)	5 (5·1%)
Not reported	2 (3·7%)	1 (2·0%)	3 (5·9%)	6 (3·8%)	2 (10·0%)	0	1 (5·0%)	3 (5·3%)	0	1 (2·9%)	2 (6·5%)	3 (3·0%)
Ethnicity												
Hispanic or Latino	37 (68·5%)	33 (64·7%)	32 (62·7%)	102 (65·4%)	12 (60·0%)	10 (58·8%)	11 (55·0%)	33 (57·9%)	25 (73·5%)	23 (67·6%)	21 (67·7%)	69 (69·7%)
Not Hispanic or Latino	15 (27·8%)	18 (35·3%)	19 (37·3%)	52 (33·3%)	7 (35·0%)	7 (41·2%)	9 (45·0%)	23 (40·4%)	8 (23·5%)	11 (32·4%)	10 (32·3%)	29 (29·3%)
Not reported	2 (3·7%)	0	0	2 (1·3%)	1 (5·0%)	0	0	1 (1·8%)	1 (2·9%)	0	0	1 (1·0%)
BMI, kg/m^2												
Median (range)	28 (18–45)	28 (17–48)	25 (16–46)	27 (16–48)	25 (19–40)	27 (17–31)	23 (16–41)	25 (16–41)	30 (18–45)	29 (21–48)	27 (18–46)	28 (18–48)
IQR	(24–32)	(25–31)	(23–29)	(24–31)	(23–29)	(24–28)	(22–27)	(23–28)	(26–32)	(26–32)	(23–30)	(25–32)
SARS-CoV-2 vaccination status												
Vaccinated within 6 months before randomisation	7 (13·0%)	8 (15·7%)	9 (17·6%)	24 (15·4%)	2 (10·0%)	3 (17·6%)	5 (25·0%)	10 (17·5%)	5 (14·7%)	5 (14·7%)	4 (12·9%)	14 (14·1%)
Vaccinated >6 months before randomisation	39 (72·2%)	37 (72·5%)	36 (70·6%)	112 (71·8%)	16 (80·0%)	13 (76·5%)	13 (65·0%)	42 (73·7%)	23 (67·6%)	24 (70·6%)	23 (74·2%)	70 (70·7%)
Unvaccinated before randomisation	8 (14·8%)	6 (11·8%)	6 (11·8%)	20 (12·8%)	2 (10·0%)	1 (5·9%)	2 (10·0%)	5 (8·8%)	6 (17·6%)	5 (14·7%)	4 (12·9%)	15 (15·2%)
Anti-spike antibody serology status												
Positive	52 (96·3%)	50 (98·0%)	51 (100%)	153 (98·1%)	20 (100%)	17 (100%)	20 (100%)	57 (100%)	32 (94·1%)	33 (97·1%)	31 (100%)	96 (97·0%)
Negative	0	1 (2·0%)	0	1 (0·6%)	0	0	0	0	0	1 (2·9%)	0	1 (1·0%)
Median anti-spike, U/mL† (IQR)	2776 (1380–9332)	2309 (290–8752)	5008 (1341–11 657)	3157 (910–10 528)	1948 (762–5421)	717 (199–4101)	1632 (146–6696)	1378 (200–6052)	4676 (1963–14 410)	3856 (709–10 307)	5451 (2698–12 108)	5008 (1882–12 378)
SARS-CoV-2 nasopharyngeal RNA, log_{10} copies per mL												
≥2	49 (90·7%)	47 (92·2%)	48 (94·1%)	144 (92·3%)	19 (95·0%)	16 (94·1%)	18 (90·0%)	53 (93·0%)	30 (88·2%)	31 (91·2%)	30 (96·8%)	91 (91·9%)
≥7	20 (37·0%)	22 (43·1%)	28 (54·9%)	70 (44·9%)	9 (45·0%)	5 (29·4%)	9 (45·0%)	23 (40·4%)	11 (32·4%)	17 (50·0%)	19 (61·3%)	47 (47·5%)
Median (range)	7 (0–9)	7 (0–9)	7 (0–9)	7 (0–9)	7 (4–9)	7 (0–9)	7 (2–9)	7 (0–9)	6 (0–9)	7 (0–9)	8 (0–9)	7 (0–9)
IQR	(4–8)	(5–8)	(5–8)	(5–8)	(6–8)	9 (6–7)	(4–8)	(6–8)	(4–8)	9 (4–8)	(5–8)	(4–8)

(Table 1 continues on next page)

	Overall population				Severely immunocompromised population				Non-severely immunocompromised population			
	5-day group (n=54)	10-day group (n=51)	15-day group (n=51)	Total (n=156)	5-day group (n=20)	10-day group (n=17)	15-day group (n=20)	Total (n=57)	5-day group (n=34)	10-day group (n=34)	15-day group (n=31)	Total (n=99)
(Continued from previous page)												
Reason for being immunocompromised												
Immunosuppressant drug therapy	46 (85·2%)	46 (90·2%)	46 (90·2%)	138 (88·5%)	13 (65·0%)	16 (94·1%)	17 (85·0%)	46 (80·7%)	33 (97·1%)	30 (88·2%)	29 (93·5%)	92 (92·9%)
Haematological malignancy	19 (35·2%)	15 (29·4%)	20 (39·2%)	54 (34·6%)	19 (95·0%)	15 (88·2%)	20 (100%)	54 (94·7%)	0	0	0	0
CAR T-cell therapy or haematopoietic stem-cell transplant infusion	7 (13·0%)	7 (13·7%)	6 (11·8%)	20 (12·8%)	7 (35·0%)	7 (41·2%)	6 (30·0%)	20 (35·1%)	0	0	0	0
Corticosteroids or TNF blockers‡	11 (20·4%)	9 (17·6%)	10 (19·6%)	30 (19·2%)	0	0	0	0	11 (32·4%)	9 (26·5%)	10 (32·3%)	30 (30·3%)

Data are n (%) unless otherwise indicated. CAR T cell=chimeric antigen receptor T cell. IC=immunocompromised. TNF=tumour necrosis factor. *Includes all randomly assigned participants. †For median calculations, n=52 among the 5-day group in the overall population and n=32 among the 5-day group in the non-severely immunocompromised population. ‡Data reflect numbers of participants for whom corticosteroids or TNF blockers were their sole reason for IC status, not the total numbers of participants using corticosteroids or TNF blockers upon study entry.

Table 1: **Demographics and baseline clinical characteristics in the full analysis set***

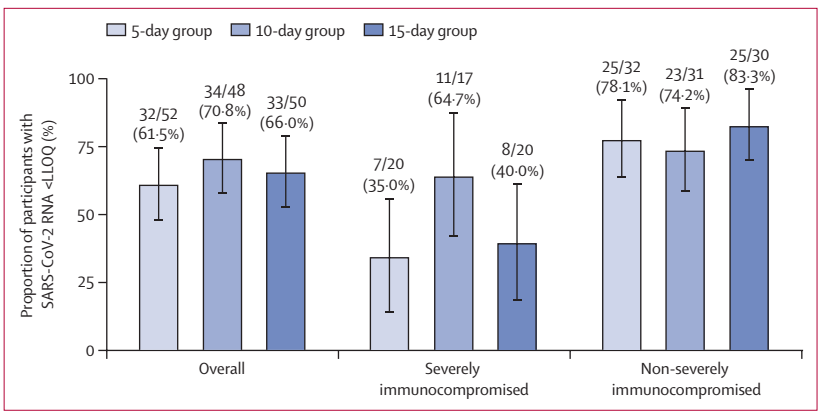

Figure 2: **Percentages of participants with sustained viral loads below LLOQ from day 15 to day 44 (evaluable analysis set)**

Error bars represent 95% CIs. LLOQ=lower limit of quantification.

regardless of whether they were severely or non-severely immunocompromised (figure 3). Overall, viral RNA rebound was observed among nine participants (17·3%, 95% CI 8·2–30·3) in the 5-day group, one participant (2·1%, 0·1–11·1) in the 10-day group, and one participant (2·0%, 0·1–10·6) in the 15-day group. Among individuals who were severely immunocompromised, viral RNA rebound was observed in five (25·0%, 8·7–49·1), zero (0·0%, 0·0–19·5), and one (5·0%, 0·1–24·9) participant in the 5-day, 10-day, and 15-day groups, respectively. Among non-severely immunocompromised participants, viral RNA rebound was observed in four (12·5%, 3·5–29·0), one (3·2%, 0·1–16·7), and zero (0·0%, 0·0–11·6) participants in the 5-day, 10-day, and 15-day groups, respectively.

Neither M^{pro} or cleavage mutations were observed in at least two among 227 eligible specimens collected from 134 participants. Some mutations were observed as singular events in participants with viral RNA rebound; these mutations were shown in vitro not to affect the susceptibility of SARS-CoV-2 M^{pro} to nirmatrelvir (appendix p 7).

In addition to nasopharyngeal swabs, RATs were collected from participants at each timepoint (data not shown). Overall, in the main study population, at least one positive RAT from days 15 to 44 was reported in seven (14·6%), one (2·1%), and zero participants in the 5-day, 10-day, and 15-day groups, respectively. Among severely immunocompromised participants, at least one positive RAT from days 15–44 was reported in six (33·3%), one (5·9%), and zero participants in the 5-day, 10-day, and 15-day groups, respectively. Among non-severely immunocompromised participants, at least one positive RAT was reported in one (3·3%), zero, and zero participants in the 5-day, 10-day, and 15-day groups, respectively.

Overall, changes from baseline in viral load over time were relatively similar across treatment groups (appendix p 15). In severely immunocompromised participants,

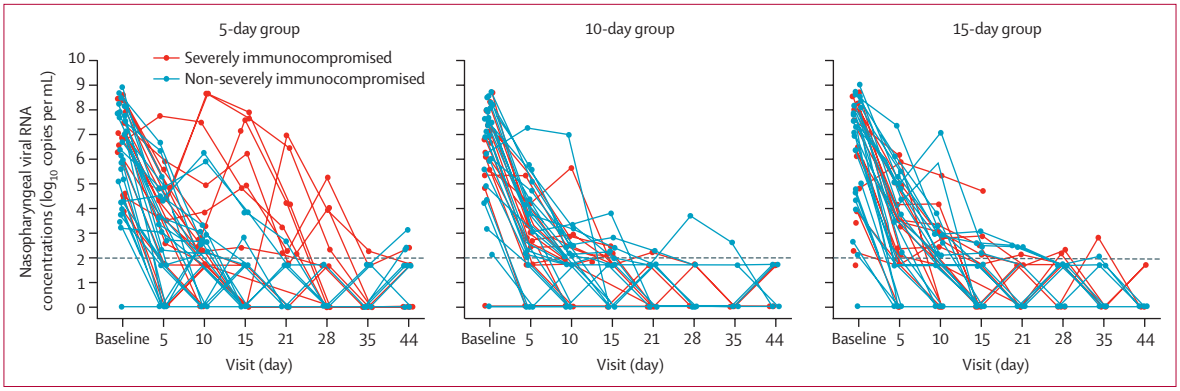

Figure 3: **Viral load over time by nirmatrelvir–ritonavir treatment duration and subgroup from baseline to day 44 (evaluable analysis set)**
Grey dashed line represents the lower limit of quantification (2·0 log_{10} copies per mL).

greater decreases were observed with 10-day or 15-day treatment compared with 5-day treatment on the two visits directly after the treatment phase. Median changes from baseline with 5-day, 10-day, and 15-day treatment, respectively, were –3·9, –5·6, and –4·9 on day 15 and –4·4, –6·3, and –6·2 on day 21 (appendix p 15).

During long-term follow-up at week 12, one participant in the 10-day treatment group had detectable nasopharyngeal SARS-CoV-2 RNA; the concentration was less than the LLOQ and was not previously detectable at day 44 or again after week 12. At week 24, two participants tested positive for SARS-CoV-2 RNA (one in each of the 10-day and 15-day treatment groups). These cases were confirmed as new infections with different viral strains than those detected at baseline (data not shown).

No deaths occurred up to day 44. Up to day 28, two participants in the EAS were hospitalised because of complications from COVID-19; both were severely immunocompromised and in the 5-day group. One of these participants was admitted to the intensive care unit and both were ultimately discharged. After day 44, two participants died because of underlying conditions or associated complications: one participant with acute myeloid leukaemia (5-day group) died on study day 129 due to herpetic encephalitis and leukaemia progression. One participant with acute lymphoblastic leukaemia (15-day group) died on study day 175 (after week 24) with a cavernous sinus thrombosis due to mucormycosis. Additional secondary outcomes are summarised in the appendix (pp 17–21).

AEs occurred in 28 (52·8%) of 53, 34 (66·7%) of 51, and 31 (60·8%) of 51 participants across the 5-day, 10-day, and 15-day groups, respectively, up to day 44 (table 2). Most AEs were grades 1 or 2 and resolved by study completion; grade 3 and 4 AEs and treatment discontinuations due to AEs were infrequent across groups. The most frequently occurring AE was dysgeusia, reported by six (11·3%) of 53, 11 (21·6%) of 51, and 14 (27·5%) of 51 participants in the 5-day, 10-day, and 15-day groups, respectively. Other AEs reported by at least 5% of participants in any group were diarrhoea, nausea, headache, and increased blood thyroid-stimulating hormone without clinical significance (appendix p 22). There was no increase in SAE incidence associated with longer treatment duration and no treatment-related SAEs occurred. Two participants reported severe AEs considered to be potentially treatment-related (dyspepsia and alanine aminotransferase concentration increase); both individuals were in the 15-day treatment group. The AEs resolved in both participants, and both continued in the study.

Discussion

Scarce clinical data exist to support nirmatrelvir–ritonavir dosing recommendations for immunocompromised patients with COVID-19, who represent a heterogeneous population with clinically significant underlying diseases and comorbidities.[26] In our study, similar percentages of participants had a sustained viral load below LLOQ from days 15 to 44 across all treatment regimens, and within similar numbers of days. This result indicates that the currently recommended 5-day course of nirmatrelvir–ritonavir is adequate for most patients who are immunocompromised.[14] Within a post-hoc subgroup analysis of severely immunocompromised participants, however, viral clearance was reached more quickly (lower median time to sustained viral load <LLOQ) among individuals treated for 10 days or 15 days compared with those treated for 5 days. Thus, extending nirmatrelvir–ritonavir treatment beyond 5 days might improve durable viral clearance among severely immunocompromised patients. Additional studies are needed to confirm the post-hoc findings in the severely immunocompromised patient population.

There were no deaths from any cause among study participants up to day 44. Also, the only two COVID-19-related hospitalisations that occurred in our study were among severely immunocompromised participants treated for 5 days. Although more AEs were reported in the 10-day and 15-day treatment arms relative to the 5-day treatment arm, no increases in the incidence of SAEs resulted from longer treatment duration. The overall safety profile of extended therapy with

nirmatrelvir–ritonavir was consistent with previous observations from placebo-controlled trials, with the AE of dysgeusia most commonly reported.[19,27] Participants were permitted to receive concomitant medications in accordance with the prescribing information for nirmatrelvir–ritonavir. Despite extensive medication use to treat underlying conditions, no AEs were specified by the investigator as resulting from a drug–drug interaction. Given that persistent replication in immunocompromised patients can lead to emerging mutations,[4,5] it is notable that viral mutations were not observed with longer treatment durations in our study.

Overall, fewer cases of viral RNA rebound were observed among participants in the 10-day and 15-day groups compared with the 5-day group. This result indicates that the broader population of all immunocompromised patients might have reduced likelihood of viral RNA rebound if nirmatrelvir–ritonavir treatment is extended beyond 5 days. The association between treatment duration and viral RNA rebound was most striking among severely immunocompromised participants—five (25·0%) individuals treated for 5 days had viral RNA rebound compared with none in the 10-day group and a single participant (5·0%) in the 15-day group. In addition, most severely immunocompromised participants in the 5-day group who experienced viral RNA rebound had high viral loads (≥4 $\log_{10}$ copies per mL) that were sustained for at least two follow-up visits. Incidence of RAT positivity showed a similar trend among severely immunocompromised participants, whereby a third of participants treated for 5 days had at least one positive RAT after treatment cessation, compared with one participant (5·9%) in the 10-day group and no participants in the 15-day group. Thus, extended durations of treatment might be required to control rebound among severely immunocompromised patients. These results have implications for the clinical management of the overall immunocompromised and the severely immunocompromised populations, who are at high risk of prolonged infection leading to viral resistance and poor clinical outcomes,[3–5] and for whom little guidance is available regarding optimal dosing of treatments for COVID-19.

Our study had some important limitations, including a relatively small number of enrolled participants due to the challenges of identifying individuals with immunocompromising conditions who met enrolment criteria of our clinical study, and particularly those who are severely immunocompromised. Thus, no formal statistical hypotheses were tested, results were purely descriptive. No meaningful comparisons could be drawn between the 10-day and 15-day treatments, and data for some conditions, such as severe primary immunodeficiency and HIV infection CDC group III, were scarce. Moreover, a primary virological endpoint was used in lieu of a more meaningful clinical endpoint, such as hospitalisation and death, given the small sample size and the anticipated low rates of hospitalisation and death among participants treated with nirmatrelvir–ritonavir within 5 days of symptom onset. This decision was supported by emerging evidence that viral clearance is a potential surrogate of clinical efficacy for the prevention of COVID-19-associated hospitalisation.[28–30] Additional investigation is needed to establish predictive biomarkers specifically among immunocompromised patients with COVID-19. Another important limitation was that virological sampling was sparse, and viral persistence beyond day 44 was not assessed. Symptoms were evaluated only based on participant reporting and were not collected daily, which restricted the potential for interpretation of all symptoms data. Also, many symptoms of COVID-19 overlap with those caused by participants' underlying medical conditions, such as chronic inflammatory diseases or haematological malignancies. Lastly, the small size of the current study restricts the generalisability of the study results to a broad range of immunocompromising conditions.

Similar percentages were observed between the three treatment durations with respect to the primary endpoint. In post-hoc analyses among severely

	5-day group (n=53)	10-day group (n=51)	15-day group (n=51)
AEs			
Number of AEs	46	71	97
Participants with AEs	28 (52·8%)	34 (66·7%)	31 (60·8%)
Participants with SAEs	5 (9·4%)	1 (2·0%)	4 (7·8%)
Participants with maximum grade 3 or 4 AEs	2 (3·8%)	5 (9·8%)	6 (11·8%)
Deaths related to AEs	0	0	0
Participants discontinuing study due to AEs	1 (1·9%)*†	0	0
Participants discontinuing study drug due to AEs and continuing study	1 (1·9%)†	1 (2·0%)†	4 (7·8%)†
Treatment-related AEs			
Number of AEs	13	21	35
Participants with AEs	12 (22·6%)	17 (33·3%)	21 (41·2%)
Participants with SAEs	0	0	0
Participants with maximum grade 3 or 4 AEs	0	0	2 (3·9%)‡
Deaths related to AEs	0	0	0
Participants discontinuing study due to AEs	1 (1·9%)*	0	0
Participants discontinuing study drug due to AEs and continuing study	1 (1·9%)†	1 (2·0%)†	3 (5·9%)†

Data are n or n (%). AE=adverse event. SAE=serious adverse event. *Participant reported moderate diarrhoea beginning on study day 1 that later resolved. †All AEs leading to treatment discontinuation included diarrhoea and urticaria in one patient each in the 5-day group; abdominal pain in one patient in the 10-day group; and neutropenia and dyspepsia in one patient; abdominal pain in one patient; constipation, nausea, and vomiting in one patient; and intracranial haemorrhage in one patient in the 15-day group. ‡One participant reported severe dyspepsia beginning on study day 2 that later resolved; study drug was withdrawn, and the participant continued in the study. In another participant, alanine aminotransferase concentrations increased beginning on study day 16 that later resolved; the participant continued in the study.

Table 2: **Summary of AEs, SAEs, and subsequent discontinuations up to day 44 (safety analysis set)**

immunocompromised participants, treatment beyond 5 days with nirmatrelvir–ritonavir resulted in a numerically shorter time to sustained SARS-CoV-2 clearance and reduced viral RNA rebound rates. Based on the results of this exploratory study, longer treatment durations in the severely immunocompromised patient population should be further explored.

Contributors

AG, SGT, SL, JAA, MMR, LC, ESF, JH, and JR were involved with the study concept and design. EW, RP, AG, MA, MLB, SG, ET, SA, and JH accessed, verified, and were involved with the analysis of the study data. All authors drafted, edited, or reviewed the manuscript; critically reviewed the manuscript for important intellectual content; and approved the final draft. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EW, AG, MA, MLB, SG, ET, SA, WW, SGT, JH, and JR were employees of Pfizer during the time of study conduct and hold stock or stock options. RP has served on advisory boards for Gilead Sciences, Pfizer, Roche Therapeutics, AstraZeneca, Merck, GlaxoSmithKline, ViiV Healthcare, Eli Lilly and Company, PharmaMar, and Atea Pharmaceuticals; and has received research grants paid to his institution from Merck, ViiV Healthcare, Gilead Sciences, and PharmaMar. CG-V has received honoraria for talks on behalf of Gilead Science, Merck Sharp & Dome, Novartis, Pfizer, Janssen, GlaxoSmithKline, and Eli Lilly, as well as a grant from Gilead Science, Pfizer, and GlaxoSmithKline. JAA reports institutional support for vaccine clinical trials sponsored by Pfizer (no direct support for this study); institutional research support for clinical trials from Emergent Biosolutions, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Regeneron, and ViiV Healthcare; personal fees for advisory boards from GlaxoSmithKline/ViiV and Merck; and declares participation on the data and safety monitoring board for Kintor Pharmaceuticals. SL reports institutional support for vaccine clinical trials sponsored by Pfizer (no direct support for this study was received); unrelated to this study, he reports institutional research support for clinical trials from Emergent Biosolutions; Gilead Sciences; Janssen; Gigagen; Immunome; National Institutes of Health; National Institute of Allergy and Infectious Diseases (NIAID); National Heart, Lung, and Blood Institute; and Regeneron. All other authors declare no competing interests.

Data sharing

The trial protocol and statistical analysis plan are available at https://www.clinicaltrials.gov/study/NCT05438602. Anonymised participant data will be made available upon reasonable request. Proposals will be reviewed and approved by Pfizer based on scientific merit. After approval of a proposal and signing of a data access agreement, data can be shared through a secure online platform. All data will be made available upon request from publication and extending for a minimum of 5 years from the end of the trial. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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