ORIGINAL ARTICLE

Oral Nirmatrelvir–Ritonavir for Covid-19 in Higher-Risk Outpatients

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ABSTRACT

BACKGROUND

Nirmatrelvir–ritonavir has been shown to reduce progression to severe illness from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in unvaccinated high-risk outpatients. The effectiveness of nirmatrelvir–ritonavir in persons who have been vaccinated, infected naturally, or both is unclear.

METHODS

In two open-label platform trials (PANORAMIC in the United Kingdom and CanTreatCOVID in Canada), we enrolled higher-risk adults (≥50 years of age or ≥18 years of age with coexisting conditions) in the community who tested positive for SARS-CoV-2 and had been unwell for 5 days or less. The participants were randomly assigned to receive usual care plus nirmatrelvir (300 mg)–ritonavir (100 mg) twice a day for 5 days or to receive usual care alone. The primary outcome was hospitalization or death from any cause within 28 days after randomization.

RESULTS

From December 8, 2021, to September 30, 2024, a total of 3516 participants in the PANORAMIC trial and 716 participants in the CanTreatCOVID trial underwent randomization. In the PANORAMIC trial, 14 of 1698 participants (0.8%) in the nirmatrelvir–ritonavir group and 11 of 1673 participants (0.7%) in the usual-care group were hospitalized or died (adjusted odds ratio, 1.18; 95% Bayesian credible interval, 0.55 to 2.62; probability of superiority, 0.334). In the CanTreatCOVID trial, 2 of 343 participants (0.6%) in the nirmatrelvir–ritonavir group and 4 of 324 participants (1.2%) in the usual-care group were hospitalized or died (adjusted odds ratio, 0.48; 95% Bayesian credible interval, 0.08 to 2.23; probability of superiority, 0.830). In a substudy involving 634 participants, viral load was reduced by the end of treatment with nirmatrelvir–ritonavir. Serious adverse events with nirmatrelvir–ritonavir were reported in 9 participants in the PANORAMIC trial and in 4 participants in the CanTreatCOVID trial.

CONCLUSIONS

In two open-label trials, nirmatrelvir–ritonavir did not reduce the incidence of hospitalization or death among vaccinated higher-risk participants with SARS-CoV-2 infection. (Funded by the National Institute for Health and Care Research, and others; PANORAMIC ISRCTN number, 2021-005748-31; CanTreatCOVID ClinicalTrials.gov number, NCT05614349.)

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This article was updated on April 23, 2026, at NEJM.org.

N Engl J Med 2026;394:1583-94.
DOI: 10.1056/NEJMoa2502457

A Quick Take is available at NEJM.org

Despite vaccination, acquired immunity, and viral evolution, some persons, particularly those at high risk, continue to have protracted illness and are admitted to the hospital because of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Early treatment with direct-acting antiviral drugs in community-dwelling patients could prevent deterioration in their condition, reduce the risk of hospital admission, hasten recovery, and decrease viral shedding and transmissibility. In the EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) trial,[2] nirmatrelvir–ritonavir[3-6] was shown to reduce the incidence of hospitalization related to coronavirus disease 2019 (Covid-19) or death from any cause through 28 days among high-risk unvaccinated patients, a finding that led to a recommendation of this treatment as first-line therapy for outpatients with Covid-19 at the highest risk for progression to severe disease, despite a large number of drug–drug interactions.[3,7] Among the standard-risk outpatients (those at high risk who were vaccinated and those at low risk who were unvaccinated) enrolled in the EPIC-SR (Standard-Risk) trial, no difference was shown in the time to sustained alleviation of symptoms and no reduction was shown in the incidence of Covid-19–related hospitalization or death from any cause.[8] Observational studies after licensure have been and are being conducted, but all of them have issues with residual confounding, confounding by indication, and immortal time bias.[9]

In the time since the EPIC-HR and EPIC-SR trials were conducted, many more people have been vaccinated multiple times, have been infected naturally, or both, so whether nirmatrelvir–ritonavir still benefits those at high risk is unclear. The PANORAMIC trial, conducted in the United Kingdom, and the CanTreatCOVID trial, conducted in Canada, assessed the effectiveness of nirmatrelvir–ritonavir in reducing the incidence of hospital admissions or death among mostly vaccinated adults in the community who had risk factors for serious Covid-19.

METHODS

OBJECTIVES, PARTICIPANTS, AND OVERSIGHT

The U.K. PANORAMIC and Canadian CanTreatCOVID trials were national, multicenter, primary care, open-label, prospective, adaptive platform clinical trials evaluating antiviral treatment for SARS-CoV-2 infection in the community.[10] Interventions assessed in the PANORAMIC trial included molnupiravir[11] (from December 2021 through April 2022) and nirmatrelvir–ritonavir (from April 20, 2022, to March 28, 2024). The CanTreatCOVID trial evaluated nirmatrelvir–ritonavir between January 16, 2023, and September 30, 2024, and continues to evaluate an antioxidant treatment.[12]

Eligible participants were higher-risk adults (≥50 years of age or ≥18 years of age with relevant coexisting conditions) in the community who had had symptoms of SARS-CoV-2 infection for 5 days or less and had a positive polymerase-chain-reaction (PCR) or rapid antigen SARS-CoV-2 test. Potential participants were excluded if they were pregnant or breast-feeding, were of childbearing potential and unwilling to use effective nonhormonal contraception, were already taking nirmatrelvir–ritonavir, or had contraindications to nirmatrelvir–ritonavir, including taking a medication with important drug–drug interactions or one requiring adjustment according to creatinine clearance or glomerular filtration rate (details for the two trials are provided in the protocol, available with the full text of this article at NEJM.org).

The U.K. Medicines and Healthcare Products Regulatory Agency and the South Central–Berkshire research ethics committee of the National Health Service Health Research Authority approved the PANORAMIC trial protocol. The CanTreatCOVID trial was approved by Health Canada and research ethics boards in the participating provinces across Canada. Separate independent trial steering committees and data and safety monitoring committees oversaw the two trials. An enhanced safety-monitoring group, the members of which performed specialized in-depth monitoring of potential adverse events and trends, monitored adverse effects and any required changes in eligibility in a blinded manner. Written or electronic informed consent was obtained from all the participants or their legal representatives. All the data were available to the authors, who vouch for the accuracy and completeness of the data and for the fidelity of each trial to the protocol.

RANDOMIZATION AND MASKING

For the PANORAMIC trial, potentially eligible participants were screened, recruited, and enrolled through 65 general practice PANORAMIC hubs (central research sites) across the United

Kingdom. Participants were also recruited online and by telephone by the central trial team. When nirmatrelvir–ritonavir was introduced to the platform, participants who were eligible to receive either molnupiravir or nirmatrelvir–ritonavir were randomly assigned in equal probabilities by medical or research professionals to receive nirmatrelvir–ritonavir plus usual care, molnupiravir plus usual care,[11] or usual care alone, depending on the time of randomization; when enrollment for the molnupiravir group ended, eligible participants were randomly assigned in a 1:1 ratio to receive nirmatrelvir–ritonavir plus usual care or usual care alone. A secure Web-based system (Spinnaker; version custom-built for the PANORAMIC trial; Spiral Software) was used for randomization, which was stratified according to age (<50 years vs. ≥50 years) and vaccination status (yes vs. no).

Participants in the CanTreatCOVID trial were invited, screened, recruited, and enrolled through public communications, outreach through health care settings, provincial Covid-19 hotlines, and community organizations, and they underwent randomization on the day of enrollment with the use of a secure interactive Web-based system (REDCap Cloud, version 1.7.2). Participants were randomly assigned in a 1:1 ratio to receive either usual care or nirmatrelvir–ritonavir plus usual care. (During a 1-month period of the trial, participants were also randomly assigned to receive antioxidant therapies.) Randomization was stratified according to age (<65 years vs. ≥65 years) and was performed with the use of varying block sizes.

In both trials, the random sequence of group assignment was concealed with the use of central randomization through a Web-based system. After randomization, participants, along with team members responsible for recruitment, follow-up, and monitoring, were aware of the group assignments.

PROCEDURES

In both trials, participants in the nirmatrelvir–ritonavir group were asked to take nirmatrelvir at a dose of 300 mg (two 150-mg tablets) along with ritonavir at a dose of 100 mg (one tablet) orally twice daily for 5 days. All the participants received a trial information booklet. Packages containing nirmatrelvir–ritonavir (along with dosing and safety information) were sent by courier to participants' homes, along with a pregnancy test, if relevant.

In the U.K. National Health Service, participants who were at very high risk were eligible to receive specific treatment at specialist regional Covid-19 clinics (for more details regarding risk categories in the U.K., see the Supplementary Appendix).[4] In Canada, higher-risk participants could also receive nirmatrelvir–ritonavir as part of usual care. (If participants who were randomly assigned to the usual-care group received nirmatrelvir–ritonavir outside the trial, this was documented accordingly.)

Participants completed an online diary daily for 28 days after randomization in the PANORAMIC trial. Participants who did not complete the online diary were contacted by telephone on days 7, 14, and 28. In the CanTreatCOVID trial, participants completed an online diary daily for 14 days, with supplemental telephone calls on days 21 and 28 after randomization (see the protocols for details).

VIROLOGY SUBSTUDY

Participants who enrolled in the PANORAMIC trial from September 10, 2022, through October 23, 2023 were offered the opportunity to participate in a virology substudy that involved interval nasopharyngeal SARS-CoV-2 PCR testing during the first 14 days after enrollment (see the protocol). Participants in the intensive-sampling cohort were asked to provide daily combined nasal and pharyngeal swabs for the first 7 days and on day 14 (±1 day). Participants in the nonintensive-sampling cohort were asked to provide combined nasal and pharyngeal swabs on days 1, 5 (±1 day), and 14 (±1 day). The all-sampling cohort was made up of the intensive and nonintensive cohorts combined.

OUTCOME MEASURES

The primary outcome was nonelective hospital admission for any cause or death from any cause within 28 days after randomization. Hospital admission was defined by at least one overnight stay in the hospital or at least one night in a hospital-at-home program (in which the patient is cared for and monitored by hospital clinicians at home after hospital assessment). Data for this outcome were obtained from both the participants and the health care system in the PANORAMIC trial, whereas data were obtained only from the participants in the CanTreatCOVID trial. Time spent during the day in a hospital emergency department and hospitalizations for elective procedures that had been planned before trial enrollment

were not included in the primary outcome. The primary outcome for the virology substudy was undetectable viral load at day 7.

Secondary outcomes included early sustained recovery, which was defined as participant-reported recovery by day 14 after randomization that was sustained to day 28. The time to participant-reported recovery was defined as the time from randomization to the first instance that a participant reported feeling fully recovered from SARS-CoV-2 infection. Other secondary outcomes, including other measures of recovery, contact with health or social services, and new household SARS-CoV-2 infections (all for the PANORAMIC trial only) are defined in the statistical analysis plans provided with the protocol.

STATISTICAL ANALYSIS

Details regarding the calculation of the sample size and statistical analysis for the two trials can be found in the Supplementary Appendix, available at NEJM.org. For the PANORAMIC trial, we assumed that the incidence of events would be lower than that observed in the PRINCIPLE trial (Platform Randomised Trial of Interventions against COVID-19 in Older People),[13-19] which was 3% in the usual-care group. We estimated that with a sample size of 5300 participants per group, the trial would have 90% power to show an incidence of 2% in the nirmatrelvir–ritonavir group at a 5% level of significance (for more details, see Table S1 in the Supplementary Appendix). However, the sample size in the PANORAMIC trial was revised in response to advice from the trial steering committee in April 2023 when the incidence of events was found to be lower than anticipated. Assuming an incidence of 1.3% in the usual-care group and a relative risk reduction of 77% (corresponding to an incidence of 0.3% in the nirmatrelvir–ritonavir group and a higher relative risk reduction than the 89% shown in the EPIC-HR trial[2]), we calculated that 1438 participants would need to be enrolled in each group to provide the trial with 80% power at a two-sided 5% significance level.

In the CanTreatCOVID trial, we calculated that with 2981 participants in each group, the trial would have 90% power at a 5% level of significance, assuming a 5% incidence of events in the usual-care group and an expected incidence of 3.3% in the nirmatrelvir–ritonavir group. However, the CanTreatCOVID trial stopped recruitment, as recommended by the trial steering committee, because of slow recruitment and because the supply of nirmatrelvir–ritonavir was discontinued as of May 31, 2024.

The primary analysis population was defined as all eligible participants who underwent randomization and were included in the analysis according to group assignment. The treatment effect (and corresponding 95% Bayesian credible intervals) for the primary outcome was estimated with the use of a Bayesian logistic-regression model with weakly informative (i.e., Cauchy) priors, with adjustments for coexisting conditions, age, and vaccination status (adaptive design report; see the protocol). Owing to slower-than-anticipated recruitment because of the many potential drug–drug interactions and changing epidemiology, no interim analyses were performed in either trial, so the threshold for success (demonstration of superiority) remained at 0.975, as prespecified. Sensitivity analyses were also carried out to assess the robustness of the primary-outcome analysis after accounting for missing data. Less than 5% of the data for the primary outcome were missing in the PANORAMIC trial, so no multiple imputation was performed, as specified in the statistical analysis plan. However, multiple imputation was performed to assess the effect of missing data in the CanTreatCOVID trial. A tipping-point analysis was performed as a post hoc sensitivity analysis.

Other analyses are shown in the adaptive design report and the statistical analysis plans for each trial. For consistency of reporting in this article, the virology analysis was also conducted with a similar approach. Results were consistent with the prespecified frequentist approach. None of the analyses of the secondary outcomes were adjusted for multiplicity, and their Bayesian credible intervals should not be used to infer definitive treatment effects.

Since the PANORAMIC and CanTreatCOVID trials were pragmatic trials of an authorized approved drug, we adopted a pharmacovigilance strategy. Data on adverse events were not collected in the usual-care group in the PANORAMIC trial; however, they were collected in both groups in the CanTreatCOVID trial (see the protocols). Because symptoms of Covid-19 and side effects of medication can be difficult to disentangle, information on symptoms was routinely reported in daily diaries and compared between the groups. All analyses were performed with the use of Stata, version 18.0, and R, version 4.2.1.

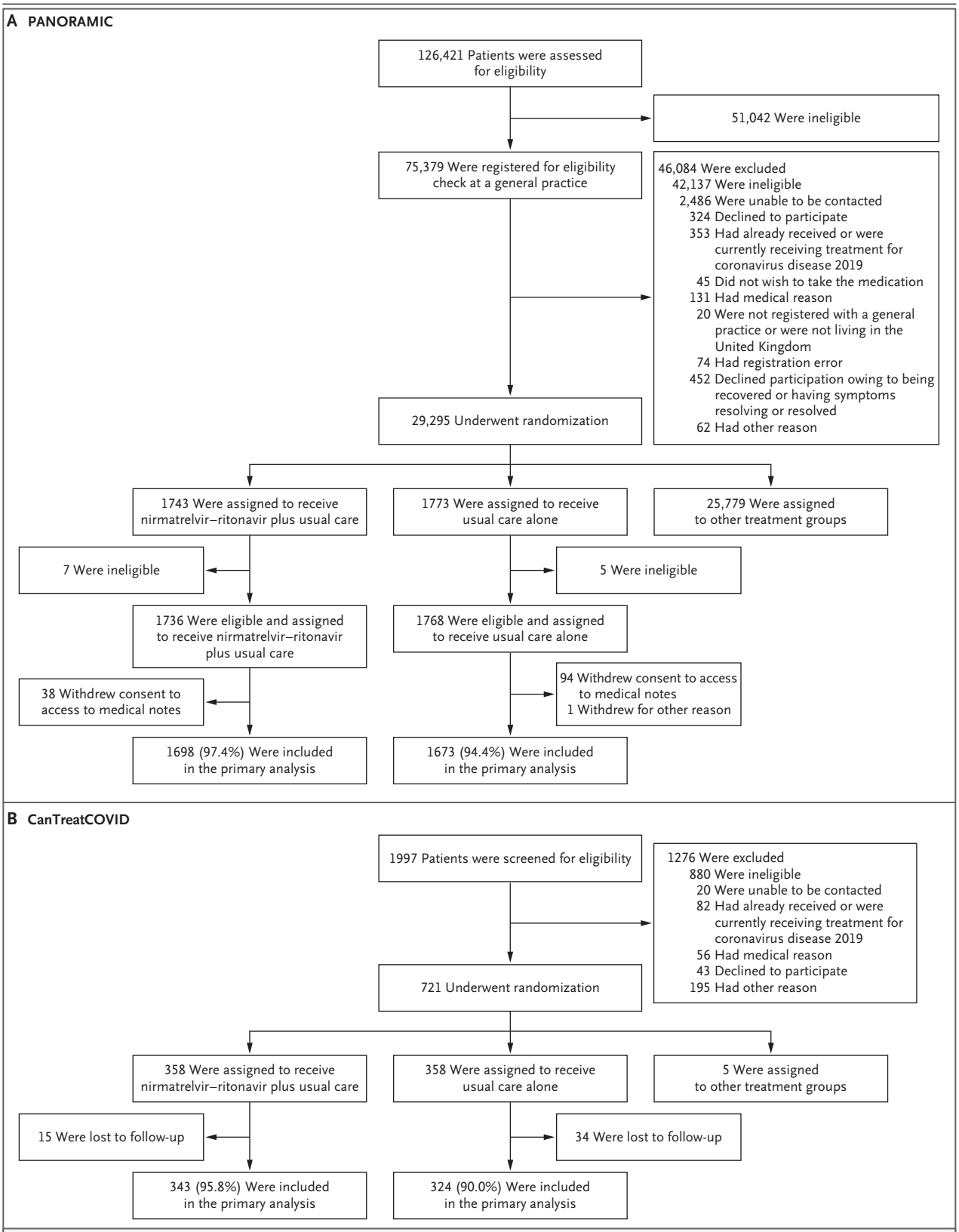

Figure 1. Enrollment, Randomization, and Follow-up.

RESULTS

PARTICIPANTS

We screened 126,421 potential participants in the PANORAMIC trial; 51,042 were ineligible (Fig. 1 and Tables S2 through S4). A total of 29,295 participants underwent randomization between December 8, 2021, and March 28, 2024, with enrollment to the nirmatrelvir–ritonavir group opening on April 20, 2022. A total of 1743 participants were assigned to receive nirmatrelvir–ritonavir plus usual care and 1773 to receive usual care alone; 25,779 participants were randomly assigned to receive other treatment.[11] Participants began to receive medication a median of 4 days after symptom onset. In the

Table 1. Baseline Characteristics of the Participants.*

Characteristic	PANORAMIC		CanTreatCOVID	
	Nirmatrelvir–Ritonavir (N=1736)	Usual Care (N=1768)	Nirmatrelvir–Ritonavir (N=358)	Usual Care (N=358)
Age — yr				
Mean	54.7±12.1	54.8±11.7	54.7±13.6	55.0±13.5
Range	18–96	18–93	19–88	18–89
Sex — no. (%)†				
Female	1182 (68.1)	1223 (69.2)	237 (66.2)	231 (64.5)
Male	554 (31.9)	545 (30.8)	118 (33.0)	100 (27.9)
Other	0	0	1 (0.3)	0
Data missing or not reported	0	0	2 (0.6)	27 (7.5)
Race or ethnic group — no. (%)‡				
White	1647 (94.9)	1661 (93.9)	290 (81.0)	272 (76.0)
Asian	36 (2.1)	45 (2.5)	50 (14.0)	36 (10.1)
Mixed race	34 (2.0)	41 (2.3)	6 (1.7)	5 (1.4)
Black	8 (0.5)	9 (0.5)	2 (0.6)	3 (0.8)
Other	11 (0.6)	12 (0.7)	8 (2.2)	15 (4.2)
Data missing or not reported	0	0	2 (0.6)	27 (7.5)
Index of multiple deprivation quintile — no. (%)§				
1	154 (8.9)	167 (9.4)	—	—
2	284 (16.4)	271 (15.3)	—	—
3	334 (19.2)	388 (21.9)	—	—
4	426 (24.5)	415 (23.5)	—	—
5	525 (30.2)	510 (28.8)	—	—
Data missing or not reported	13 (0.7)	17 (1)	—	—
Household income, Canadian dollars — no. (%)				
<$40,000	—	—	38 (10.6)	46 (12.8)
≥$40,000	—	—	313 (87.4)	280 (78.2)
Data missing or not reported	—	—	7 (2.0)	32 (8.9)
Duration of symptoms — days				
Mean	2.7±1.2	2.7±1.2	2.4±1.1	2.4±1.1
Median (IQR)	3 (2–4)	3 (2–4)	2 (2–3)	2 (2–3)
Received ≥4 doses of nirmatrelvir–ritonavir — no. (%)	1504 (86.6)	—	314 (87.7)	—
Data missing	74 (4.3)	—	7 (2.0)	—
Received ≥1 vaccine dose — no. (%)	1715 (98.8)	1740 (98.4)	356 (99.4)	355 (99.2)
Data missing or not reported	0	0	0	1 (0.3)
No. of vaccine doses — no. (%)				
0	21 (1.2)	28 (1.6)	2 (0.6)	2 (0.6)
<2	16 (0.9)	7 (0.4)	6 (1.7)	5 (1.4)
≥2	1699 (97.9)	1733 (98.0)	350 (97.8)	350 (97.8)
Data missing or not reported	0	0	0	1 (0.3)

Table 1. (Continued.)

Characteristic	PANORAMIC		CanTreatCOVID	
	Nirmatrelvir–Ritonavir (N=1736)	Usual Care (N=1768)	Nirmatrelvir–Ritonavir (N=358)	Usual Care (N=358)
Wellness score¶				
Mean	4.7±1.7	4.7±1.7	—	—
Median (IQR)	5 (3–6)	5 (3–6)	—	—
Coexisting condition — no. (%)	1127 (64.9)	1185 (67.0)	173 (48.3)	160 (44.7)
Coexisting condition, CanTreatCOVID definition — no. (%)‖	898 (51.7)	936 (52.9)	173 (48.3)	160 (44.7)

* Plus–minus values are means ±SD. IQR denotes interquartile range.
† Sex was reported by the participant.
‡ Race and ethnic group were reported by the participant.
§ The index of multiple deprivation is a national indication of the level of social, health-related, and economic deprivation according to local geographic area of residence, assessed in quintiles. Quintile 1 indicates most deprived, and quintile 5 least deprived.
¶ The wellness scale ranges from 0 to 10, with 0 indicating the worst possible health and 10 the best possible.
‖ Coexisting conditions in the CanTreatCOVID trial were defined as high blood pressure, long-term lung disease, long-term heart or vascular disease, long-term kidney disease, long-term liver disease, long-term neurologic disease, severe and profound learning disability, Down syndrome, diabetes mellitus, weakened immune system owing to a condition the participant was born with or owing to a disease or treatment, history of organ transplantation, a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 35, or severe mental illness.

CanTreatCOVID trial, 1997 participants were screened and 880 were ineligible (Tables S5 through S7); 721 participants underwent randomization between January 16, 2023, and September 30, 2024. A total of 358 participants were assigned to receive nirmatrelvir–ritonavir plus usual care and 358 to receive usual care alone; 5 participants were randomly assigned to receive other treatment (Fig. 1). Participants began to receive medication a median of 3 days after symptom onset. Eight participants (0.5%) in the PANORAMIC trial and 11 participants (3.1%) in the CanTreatCOVID trial who were assigned to the usual-care group subsequently received nirmatrelvir–ritonavir outside the trials. The baseline characteristics of the participants were well matched among the groups overall and within each trial (Table 1 and Table S8) and were largely representative of the potential population for which the use of the drug was intended, apart from including fewer men and participants of minority ethnic origin in the United Kingdom and Canada (Table S8).

PRIMARY OUTCOME

In the PANORAMIC trial, 14 of 1698 participants (0.8%) in the nirmatrelvir–ritonavir group and 11 of 1673 participants (0.7%) in the usual-care group were hospitalized or died (Table 2); in the CanTreatCOVID trial, 2 of 343 participants (0.6%) in the nirmatrelvir–ritonavir group and 4 of 324 participants (1.2%) in the usual-care group were hospitalized or died (Table 3). No deaths were reported during the time the trial was recruiting participants for the nirmatrelvir–ritonavir group in either trial. In both trials, there was no significant difference in the incidence of primary outcome events between the two groups; in the PANORAMIC trial, the adjusted odds ratio for hospitalization or death was 1.18 (95% Bayesian credible interval, 0.55 to 2.62; probability of superiority, 0.334), and in the CanTreatCOVID trial, the adjusted odds ratio was 0.48 (95% Bayesian credible interval, 0.08 to 2.23; probability of superiority, 0.830).

SECONDARY OUTCOMES

In both trials, the incidence of early sustained recovery appeared to be higher in the nirmatrelvir–ritonavir group than in the usual-care group (Tables 2 and 3). In the PANORAMIC trial, early sustained recovery was reported by 33.0% of the participants in the nirmatrelvir–ritonavir group and by 22.1% of those in the usual-care group (adjusted odds ratio, 1.74; 95% Bayesian credible interval, 1.48 to 2.04); in the CanTreatCOVID trial, early sustained recovery was reported by 69.0% and 53.1% of the participants, respectively (adjusted odds ratio, 1.99; 95% Bayesian credible interval, 1.40 to 2.87). The time to participant-reported recovery appeared to be shorter in the nirmatrelvir–ritonavir group than in the usual-care group in both trials. Other secondary time-to-event outcomes are shown in Tables S10

Table 2. Primary, Secondary, Safety, and Viral-Load Outcomes in the PANORAMIC Trial.*

Outcome	Nirmatrelvir–Ritonavir	Usual Care	Estimated Treatment Effect (95% Bayesian Credible Interval)
Primary outcome			
Hospitalization or death — no./total no. (%)	14/1698 (0.8)	11/1673 (0.7)	1.18 (0.55–2.62)†
Secondary outcomes			
Early sustained recovery — no./total no. (%)‡	510/1546 (33.0)	330/1492 (22.1)	1.74 (1.48–2.04)†
Time to participant-reported recovery			
Recovered by day 28 — no./total no. (%)	1147/1690 (67.9)	919/1646 (55.8)	
Median days to recovery (IQR)§	14 (7 to not reached)	21 (11 to not reached)	
Time interval of recovery¶			
Day 1 or 2			0.845 (0.390–1.796)
Day 3–7			2.123 (1.792–2.511)
Day 8–11			1.599 (1.334–1.922)
Day 12–28			1.121 (0.987–1.271)
Adverse events‖			
No. of adverse events	4030	—	
No. of participants with event/total no. (%)	1551/1612 (96.2)	—	
No. of serious adverse events	10	—	
No. of participants with serious event/total no. (%)	9/1612 (0.6)	—	
Virologic testing, intensive-sampling cohort**			
Viral load below detection level at day 7 — no./total no. (%)	12/32 (38)	10/33 (30)	1.53 (0.52–4.56)††
Geometric mean viral load at day 7	759.3±10.8	3095.2±30.0	0.19 (0.06–0.63)‡‡
Virologic testing, all-sampling cohort**			
Viral load below detection level — no./total no. (%)			
Day 1	13/330 (3.9)	18/304 (5.9)	
Day 5	78/267 (29.2)	36/218 (16.5)	2.15 (1.37–3.44)††
Day 14	131/183 (71.6)	106/156 (67.9)	1.30 (0.77–2.15)††
Geometric mean viral load			
Day 1	1,988,856.5±51.2	1,713,635.8±47.5	
Day 5	3,587.0±26.6	30,267.1±52.3	0.13 (0.08–0.21)‡‡
Day 14	288.7±9.5	314.0±9.0	0.93 (0.51–1.68)‡‡

* Plus–minus values are means ±SD. The analyses of the primary and secondary outcomes were performed in the population of participants who underwent randomization and those who were eligible to undergo randomization during the time frame when participants were being assigned to the nirmatrelvir–ritonavir group, and the safety analysis was performed in the as-treated population, defined as participants who received at least one dose of nirmatrelvir–ritonavir or who received usual care. The widths of the credible intervals for the secondary and virology outcomes have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects. Dashes indicate incomplete data; adverse events were not assessed in all participants who received usual care alone, as stated in the protocol.

† Adjusted odds ratios were obtained from a Bayesian logistic-regression model adjusted for age, vaccination status, and coexisting conditions at baseline, with a 95% Bayesian credible interval. An odds ratio of less than 1 favors nirmatrelvir–ritonavir. Treatment superiority was declared if the probability of superiority was at least 0.975 in the comparison of nirmatrelvir–ritonavir with usual care. The probability of superiority for the primary outcome was 0.334.

‡ Early sustained recovery was a binary outcome defined as participant-reported recovery by day 14 with no subsequent instances of "not recovered" until day 28.

§ Data shown are Kaplan–Meier estimates of the median time to event and interquartile range from the raw data.

¶ The treatment effect for this category is shown as a nonproportional hazard ratio with a 95% Bayesian credible interval. Hazard ratios and 95% credible intervals for each time interval were calculated with the use of a Bayesian time-varying piecewise exponential model, with adjustment for age, vaccination status, and coexisting conditions at baseline. Time intervals were chosen on the basis of information from a clinician who did not have knowledge of or access to the data.

‖ The trial did not routinely collect information on adverse events in the usual-care group.

** The virology substudy involved interval nasopharyngeal SARS-CoV-2 PCR testing during the first 14 days after enrollment in the PANORAMIC trial. Participants in the intensive-sampling cohort were asked to provide daily combined nasal and pharyngeal swabs for the first 7 days and on day 14 (±1 day). Participants in the nonintensive-sampling cohort were asked to provide combined nasal and pharyngeal swabs on days 1, 5 (±1 day), and 14 (±1 day). The all-sampling cohort was made up of the intensive and nonintensive cohorts combined.

†† The treatment effect for this category was calculated with the use of a Bayesian logistic-regression model with adjustments for sex, age, and baseline $\log_{10}$(viral load). An adjusted odds ratio of more than 1 favors nirmatrelvir–ritonavir.

‡‡ The treatment effect for this category was calculated with the use of a Bayesian mixed-effect model for $\log_{10}$(viral load) with adjustments for sex, age, and baseline $\log_{10}$(viral load). An adjusted geometric mean ratio of less than 1 favors nirmatrelvir–ritonavir.

Table 3. Primary, Secondary, Safety, and Viral-Load Outcomes in the CanTreatCOVID Trial.*

Outcome	Nirmatrelvir–Ritonavir	Usual Care	Estimated Treatment Effect (95% Bayesian Credible Interval)
Primary outcome			
Hospitalization or death — no./total no. (%)	2/343 (0.6)	4/324 (1.2)	0.48 (0.08–2.23)†
Secondary outcomes			
Early sustained recovery — no./total no. (%)‡	191/277 (69.0)	130/245 (53.1)	1.99 (1.40–2.87)†
Time to participant-reported recovery			
Recovered by day 14 — no./total no. (%)	272/345 (78.8)	194/306 (63.4)	
Median days to recovery (IQR) §	6 (4 to 11)	9 (4 to not reached)	
Time interval of recovery¶			
Day 1 or 2			0.94 (0.55–1.53)
Day 3–7			1.72 (1.35–2.23)
Day 8–11			1.54 (1.06–2.26)
Day 12–14			1.07 (0.58–1.90)
Adverse events			
No. of adverse events	190	38	
No. of participants with event/total no. (%)	112/312 (35.9)	20/358 (5.6)	
No. of serious adverse events	7	16	
No. of participants with serious event/total no. (%)	4/312 (1.3)	12/358 (3.4)	

* The analyses of the primary and secondary outcomes were performed in the population of participants who underwent randomization and those who were eligible to undergo randomization during the time frame when participants were being assigned to the nirmatrelvir–ritonavir group, and the safety analysis was performed in the as-treated population, defined as participants who received at least one dose of nirmatrelvir–ritonavir or who received usual care. The widths of the credible intervals for the secondary outcomes have not been adjusted for multiplicity and cannot be used to infer definitive treatment effects.

† Adjusted odds ratios were obtained from a Bayesian logistic-regression model adjusted for age, vaccination status, and coexisting conditions at baseline, with a 95% Bayesian credible interval. An odds ratio of less than 1 favors nirmatrelvir–ritonavir. Treatment superiority was declared if the probability of superiority was at least 0.975 in the comparison of nirmatrelvir–ritonavir with usual care. The probability of superiority for the primary outcome was 0.830.

‡ Early sustained recovery was a binary outcome defined as recovered by day 14 with no subsequent instances of "not recovered." If the participant reported by telephone calls on both day 21 and day 28 that they were recovered, we assumed that they remained recovered. Adjusted odds ratios were obtained from a Bayesian logistic-regression model with adjustments for age, vaccination status, and coexisting conditions at baseline. An odds ratio of more than 1 favors nirmatrelvir–ritonavir.

§ Data shown are Kaplan–Meier estimates of the median time to event and the interquartile range from the raw data.

¶ The treatment effect for this category is shown as a nonproportional hazard ratio with a 95% Bayesian credible interval. Hazard ratios and 95% credible intervals for each time interval were calculated with the use of a Bayesian time-varying piecewise exponential model, with adjustments for age, vaccination status, and coexisting conditions at baseline. Time intervals were chosen on the basis of information from a clinician who did not have knowledge of the data.

and S11 and in Figures S1 through S6 for the PANORAMIC trial and in Tables S16 and S17 and in Figures S11 through S16 for the CanTreatCOVID trial.

SUBGROUP AND SENSITIVITY ANALYSES

Results of the analyses were similar across the prespecified subgroups in the PANORAMIC trial (Figs. S7 and S8) and across those in the CanTreatCOVID trial (Figs. S17 and S18). Sensitivity analyses of the effect of prior distribution, missing data, and treatment received showed that the results for the primary outcome were robust in both trials (Table S12 and Tables S18 through S20 and Figs. S9, S10, S19, and S20).

SAFETY

Most of the participants (96.2%) in the nirmatrelvir–ritonavir group in the PANORAMIC trial had adverse events, and 9 of 1612 participants (0.6%) had serious adverse events (Table 2 and Tables S13 through S15). In the CanTreatCOVID trial, the percentage of participants with serious adverse events was higher in the usual-care group than in the nirmatrelvir–ritonavir group (12 of 358 participants [3.4%] vs. 4 of 312 participants [1.3%]) (Table 3 and Tables S21 through S23). In the PANORAMIC trial, 242 participants assigned to receive nirmatrelvir–ritonavir discontinued treatment; in 128 of these participants, the reason for discontinuation was side effects, with dysgeusia, nausea, or both reported as the most

common reason (in 99 participants). None of the participants in the CanTreatCOVID trial discontinued treatment because of adverse events.

VIROLOGY SUBSTUDY (PANORAMIC TRIAL ONLY)

The virology substudy involved 634 participants in the PANORAMIC trial (72 in the intensive-sampling cohort and 562 in the nonintensive-sampling cohort). In the intensive-sampling cohort, viral load at day 7 had been reduced to below the lower limit of detection in 12 of 32 participants (38%) in the nirmatrelvir–ritonavir group, as compared with 10 of 33 participants (30%) in the usual-care group (adjusted odds ratio, 1.53; 95% Bayesian credible interval, 0.52 to 4.56), and the geometric mean ratio of the viral load in the nirmatrelvir–ritonavir group as compared with that in the usual-care group was 0.19 (i.e., the viral load was 81% lower in the nirmatrelvir–ritonavir group than in the usual-care group) (Table 2). In the all-sampling cohort, the viral load at day 5 had been reduced to below the lower limit of detection in 78 of 267 participants (29%) in the nirmatrelvir–ritonavir group as compared with 36 of 218 participants (17%) in the usual-care group (adjusted odds ratio, 2.15; 95% Bayesian credible interval, 1.37 to 3.44), and the viral load was 87% lower in the nirmatrelvir–ritonavir group than in the usual-care group. At day 14, this difference was smaller (Table 2). Results were consistent in the intensive-sampling cohort (Table S10), and a Bayesian analysis was consistent with the prespecified frequentist approach.

DISCUSSION

The U.K. (PANORAMIC) and Canadian (CanTreatCOVID) trials were randomized, controlled evaluations of nirmatrelvir–ritonavir treatment for SARS-CoV-2 infection and showed outcomes for predominantly vaccinated adults in the community who were at increased risk for severe outcomes. We found no evidence that early treatment with nirmatrelvir–ritonavir reduced the already-low incidence of hospitalization or death in either trial and were unable to identify any prespecified subgroup with compelling evidence of treatment effect.

Although no definitive conclusions can be drawn for secondary outcomes, we found that the participant-reported time to recovery appeared to be shorter with open-label nirmatrelvir–ritonavir than with usual care alone. Although the incidence of serious adverse events was low, most of the participants who received nirmatrelvir–ritonavir reported adverse events, which were related mainly to taste and gastrointestinal side effects; treatment discontinuation was relatively common. By the end of treatment, viral load was lower in the nirmatrelvir–ritonavir group than in the usual-care group.

In the EPIC-HR trial involving unvaccinated patients without previous infection, among those who received treatment within 5 days after randomization, 0.8% of the participants in the nirmatrelvir–ritonavir group had been hospitalized for Covid-19 or died from any cause by day 28, as compared with 6.3% in the placebo group (relative risk reduction, 89%).[2] The EPIC-HR trial also showed that the median time to sustained symptom alleviation (defined as the time from the onset of symptoms until the first day of 4 consecutive days during which all targeted symptoms that had been scored as moderate or severe at trial enrollment were scored as mild or absent) was significantly shorter with nirmatrelvir–ritonavir than with placebo (13 days vs. 15 days).[20] Differences in definitions of measures of recovery may partly explain our slightly greater estimates of benefit on recovery.

The EPIC-SR trial assessed the efficacy of nirmatrelvir–ritonavir in unvaccinated adults at standard risk (i.e., those without an identified risk factor for progression to severe illness) as well as vaccinated adults with one or more risk factor.[8] The EPIC-SR trial did not show a significant difference in the participant-reported median time to sustained alleviation of symptoms (12 days with nirmatrelvir–ritonavir vs. 13 days with placebo; P=0.60 by log-rank test).[8] We found an estimated median time to sustained alleviation of all symptoms of 8 days with nirmatrelvir–ritonavir treatment and 12 days with usual care in the PANORAMIC trial, but participants in our trials were, on average, approximately 10 years older than the participants in the EPIC-SR trial and more often had coexisting conditions.

Both the PANORAMIC and CanTreatCOVID trials were pragmatic trials with applicability to the populations in which nirmatrelvir–ritonavir might be used in countries with already well-vaccinated populations. Medication was given a median of 3 to 4 days after the start of symptoms. We combined traditional site-based recruitment methods with additional approaches

to enrollment, which enabled persons with SARS-CoV-2 infection to participate without leaving home, an approach that enhanced research equity and added to the generalizability of the findings. The sample size in our trial exceeded that required to detect the effect size shown in the EPIC-HR trial.[2]

In contrast to efficacy trials, our trial had an open-label design, suited to answering pragmatic questions of the effectiveness of the drug during routine clinical care, because placebos are generally not used in routine care. Such a design facilitates trial conduct and is unlikely to lead to bias that can be associated with primary outcomes such as hospital admission and mortality.[21-23] An open-label design does not allow estimation of the contribution of either placebo or nocebo effects to any observed differences in participant-reported outcomes, such as time to recovery.[23,24] However, by the end of treatment (day 5), viral load had decreased more substantially in the nirmatrelvir–ritonavir group than in the usual-care group, which implied a mechanistic basis for participant-reported recovery outcomes.[25] Of note, the time to participant-reported sustained alleviation of symptoms was similar in our open-label trial and the EPIC-SR placebo-controlled trial,[8] but with larger estimates than those in the placebo-controlled EPIC-HR trial, which used more-stringent definitions of recovery. Our PRINCIPLE trial, which had a similar open-label design, showed no meaningful effect with doxycycline,[13] azithromycin,[14] or ivermectin,[15] a trend of harm with colchicine,[16] and a trend of benefit with inhaled budesonide in a largely unvaccinated population.[17]

There were small differences between the PANORAMIC and CanTreatCOVID trials. The median time to recovery differed, the CanTreatCOVID trial started recruitment later than PANORAMIC, and the CanTreatCOVID trial followed participants daily for the first 14 days, so it had less data on potential rebound of symptoms.

Many similar national and single-institution–led trials were conducted during the pandemic, most of which did not recruit sufficient numbers of participants to provide clinically useful findings.[26] Coordinating studies and combining data collected in the national PANORAMIC and CanTreatCOVID trials, which used closely matched protocols, identifies a route forward for more efficient and collaborative trials to evaluate questions of urgent, international public-health importance.

In these U.K. and Canadian national randomized trials, early treatment with open-label nirmatrelvir–ritonavir for Covid-19 in community-dwelling vaccinated adults at increased risk for poor outcomes did not reduce an already low incidence of hospitalization or death.

Supported by a grant (NIHR135366) from the National Institute for Health and Care Research for the PANORAMIC trial and by the Canadian Institutes of Health Research and grants (FRN 183092 and PPE 190332) from Health Canada for the CanTreatCOVID trial. Nirmatrelvir–ritonavir for the CanTreatCOVID trial was provided by the Public Health Agency of Canada.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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