Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

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Summary

Background The safety, effectiveness, and cost-effectiveness of molnupiravir, an oral antiviral medication for SARS-CoV-2, has not been established in vaccinated patients in the community at increased risk of morbidity and mortality from COVID-19. We aimed to establish whether the addition of molnupiravir to usual care reduced hospital admissions and deaths associated with COVID-19 in this population.

Methods PANORAMIC was a UK-based, national, multicentre, open-label, multigroup, prospective, platform adaptive randomised controlled trial. Eligible participants were aged 50 years or older—or aged 18 years or older with relevant comorbidities—and had been unwell with confirmed COVID-19 for 5 days or fewer in the community. Participants were randomly assigned (1:1) to receive 800 mg molnupiravir twice daily for 5 days plus usual care or usual care only. A secure, web-based system (Spinnaker) was used for randomisation, which was stratified by age (<50 years *vs* ≥50 years) and vaccination status (yes *vs* no). COVID-19 outcomes were tracked via a self-completed online daily diary for 28 days after randomisation. The primary outcome was all-cause hospitalisation or death within 28 days of randomisation, which was analysed using Bayesian models in all eligible participants who were randomly assigned. This trial is registered with ISRCTN, number 30448031.

Findings Between Dec 8, 2021, and April 27, 2022, 26 411 participants were randomly assigned, 12 821 to molnupiravir plus usual care, 12 962 to usual care alone, and 628 to other treatment groups (which will be reported separately). 12 529 participants from the molnupiravir plus usual care group, and 12 525 from the usual care group were included in the primary analysis population. The mean age of the population was 56·6 years (SD 12·6), and 24 290 (94%) of 25 708 participants had had at least three doses of a SARS-CoV-2 vaccine. Hospitalisations or deaths were recorded in 105 (1%) of 12 529 participants in the molnupiravir plus usual care group versus 98 (1%) of 12 525 in the usual care group (adjusted odds ratio 1·06 [95% Bayesian credible interval 0·81–1·41]; probability of superiority 0·33). There was no evidence of treatment interaction between subgroups. Serious adverse events were recorded for 50 (0·4%) of 12 774 participants in the molnupiravir plus usual care group and for 45 (0·3%) of 12 934 in the usual care group. None of these events were judged to be related to molnupiravir.

Interpretation Molnupiravir did not reduce the frequency of COVID-19-associated hospitalisations or death among high-risk vaccinated adults in the community.

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Introduction

Early treatment of COVID-19 with direct-acting antiviral drugs in the community could plausibly prevent deterioration, speed up recovery, and reduce health-care use in the community, viral shedding, and, the need for hospital admission. Molnupiravir is an oral antiviral that was initially developed for influenza,[1] but has subsequently been assessed as a treatment of COVID-19.[2] Molnupiravir is a prodrug: the ribonucleoside analogue β-d-N4-hydroxycytidine is metabolised to its triphosphate form in cells, and then competes with the naturally occurring nucleotides

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Research in context

Evidence before this study

We searched PubMed with the terms (randomised OR trial) AND (molnupiravir) AND (COVID* OR SARS-CoV-2 OR SARS-CoV) AND (systematic review) for articles published in any language up to Sept 5, 2022. Our search identified ten results. The two most comprehensive reviews were living reviews synthesising the findings of six trials of molnupiravir compared with either standard of care or placebo. These reviews suggested that molnupiravir reduces the frequency of hospital admissions in patients with mild-to-moderate COVID-19. WHO's living guideline recommends use of molnupiravir in outpatients with mild-to-moderate COVID-19 who are at the highest risk of hospital admission. The largest randomised clinical trial identified by the evidence syntheses was the placebo-controlled, phase 3 MOVe-OUT trial. In this trial of 1433 unvaccinated outpatients with COVID-19, molnupiravir was associated with a relative reduction of roughly 30% in the primary outcome—hospitalisations and deaths—up to 29 days after randomisation. Notably, the reduction in hospitalisations and deaths had been closer to 50% in the trial's interim analysis (after 762 participants had been recruited). The reason for this difference is unclear. Several trials of molnupiravir have been done in India, but full peer-reviewed findings have not yet been published. In the AGILE CST-2 trial, which included 180 participants (both vaccinated and unvaccinated), time to a negative PCR test was shorter in the molnupiravir group than in the placebo group (8 days *vs* 11 days), but this difference was not significant.

Added value of this study

Molnupiravir did not reduce hospitalisations or deaths in a community-based vaccinated adult population with COVID-19 who were at increased risk of an adverse outcome, either overall or in any patient subgroups. However, molnupiravir was associated with reduced time to recovery overall and for key individual symptoms, reduced health-care seeking for some primary care services, and reduced viral load. Trials of molnupiravir have previously been done in largely unvaccinated participants before the emergence of the omicron variant. Our trial provides an estimate of the effectiveness of molnupiravir in a multiply vaccinated population when the omicron SARS-CoV-2 strain was dominant.

Implications of all the available evidence

The use of molnupiravir to treat confirmed SARS-CoV-2 infection in vaccinated adults who are at increased risk of an adverse outcomes when omicron was the dominant circulating variant did not reduce hospital admissions or deaths, both of which are already very infrequent, but did reduce time to recovery (and viral detection and load in a substudy).

cytidine triphosphate and uridine triphosphate.[3] Once incorporated into viral RNA, the errant nucleotide induces so-called viral error catastrophe, impeding viral fitness and inhibiting replication.[3] Molnupiravir has shown anti-SARS-CoV-2 activity in animal models,[4–6] and was safe and well tolerated at a dose of 800 mg twice daily in phase 1 human trials[7,8] and phase 2 and 3 outpatient trials.[2,9,10]

The largest trial of molnupiravir so far is MOVe-OUT,[10] a placebo-controlled, industry-funded phase 3 trial in unvaccinated, non-hospitalised patients with COVID-19 at high risk of adverse outcomes. The final results suggest a 30% reduction in hospital admissions and deaths with molnupiravir treatment compared with placebo.[10] Phase 3 trials in non-hospitalised patients in India had mixed findings,[11] but the full peer-reviewed results of these trial have yet to be published. The AGILE CST-2 trial,[12] which included 180 vaccinated and unvaccinated participants, suggested that molnupiravir was associated with a shorter time to a negative PCR test compared with placebo (8 days *vs* 11 days), although this difference was not significant.

The effectiveness of molnupiravir in vaccinated patients in the community at increased risk of morbidity and mortality from COVID-19 has not yet been established. We aimed to assess the effectiveness of molnupiravir in reducing hospital admissions or death, or both, in this population.

Methods

Study design and participants

PANORAMIC is a national, multicentre, primary care, open-label, multigroup, prospective, platform adaptive trial of early treatments for COVID-19 in the UK. The trial opened for recruitment on Dec 8, 2021, and is ongoing. Full details of the protocol are in the appendix (p3). Platform trials allow for multiple treatments for the same disease to be tested simultaneously. A master protocol defines prospective decision criteria for stopping randomisation to interventions for futility, declaring interventions superior, or adding new interventions.[13] Interventions assessed in PANORAMIC include molnupiravir (from December, 2021, to April, 2022) and nirmatrelvir–ritonavir (which remains open to recruitment as of December, 2022). However, there were no trial adaptations, and there was only a short period of overlap with nirmatrelvir–ritonavir recruitment while participants were being recruited to the interventions discussed in the Article.

Eligible people were in the community (ie, not in hospital), aged 50 years or older (or 18 years or older with relevant comorbidities; appendix p 14), had COVID-19 symptoms that had started within the previous 5 days, and had had a positive PCR or rapid antigen SARS-CoV-2 test within the past 7 days. People were excluded from participating if they were pregnant or breastfeeding, of childbearing potential and unwilling to use effective

contraception, already taking molnupiravir, or allergic to molnupiravir. The complete inclusion and exclusion criteria are in the appendix (p 14).

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee of the Health Research Authority approved the trial protocol. Online informed consent was obtained from all participants. We vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent trial steering committee and data and safety monitoring committee provided trial oversight.

Randomisation and masking

Potentially eligible people were screened, recruited, and enrolled via 65 PANORAMIC General Practice Hubs encompassing 4509 general practices across the UK. Participants were also recruited online and by telephone by the central trial team. Eligible participants were randomly assigned (1:1) by medical or research professionals to receive molnupiravir plus usual care or usual care only. A secure, web-based system (Spinnaker) was used for randomisation, which was stratified by age (<50 years *vs* ≥50 years) and vaccination status (yes *vs* no). Participants and members of the trial team responsible for recruitment, follow-up, and monitoring of participants were aware of group assignment. Trial investigators and recruiting clinicians were masked to emerging results; only unmasked statisticians and the independent members of the data and safety monitoring committee were granted access to unmasked results until the decision was made to close recruitment to molnupiravir.

Procedures

Participants in the molnupiravir group were asked to take 800 mg molnupiravir orally twice daily for 5 days. These participants were urgently couriered a participant pack

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See Online for appendix

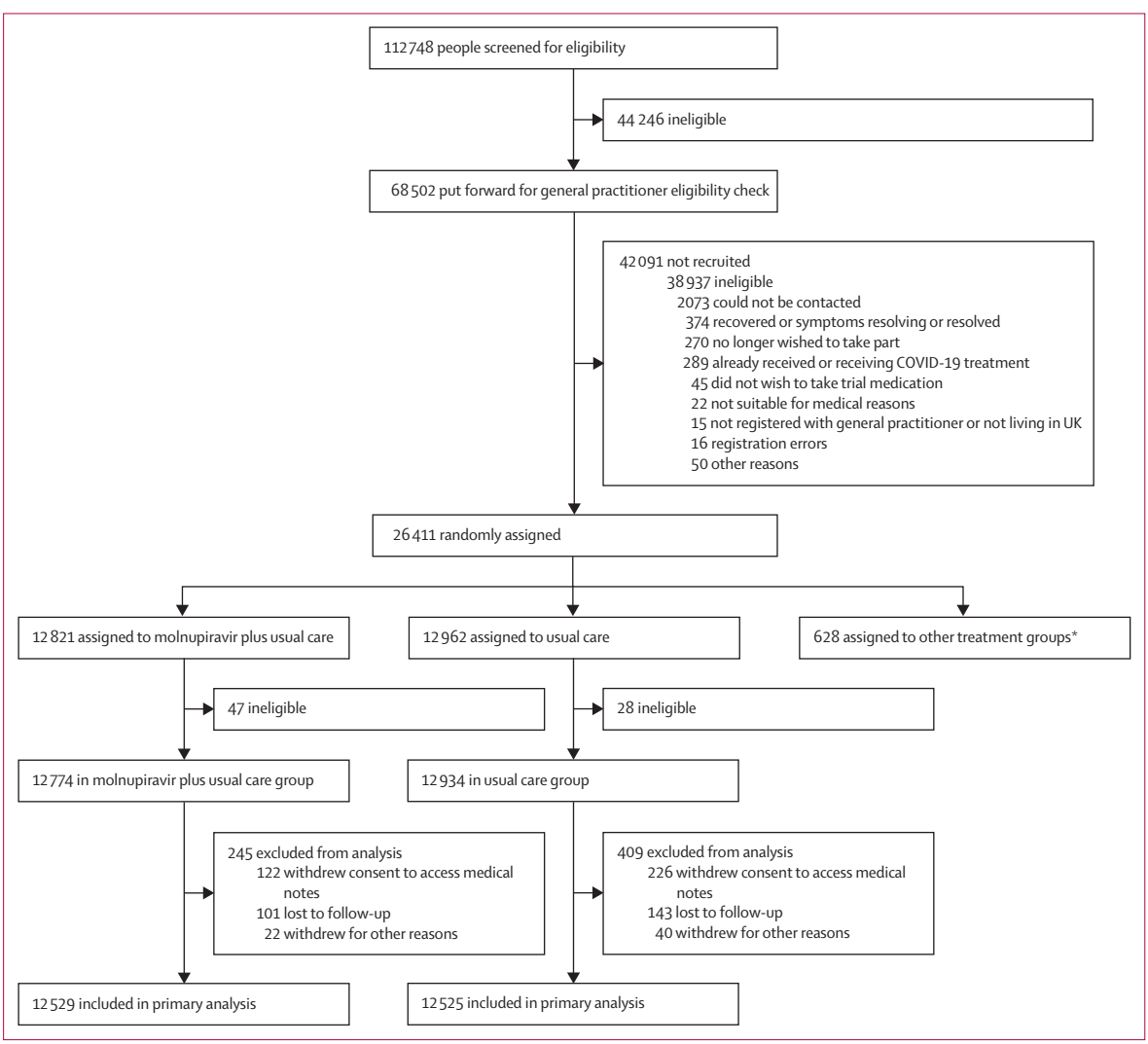


Figure 1: **Trial profile**
*Results related to these groups are not discussed in this Article.

containing molnupiravir (along with dosing and safety information) and a pregnancy test (only for use by participants of childbearing potential). Participants in both groups were emailed or posted a trial information booklet. Usual care in the UK National Health Service (NHS) for COVID-19 in the community is largely focused on managing symptoms with antipyretics.[14] However, patients at very high risk (ie, those with impaired immune systems or who are extremely clinically vulnerable—roughly 1·8 million people in the UK) are eligible to receive monoclonal antibodies (sotrovimab), intravenous antivirals (remdesivir), and oral antivirals (molnupiravir or nirmatrelvir–ritonavir) from specialist regional COVID-19 clinics.[15,16]

Prescription of monoclonal antibodies and antiviral agents other than molnupiravir in the course of usual care was permitted, and monoclonal antibody use was recorded in an online diary. Participants assigned to the molnupiravir plus usual care group would not have received additional molnupiravir, but those assigned to the usual care group could have received molnupiravir through the NHS.

Participants were followed up through an online daily diary for 28 days after randomisation. Non-responders were telephoned on days 7, 14, and 28. Participants were asked to rate symptoms (eg, fever, cough, breathlessness) on an ordinal scale as "no problem", "mild problem", "moderate problem", or "major problem", to rate how they were feeling on a scale from zero to ten (in which zero corresponded with the worst one can imagine, and ten with the best one can imagine), and to report whether they had been hospitalised or required contact with health and social services, whether they felt fully recovered, whether they were taking over-the-counter medication for their COVID-19 symptoms, whether the number of people in the household with COVID-19 had changed, and whether they had taken molnupiravir (if applicable). At day 14 and 28, participants were also asked to complete the EQ-5D-5L to assess health-related quality of life. Participants could nominate a trial partner to help to provide follow-up data. We obtained consent from participants to access health-care use data from their general practices and health-care records. Additional questions about long-term symptoms and health-care use were asked 3 months and 6 months after randomisation, but these results are not reported here.

Virology substudy

Participants enrolled at all sites between March 23 and April 27, 2022, were offered the opportunity to participate in an intensively and non-intensively sampled virology cohort. Those who took part were couriered European In-Vitro Diagnostic Devices Directive-approved sampling kits and instructions for nasal and pharyngeal swab and dried blood spot self-sampling. They were asked to post the samples to the virology-processing site (postage and packaging were pre-paid). Participants in the intensive sampling cohort were asked to provide daily nasal or pharyngeal swabs for the first 7 days and on day 14 (or day 13 or 15). In the non-intensive sampling cohort, participants were asked to provide nasal or pharyngeal swabs on days 1, 5 (or day 4 or 6) and 14 (or day 13 or 15). Participants in the molnupiravir plus usual care group were asked to take their first sample before the first dose of molnupiravir, whereas those in the usual care group were asked to provide their first sample the day after randomisation. All participants in the virology substudy were asked to provide three finger-prick dried blood spot samples, one each on days 1, 5 (or day 4 or 6), and 14 (or day 13 or 15).

Outcomes

The primary outcome was all-cause, non-elective hospital admission or death within 28 days of randomisation. Hospital admission was defined as at least one overnight stay in hospital, or at least one night in a hospital-at-home programme (a service in which patients who are not formally admitted to hospital are cared for and monitored by hospital clinicians at home) after hospital assessment. Spending time during the day in a hospital emergency department was classified as an emergency department attendance. Overnight stays in the emergency department were counted as admissions. Hospitalisation for elective procedures planned before trial entry was not counted in our primary outcome.

Secondary outcomes included time to self-reported recovery (which was defined as the first instance that a participant reported feeling fully recovered from COVID-19), time to early sustained recovery (recovery by day 14 sustained until day 28), time to sustained recovery (ie, time to the date the participant first reported recovery that was maintained until 28 days), self-reported wellness, time to initial alleviation of symptoms (ie, time to the first day participants reported no or only minor symptoms), time to sustained alleviation of symptoms (ie, time to first day participants reported no or only minor symptoms that subsequently remained minor or non-existent until 28 days), time to initial reduction of symptom severity, contact with health or social services, hospital assessment without admission, oxygen administration, new household COVID-19 infections, and safety outcomes. The appendix (pp 109–10) contains full details of all secondary outcomes. The primary outcome of the virology substudy was undetectable viral load at day 7. Other outcomes for the virology substudy are detailed in the appendix (p 155–56).

Statistical analysis

The sample size calculation and statistical analysis are detailed in the appendix (pp 98, 164). The sample size was initially calculated on the basis of a 3% event rate with usual care, with an intervention expected to reduce the frequency of hospitalisation or death rate to 2% (ie, a 33% relative reduction). Based on this calculation, we needed to recruit at least 5300 participants to each group to

ensure a 5% level of significance and 90% power. However, the aggregate (masked) proportion of participants admitted to hospital was lower than anticipated, so the sample size calculation was revised to 16 578 per group (90% power) or 12 534 per group (80% power), which involved assuming event frequencies of 1% in the control group and 0·67% in the intervention group. This recalculation of sample size was done for the overall proportion of hospitalisations and deaths, and did not affect any decision criteria thresholds or interpretation of the final results.

The primary analysis population was defined as all eligible participants who were randomly assigned. Participants who were randomly assigned but subsequently found to be ineligible for inclusion were excluded from the analysis. Participants were analysed according to the group they were allocated to, irrespective of protocol deviations. To analyse the primary outcome, we used a Bayesian logistic regression model with weakly informative Cauchy priors (appendix p 167) that was regressed on treatment group, comorbidity, and stratification covariates (age and vaccination status). 95% Bayesian credible intervals (95% BCIs) were calculated. The success thresholds at final and interim analysis were prespecified (appendix pp 170–71) and were dependent on the number of interim analyses, which was a function of the speed of enrolment. If no interim analyses were done (eg, in the case of very fast enrolment), the success threshold at the final analysis was 0·975. Only one participant in the analysis population received treatment that differed from their randomised allocation, so the model fit in the sensitivity analysis was nearly identical to the primary analysis model fit. If data for the primary outcome were missing for more than 5% of the study population, a sensitivity analysis, in which missing data would be imputed by multiple imputation, was planned (appendix pp 141–42).

The sample size for the virology substudy was based on simulations from a viral dynamic model from early 2020,[17] which suggested that inclusion of 30 patients per group would detect a 2·5 times increase in viral clearance (which translates into roughly double the rate of undetectable viral loads at day 7) in patients who started treatment within 5 days of symptom onset (with 90% power and an α of 0·05) compared with those receiving usual care. Clinical improvement could be associated with smaller decreases in viral load, and viral dynamic modelling leveraging time-series viral-load data can detect much smaller drug effect sizes.[18] Furthermore, 300 participants would provide a 95% probability of seeing at least one example of a SARS-CoV-2 mutation occurring in at least 1% of participants. Viral sequencing analysis will be reported in another paper.

For secondary time-to-event outcomes we used a Bayesian piecewise exponential model with weakly informative normal priors and four time segments (based on quartiles for the observed time to response) to estimate the hazard ratio for the treatment versus the control

	Molnupiravir plus usual care (n=12 774)	Usual care (n=12 934)
Age, years	56·7 (12·5)	56·5 (12·7)
Sex		
Female	7422 (58%)	7631 (59%)
Male	5349 (42%)	5299 (41%)
Other	3 (<1%)	4 (<1%)
Days from symptom onset to randomisation	2 (1–3)	2 (1–3)
Days from randomisation to molnupiravir receipt*	1 (1–1)	..
Days from symptom onset to taking molnupiravir†	3 (3–5)	..
Ethnicity		
White	12 043 (94%)	12 155 (94%)
Asian	365 (3%)	434 (3%)
Mixed race	202 (2%)	189 (1%)
Black	78 (1%)	77 (1%)
Other	86 (1%)	79 (1%)
NHS priority category		
Age ≥80 years	256 (2%)	271 (2%)
Age 75–79 years	537 (4%)	574 (4%)
Age 70–74 years or 18–69 years and clinically extremely vulnerable	1116 (9%)	1111 (9%)
Age 65–69 years, not clinically extremely vulnerable	1493 (12%)	1464 (11%)
Age 18–64 years and in an at-risk group	6514 (51%)	6576 (51%)
Age 60–64 years, not clinically extremely vulnerable or in an at-risk group	745 (6%)	766 (6%)
Age 55–59 years, not clinically extremely vulnerable or in an at-risk group	994 (8%)	1060 (8%)
Age 50–54 years, not clinically extremely vulnerable or in an at-risk group	1119 (9%)	1112 (9%)
Predicted risk quintile‡		
1	2483 (19%)	2553 (20%)
2	2672 (21%)	2632 (20%)
3	2511 (20%)	2656 (21%)
4	2774 (22%)	2760 (21%)
5	2334 (18%)	2333 (18%)
Confirmed positive PCR test	5936 (46%)	5882 (45%)
Indices of multiple deprivation quintile§		
1	1231 (10%)	1180 (9%)
2	1907 (15%)	1952 (15%)
3	2563 (20%)	2587 (20%)
4	3203 (25%)	3207 (25%)
5	3821 (30%)	3949 (31%)
Data unavailable	49 (<1%)	59 (<1%)
COVID-19 vaccine doses		
At least one	12 632 (99%)	12 803 (99%)
One	86 (1%)	87 (1%)
Two	518 (4%)	454 (4%)
Three	11 795 (92%)	12 022 (93%)

(Table 1 continues on next page)

	Molnupiravir plus usual care (n=12 774)	Usual care (n=12 934)
(Continued from previous page)		
Four	233 (2%)	240 (2%)
Data unavailable	142 (1%)	131 (1%)
Current smoker	789 (6%)	804 (6%)
Baseline symptoms		
Shortness of breath		
No problem	6091 (48%)	6114 (47%)
Minor problem	4499 (35%)	4672 (36%)
Moderate problem	1926 (15%)	1893 (15%)
Major problem	258 (2%)	255 (2%)
Fatigue		
No problem	1245 (10%)	1213 (9%)
Minor problem	4708 (37%)	4845 (37%)
Moderate problem	5061 (40%)	5115 (40%)
Major problem	1760 (14%)	1761 (14%)
Muscle ache		
No problem	3465 (27%)	3421 (26%)
Minor problem	4491 (35%)	4782 (37%)
Moderate problem	3749 (29%)	3671 (28%)
Major problem	1069 (8%)	1060 (8%)
Vomiting		
No problem	10 402 (81%)	10 483 (81%)
Minor problem	1840 (14%)	1905 (15%)
Moderate problem	476 (4%)	477 (4%)
Major problem	56 (<1%)	69 (1%)
Diarrhoea		
No problem	10 558 (83%)	10 709 (83%)
Minor problem	1645 (13%)	1676 (13%)
Moderate problem	470 (4%)	457 (4%)
Major problem	101 (1%)	92 (1%)
Loss of smell or taste		
No problem	9034 (71%)	9386 (73%)
Minor problem	2475 (19%)	2360 (18%)
Moderate problem	821 (6%)	798 (6%)
Major problem	444 (3%)	390 (3%)
Headache		
No problem	2689 (21%)	2811 (22%)
Minor problem	5180 (41%)	5211 (40%)
Moderate problem	3767 (29%)	3826 (30%)
Major problem	1138 (9%)	1086 (8%)
Dizziness		
No problem	8412 (66%)	8362 (65%)
Minor problem	3076 (24%)	3287 (25%)
Moderate problem	1094 (9%)	1087 (8%)
Major problem	192 (2%)	198 (2%)
Abdominal pain		
No problem	10 352 (81%)	10 419 (81%)
Minor problem	1828 (14%)	1915 (15%)
Moderate problem	522 (4%)	540 (4%)
Major problem	72 (1%)	60 (<1%)

(Table 1 continues on next page)

group, adjusting for age, vaccination status, and any comorbidity. We used the χ^2 test or Fisher's exact test to analyse binary outcomes with a low event frequency. These results were reported descriptively by treatment group. Early sustained recovery was analysed with a Bayesian logistic regression model, in which group assignment, age, vaccination status, and comorbidity status were covariates.

Because PANORAMIC is a pragmatic trial of a licensed, approved drug in its licensed population, we adopted a pharmacovigilance strategy. Thus, standard adverse event data were not routinely captured. Our strategy was to comprehensively capture safety data for serious adverse events and adverse events for which data are scarce. There was, however, a robust mechanism in place for participants to seek advice on the management of troublesome adverse events. All analyses were done in STATA (version 16.1) and R (version 4.2.1). This trial is registered with ISRCTN, number 30448031.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 8, 2021, and April 27, 2022, 25 783 participants were enrolled and randomly assigned, 12 821 to molnupiravir plus usual care and 12 962 to usual care alone (figure 1). After randomisation, 47 people in the molnupiravir plus usual care group and 28 in the usual care group were judged ineligible. Data were extracted on Oct 11, 2022. A further 628 participants were randomised to other treatment groups after April 27, 2022, but they were not included in the analyses presented here.

The mean age of participants was 56·6 years (SD 12·6). 17 703 (69%) of 25 708 had comorbidities and 24 290 (94%) of 25 708 had received at least three doses of a SARS-CoV-2 vaccine. Baseline characteristics were similar between groups (table 1).

Of the 12 338 participants assigned to molnupiravir plus usual care who provided medication-use information, 11 731 (95%) reported taking molnupiravir for 5 days. Less than 1% of participants in both groups received monoclonal antibody treatment separate from the PANORAMIC trial (table 1).

Because of the rapid accrual of participants relative to the period during which the primary endpoint could be reached (28 days), no interim analyses were done. Thus, there was no adjustment to the success thresholds as prospectively outlined in the analysis plan. Data for the primary outcome were missing for only 654 (3%) of the population, and therefore no prespecified imputation of missing data was done.

Data for the primary outcome were available for 25 054 (97%) participants and included in this analysis. Hospitalisations or deaths were recorded in 105 (1%) of

	Molnupiravir plus usual care (n=12 774)	Usual care (n=12 934)
(Continued from previous page)		
Generally unwell		
No problem	523 (4%)	534 (4%)
Minor problem	5013 (39%)	5134 (40%)
Moderate problem	5764 (45%)	5829 (45%)
Major problem	1474 (12%)	1437 (11%)
Fever		
No problem	5647 (44%)	5757 (45%)
Minor problem	4798 (38%)	4942 (38%)
Moderate problem	2103 (16%)	2035 (16%)
Major problem	226 (2%)	200 (2%)
Cough		
No problem	1408 (11%)	1336 (10%)
Minor problem	6132 (48%)	6373 (49%)
Moderate problem	4481 (35%)	4502 (35%)
Major problem	753 (6%)	723 (6%)
Wellness score	5·1 (1·7)	5·2 (1·7)
Other people in household		
None	1651 (13%)	1658 (13%)
One	6090 (48%)	6006 (46%)
Two	2122 (17%)	2171 (17%)
Three	1760 (14%)	1973 (15%)
Four	805 (6%)	771 (6%)
Five or more	346 (3%)	355 (3%)
Taking inhaled corticosteroids	2978 (23%)	3150 (24%)
Taking inhaled corticosteroids for COVID-19	182 (1%)	158 (1%)
Taking monoclonal antibodies for COVID-19	26 (<1%)	18 (<1%)
Comorbidities		
Any	8803 (69%)	8900 (69%)
Lung disease	3000 (23%)	3169 (25%)
Heart disease	996 (8%)	955 (7%)
Kidney disease	225 (2%)	253 (2%)
Liver disease	159 (1%)	143 (1%)
Neurological disease	426 (3%)	436 (3%)
Learning disability	36 (<1%)	27 (<1%)
Down's syndrome	24 (<1%)	29 (<1%)
Diabetes	1478 (12%)	1510 (12%)
Weakened immune system	1119 (9%)	1062 (8%)
Transplant recipient	55 (<1%)	70 (1%)
Obesity	1964 (15%)	1935 (15%)
Mental illness	198 (2%)	220 (2%)
Hypertension	2864 (22%)	2897 (22%)
Other vulnerability	2281 (18%)	2334 (18%)

Data are mean (SD), n (%), or median (IQR). *Data available for 12 507 participants. †Data available for 12 013 participants. ‡Risk categorisation derived from COVID-19 vaccination categories and baseline summary symptom scores based on penalised logistic regression (appendix p 145); quintile 1 corresponds to lowest risk, whereas quintile 5 corresponds to highest risk. §Quintile 1 corresponds to highest risk, whereas quintile 5 corresponds to lowest risk.

Table 1: **Baseline characteristics**

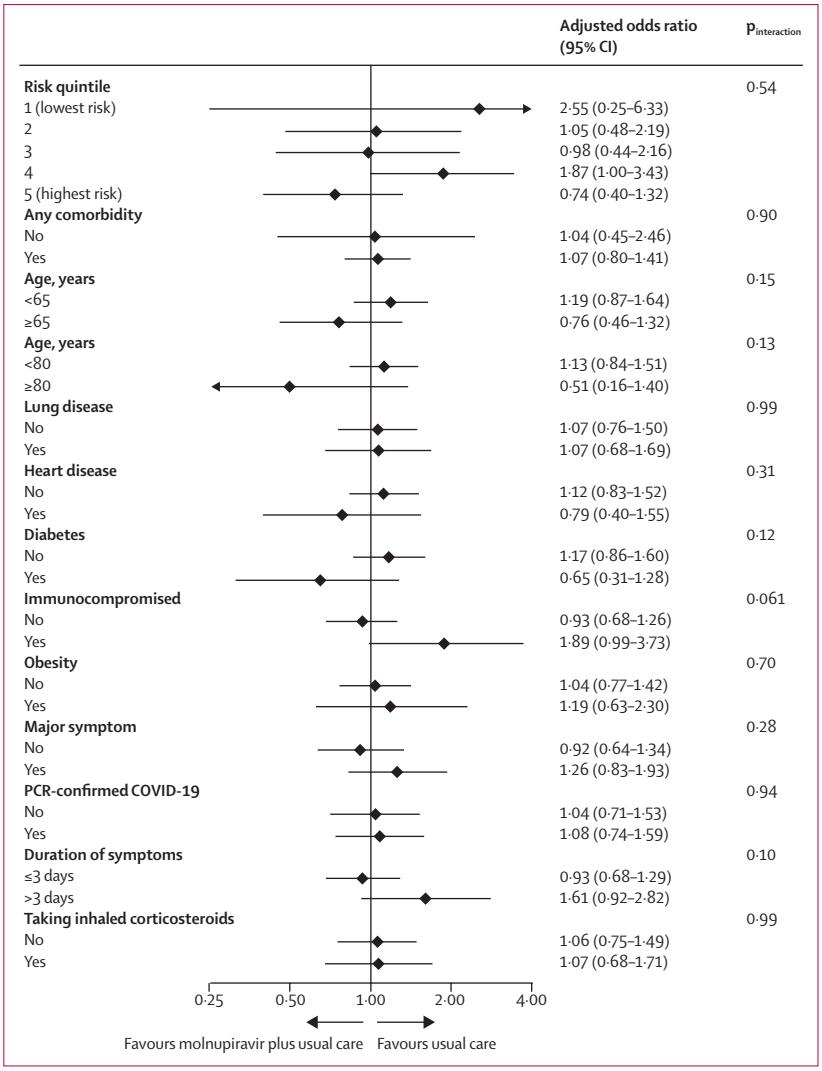


Figure 2: **Forest plot of subgroup analyses of hospitalisation or death, or both**
95% BCI=95% Bayesian credible interval.

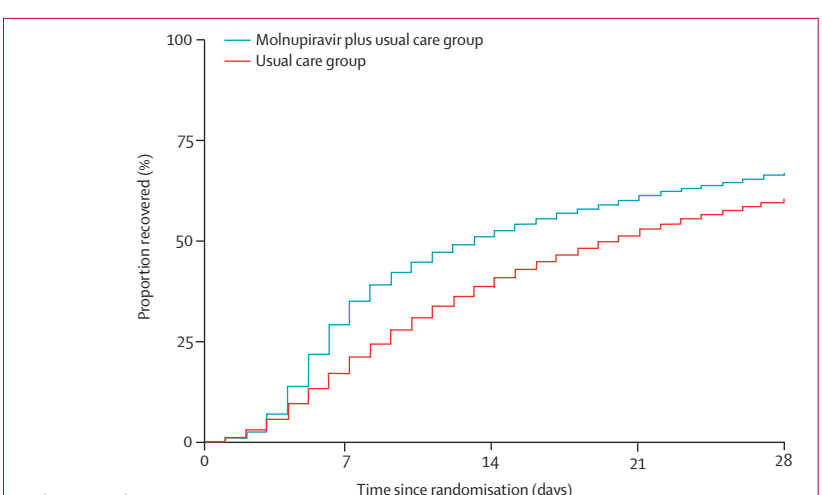
12 529 participants in the molnupiravir plus usual care group versus 98 (1%) of 12 525 (1%) in the usual care group (adjusted odds ratio 1·06 [95% BCI 0·81–1·41]; probability of superiority 0·33). Results in an analysis unadjusted for baseline covariables were identical. There was no evidence of a treatment interaction in any patient subgroups (figure 2).

Median time from randomisation to first recovery was 9 days (IQR 5–23) in the molnupiravir plus usual care group and 15 days (7–not reached) in the usual care group (estimated benefit 4·2 days [95% BCI 3·8–4·6]; posterior probability of superiority of >0·99; figure 3; table 2). Estimated median time to first recovery was 10·4 days (95% BCI 10·1–10·6) in the molnupiravir plus usual care versus 14·6 days (14·2–15·0) in the usual care group (hazard ratio 1·36 [95% BCI 1·32–1·40]), which met the prespecified

superiority threshold (table 2). Subgroup analyses showed that this benefit was consistent across all studied groups (figure 4).

Compared with the usual care group, participants in the molnupiravir plus usual group more often reported early sustained recovery, higher self-rated wellness (appendix p 182), reduced time to sustained recovery, reduced time to alleviation of all symptoms (and each symptom; appendix pp 183–84), reduced time to sustained alleviation of all symptoms (appendix pp 183–84), reduced time to reduction of symptom severity (appendix p 185), fewer moderate or severe symptoms at days 7, 14, and 28 (table 2), and less contact with general practitioners (table 2). Emergency department attendance and the number of new infections in participants' households were similar in both groups (table 2).

In the intensively sampled virology cohort, SARS-CoV-2 viral load was undetectable on day 7 in seven (21%) of 34 participants in the molnupiravir plus usual care group and one (3%) of 39 in the usual care group (p=0·039; table 3). The geometric mean viral load was 6603 (SD 25) in the molnupiravir plus usual care group and 8 5025 (24) in the usual care group (p<0·0001; table 3). In the less intensively sampled virology cohort, viral loads were lower in the molnupiravir plus usual care group than in the usual care group at day 5 (table 3). Viral load at day 14 was low overall but slightly higher in the molnupiravir plus usual care group than in the usual care group (table 3). Serious adverse events were reported for 50 (0·4%) of 12774 participants in the molnupiravir plus usual care group and for 45 (0·3%) of 12934 in the usual care group (appendix p 188). No serious adverse events that were definitely related to the intervention were reported. 145 (1·1%) of 12774 participants in the molnupiravir plus usual care group withdrew because of adverse effects that were attributed to molnupiravir. No adverse events of special interest were reported.



Molnupiravir plus usual care group					
Not yet recovered	12403	7934	4661	3221	2168
Censored	0	141	260	387	594
Recovered	0	4328	7482	8795	9641
Usual care group					
Not yet recovered	12140	9411	6121	4175	2774
Censored	0	271	542	781	1113
Recovered	0	2458	5477	7184	8253

Figure 3: **Time from randomisation to first reported recovery from COVID-19**

Discussion

This analysis of the largest randomised trial involving people vaccinated against SARS-CoV-2 infection who are at increased risk of adverse outcomes in the community and unwell with COVID-19 showed that the early addition of molnupiravir to usual care did not reduce hospital admissions or death (which were low in both treatment groups). However, participants in the molnupiravir plus usual care group recovered faster than those in the usual care group, had a higher rate of early sustained recovery, and had fewer general practitioner consultations. This faster patient-reported recovery was consistent with a reduction in detectable virus and viral load in participants who received molnupiravir compared with those who received usual care only. We did not identify any patient subgroup in which molnupiravir was associated with a reduced chance of hospital admission, and benefits in terms of time to first self-report of recovery were evenly distributed across subgroups. We recorded few serious adverse events in the trial, and none definitely related to molnupiravir.

Two living reviews of treatments for COVID-19—a WHO living guideline[19] and a living review and network analysis that informs WHO on drug treatments[20]—identified six trials of molnupiravir. Of these trials, one was phase 1,[7] another was phase 2a,[2] and one was the phase 3 MOVe-OUT trial.[10] Data from the other three trials were made accessible to WHO but have not been shared publicly. Concern has been raised about the lack of public sharing or formal publication of the findings of these three trials, along with those of nine others, all of which were done in India.[21] The reviews[19,20] reported that molnupiravir probably reduces hospitalisation (odds ratio 0·54 [95% CI 0·30 to 0·90]; based on five trials) and time to symptom resolution (–3·3 days [–4·8 days to –1·6 days]; based on three trials). WHO therefore advises that molnupiravir might benefit outpatients with mild-to-moderate COVID-19 at the highest risk of adverse outcomes.[19]

In the placebo-controlled, pivotal MOVe-OUT trial[10] of 1433 outpatients with confirmed SARS-CoV-2 infection recruited in more than 20 countries, molnupiravir was associated with a reduced risk of all-cause hospitalisation or death (risk difference –3·0% [95% CI –5·9% to –0·1%]). The MOVe-OUT participants were unvaccinated, all had at least one risk factor for progression to serious illness, and were most commonly infected with delta, gamma, and mu SARS-CoV-2 variants.[22] Participants in PANORAMIC were mostly multiply vaccinated, older, and infected with omicron.[23] The reported benefit of

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
Primary outcomes					
Hospitalisations	103	96	..	..	..
Deaths	3	5	..	..	..
Hospitalisation or death	105/12 529 (1%)	98/12 525 (1%)	1·06 (0·81–1·41)*	..	0·33*
Secondary outcomes					
First reported recovery	9728/12 403 (78%)	8374/12 140 (69%)	..	..	..
Days to first reported recovery	9 (5–23)	15 (7–not reached)	1·36 (1·32–1·40)†	4·2 (3·8–4·6)†	>0·99†
Early sustained recovery	3628/11 395 (32%)	2446/10 823 (23%)	1·62 (1·53–1·72)‡	..	>0·99‡
Sustained recovery	8547/12 403 (69%)	7302/12 140 (60%)	..	..	..
Days to sustained recovery	21 (10–not reached)	24 (14–not reached)	1·24 (1·21–1·28)†	3·5 (3·0–3·9)†	>0·99†
Alleviation of all symptoms	8992/9664 (93%)	8351/9395 (89%)	..	..	..
Days to alleviations of all symptoms	4 (2–7)	4 (2–9)	1·18 (1·15–1·22)†	0·66 (0·54–0·78)†	>0·99†
Sustained alleviation of all symptoms	8164/9664 (84%)	7510/9395 (80%)	..	..	..
Days to sustained alleviation of all symptoms	9 (3–22)	12 (4–25)	1·15 (1·11–1·19)†	2·01 (1·58–2·45)†	>0·99†
Initial reduction of symptom severity	10 850/12 375 (88%)	9819/12 123 (81%)	..	..	..
Days to initial reduction of symptom severity	7 (4–14)	9 (5–19)	1·28 (1·24–1·31)†	1·8 (1·60–2·00) †	>0·99†
Participant rating of wellness§					
Day 7	7·3 (1·7)	6·8 (1·8)	0·5 (0·5–0·6)¶	..	<0·0001¶
Day 14	7·9 (1·7)	7·6 (1·7)	0·3 (0·2–0·3)¶	..	<0·0001¶
Day 21	8·2 (1·6)	8·0 (1·7)	0·2 (0·1–0·2)¶	..	<0·0001¶
Day 28	8·4 (1·5)	8·3 (1·6)	0·2 (0·1–0·2)¶	..	<0·0001¶
New infections in household	3887/10 803 (36%)	3873/10 548 (37%)	0·97 (0·91–1·02)*	..	0·88*
Contact with health and social care services					
NHS 111	583/12 401 (5%)	776/12 134 (6%)	0·72 (0·64–0·80)*	..	>0·99*
General practitioner	2425/12 401 (20%)	2876/12 135 (24%)	0·77 (0·73–0·82)*	..	>0·99*
Ambulance service (not hospitalised)	342/12 396 (3%)	331/12 120 (3%)	1·01 (0·87–1·18)*	..	0·46*
Community nurse	265/12 401 (2%)	275/12 131 (2%)	0·94 (0·79–1·11)*	..	0·78*
Physiotherapist	141/12 401 (1%)	90/12 131 (1%)	1·55 (1·18–2·01)*	..	0·0006*
Counsellor	91/12 401 (1%)	106/12 131 (1%)	0·84 (0·63–1·10)*	..	0·90*
Social worker	27/12 401 (<1%)	32/12 131 (<1%)	0·84 (0·49–1·35)*	..	0·78*
Home carer	88/12 400 (1%)	95/12 129 (1%)	0·90 (0·66–1·20)*	..	0·78*
Occupational therapist	261/12 400 (2%)	240/12 131 (2%)	1·07 (0·90–1·26)*	..	0·26*
Hospital emergency department	702/12 401 (6%)	674/12 132 (6%)	1·02 (0·92–1·14)*	..	0·37*
Outpatient respiratory clinic	234/12 401 (2%)	252/12 130 (2%)	0·90 (0·75–1·07)*	..	0·88*
Hospital at home for COVID-19	350/12 401 (3%)	430/12 131 (4%)	0·79 (0·68–0·91)*	..	>0·99*
Other services	583/12 401 (5%)	646/12 130 (5%)	0·87 (0·77–0·98)*	..	0·99*

Data are n, n/N (%), median (IQR), or mean (SD). 95% BCI=95% Bayesian credible interval. *Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline. An odds ratio <1 favoured molnupiravir plus usual care over usual care only. †Estimated benefit in median time to recovery derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline. A positive value in estimated benefit (or hazard ratio >1) favoured molnupiravir plus usual care compared with usual care only. ‡Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline. An odds ratio >1 favoured molnupiravir plus usual care compared with usual care only. §0 was the worst score and 10 was the best. In the molnupiravir plus usual care group, data were available for 11 837 participants at day 7, 11 505 at day 14, 10 752 at day 21, and 10 643 at day 28; the corresponding figures in the usual care group were 11 231, 10 739, 9697, and 9774. ¶Linear mixed-effect model adjusted for age, comorbidity, and vaccination status, with participants fitted as a random effect. An estimated mean difference with (95% CIs rather than 95% BCIs) >0 favoured molnupiravir plus usual care compared with usual care only. p values rather than a probability of superiority are provided.

Table 2: **Primary and secondary outcomes**

molnupiravir in MOVe-Out was lower in the final analysis than in the initial interim results, and the post-interim data in isolation did not suggest benefit.[24] Possible explanations for this seeming reduction in benefit include changes in circulating SARS-CoV-2 variants, recruitment from new sites with different hospitalisation policies, and recruitment of participants with less severe illness.[10]

In MOVe-OUT, molnupiravir increased sustained recovery from anosmia and fatigue, but not other symptoms.[10] In PANORAMIC, molnupiravir was associated with faster alleviation of fever, cough, fatigue, and feeling generally unwell, and shortened time to self-reported recovery. We postulate that molnupiravir might also have shortened the time to resumption of normal

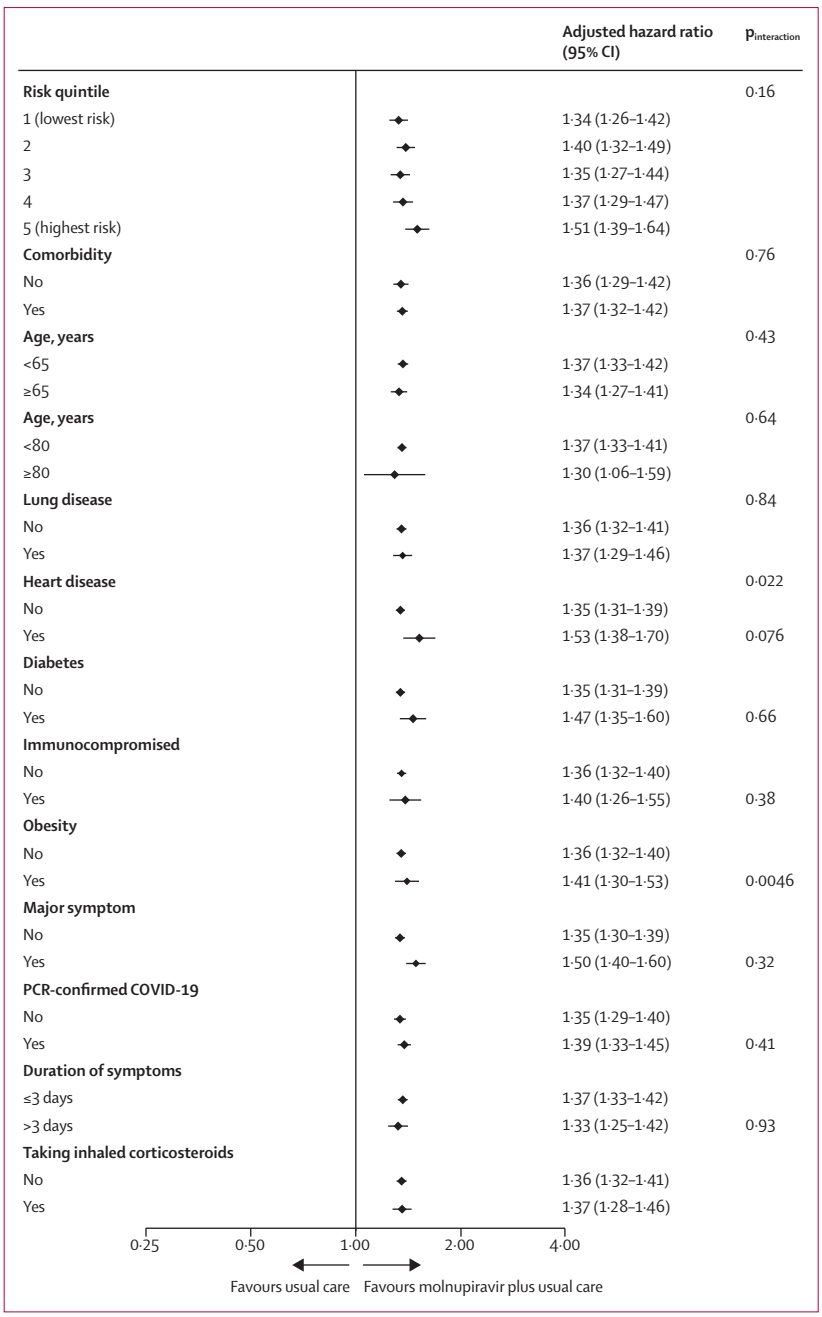


Figure 4: **Forest plot of subgroup analysis of time to first reported recovery from COVID-19**

activities, which is closely related to the duration of feeling unwell, but we did not measure this outcome directly.[25,26] Exploratory analyses from MOVe-OUT showed that, compared with placebo, molnupiravir was associated with a greater reduction from baseline in mean viral load at days 3, 5, and 10.[10] In the AGILE CST-2 placebo-controlled trial[12] of 180 participants (both vaccinated and unvaccinated) molnupiravir was associated with reduced time to a negative PCR test (8 days *vs* 11 days). These findings are consistent with findings in PANORAMIC of a reduction in viral detection and viral load with molnupiravir plus usual care compared with usual care from day 4 onwards in a subgroup of the trial cohort. The proportion of participants with undetectable viral loads in the usual care group was 3% by day 7, whereas based on the placebo group in the FLARE trial[27] we would have expected this proportion to be 15–36%. Nonetheless, we noted a significant increase in the proportion of patients with undetectable viral loads in the molnupiravir plus usual care group compared with the placebo group. Viral whole-genome sequencing, pharmacodynamic analyses, and antibody modelling are underway to further investigate this finding.

PANORAMIC is the largest randomised trial of novel antiviral agents for COVID-19 so far. Ascertainment for the primary outcome was 97%. Participants were randomised a mean of 2 days and treated a mean of 3 days after symptom onset, and nearly all participants reported full compliance with their assigned treatment.

The design of PANORAMIC breaks with the traditional trial paradigm in which the participant comes to the research. The study of molnupiravir in PANORAMIC allowed for remote recruitment of participants from all four UK devolved administrations, irrespective of where people live or receive their health care. PANORAMIC strives to be a democratic trial, with a proactive outreach strategy led by the trial's national pharmacy and inclusion and diversity lead. These efforts are important: research suggests that one reason for the often-low representation of people from diverse and minority ethnic backgrounds in clinical studies is that these populations find it more difficult to access research.[28] Yet these groups are often at increased risk of more and worse disease, as is the case with COVID-19. The ability of participants to be recruited, enrolled, and followed up without having to leave their homes reduced the burden of trial procedures on participants and might have reduced the spread of infection. Participants from ethnic minorities accounted for nearly 6% of the trial population (whereas ethnic minorities account for 12% of the population of England and Wales in the age groups recruited). However, the mean age of participants in PANORAMIC was 56·6 years, and there are proportionally fewer people of minority ethnic origin in older age groups in the UK.[29] The proportion of PANORAMIC participants older than 50 years who were from ethnic minorities was 5·1%, which is broadly similar to that in the English and Welsh general population (6·3%).[30]

The primary analysis estimated a 33% probability of superiority—that is, there is a 33% chance that the addition of molnupiravir to usual care reduces hospitalisation or death by any non-zero amount. The analysis can also be interpreted in terms of inferiority: the estimated probability of molnupiravir use increasing hospitalisation or death by any non-zero amount is 67%.

The primary analysis does not provide compelling evidence for either conclusion. The 95% BCI for the primary outcome (0·81–1·41) indicates that plausible effects for molnupiravir could range from a 19% reduction to a 41% increase in the risk of hospitalisation or death. Taken together, these estimates suggest that the effect of molnupiravir is modest (in either direction). Under the best-case assumption of a 19% risk reduction, the number needed to treat in the population is 677.

Although it is critical to ensure that patients who are likely to benefit receive treatment with antiviral agents, use of antivirals in patients unlikely to benefit risks driving resistance, wastes resources, and potentially exposes people unnecessarily to harm. There is a theoretical risk that molnupiravir use at scale could lead to the emergence of new SARS-CoV-2 variants. This risk is being assessed in PANORAMIC trial's virology substudy. However, animal studies[31,32] suggest that viral mutations induced by molnupiravir are likely to lead to reduced viral viability, with low potential to develop resistant strains. Analysis of mutation frequency and the infectivity of persisting strains after molnupiravir use is underway and will be reported separately.

The open-label design of PANORAMIC means that we cannot estimate the proportion of the effect of molnupiravir on symptoms that might result from any placebo effect. However, the primary outcome in PANORAMIC (non-elective hospitalisation or death) is unlikely to be affected by a placebo effect. Furthermore, the virology substudy findings support a mechanism to explain self-reported reduction in illness duration. We can also draw some positive inference from the four reported intervention arms of the open-label community PRINCIPLE trial of repurposed medicines for COVID-19, in which similar patient-reported measures of improvement were used and only one intervention (inhaled budesonide) was associated with a meaningful effect on self-reported symptoms.[33–35] Furthermore, in keeping with pragmatic trial design, PANORAMIC is designed to closely mirror possible real-world practice.[36] Our results are likely to reflect what would happen if molnupiravir were introduced into routine clinical practice[36] and facilitate a more realistic cost-effectiveness and cost-utility assessment, given that subsequent health-care utilisation might be influenced by knowledge of receiving a potentially active treatment.

Patients with COVID-19 who were extremely clinically vulnerable, although eligible for participation in PANORAMIC, were referred and encouraged to access and be considered for monoclonal antibody or antiviral treatment directly from the NHS. Our findings might therefore be less applicable to patients in this highest-risk category.

In conclusion, this trial of vaccinated adults at increased risk of an adverse outcome and unwell with confirmed SARS-CoV-2 infection showed that early treatment with molnupiravir did not reduce already low hospital admission or deaths. Our findings suggest that, in a highly vaccinated population at high risk (but not the highest risk) of complications from COVID-19, the avoidance of hospitalisation and death is primarily achieved via extensive vaccination. The benefits of molnupiravir in terms of faster time to recovery, reduced contact with general practitioner services, and reduced viral load need to be considered in the context of the prevailing disease, burden on health-care services, drug-acquisition cost, social circumstances, cost-effectiveness, and opportunity costs. Further virological and health economic analyses are underway, and participants are still being followed up to establish the effect of acute COVID-19 treatment with molnupiravir on longer-term symptoms.

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% CI)	p value
Intensive samples				
Undetectable viral load*				
Day 2	1/33 (3%)	0/38 (0)	..	..
Day 3	1/34 (3%)	0/38 (0)	..	..
Day 4	2/34 (6%)	0/39 (0)	..	..
Day 5	5/28 (15%)	0/38 (0)	..	..
Day 6	6/33 (18%)	1/39 (3%)	11·50 (1·07–123·87)	0·044
Day 7	7/34 (21%)	1/39 (3%)	20·72 (1·12–102·23)	0·039
Viral load†				
Day 1	18 589 084 (17)	22 218 974 (15)	..	
Day 2	4 599 027 (39)	12 970 986 (11)	0·33 (0·11–1·03)	0·056
Day 3	1 164 102 (30)	2 960 745 (12)	0·38 (0·12–1·17)	0·092
Day 4	207 097 (41)	736 604 (16)	0·28 (0·09–0·86)	0·026
Day 5	28 244 (33)	665 281 (12)	0·04 (0·01–0·12)	<0·0001
Day 6	13 145 (32)	208 776 (19)	0·06 (0·02–0·19)	<0·0001
Day 7	6603 (25)	85 025 (24)	0·08 (0·02–0·24)	<0·0001
All samples				
Undetectable viral load‡				
Day 5	20/238 (8%)	8/280 (3%)	5·02 (1·61–15·68)	0·0055
Day 14	96/203 (47%)	134/241 (56%)	0·63 (0·35–1·13)	0·12
Viral load†				
Day 5	76 565 (33)	767 941 (26)	0·08 (0·05–0·14)	<0·0001
Day 14	525 (21)	256 (11)	1·95 (1·15–3·31)	0·014

Data are n/N (%) or geometric mean (geometric SD). *Firth logistic regression adjusted for sex, age, and baseline $\log_{10}$(viral load). Adjusted odds ratio >1 favours molnupiravir plus usual care compared with usual care only. †Mixed-effect model adjusted for sex, age, and baseline $\log_{10}$(viral load). Adjusted geometric ratio <1 favours molnupiravir plus usual care compared with usual care only. ‡Mixed-effect logistic regression model adjusted for sex, age, and baseline $\log_{10}$(viral load). Adjusted odds ratio >1 favours molnupiravir plus usual care compared with usual care only.

Table 3: **Outcomes from the viral substudy**

PANORAMIC collaborative group
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Contributors

CCB and JSN-V-T conceived the study. CCB is chief investigator and PL and FDRH are co-chief investigators. BRS, L-MY, JH, MD, CCB, FDRH, PL, GH, OAG, JD, NMR, DBR, SP, DML, JFS, KH, PE, and OvH, contributed to trial design. EO, JA, PE, LL, EH, LC, MB, MM, MC, SB, CB, JCD, IR-W, AC-S, HA, and DB were responsible for study implementation and data acquisition. HR led the clinical team. L-MY, BRS, JH, VH, UG, JM, MAD, CTS, MF, LM, SM, and NSB contributed to statistical analysis. SK, DBR, GH, NMR and MD contributed to safety assessments, monitoring, and oversight of drug interactions. MGP was the national pharmacy and inclusion and diversity lead for the trial. SP and MEP ran the economic assessments. JFS, DML, and JB led the virology sub-study. GH led on patient and public involvement. JC led on the information systems. MB led on data management. CCB, PL, OAG, NMR, SP, DBR, KH, MGP, BRS, EO, JD, DML, SK, NF, NPBT, PE, JFS, JB, JA, MD, T-AM, MEP, GH, ML, BDJ, NDH, MM, JC, EH, LC, MB, MA, OvH, AU, L-MY, and FDRH were members of the trial management group, supporting site recruitment, activity, and delivery. All authors contributed to trial conduct. OAG and CCB produced the first draft of the Article. CCB, OAG, L-MY, PL, FDRH, GH, NMR, DBR, MGP, DML, JFS, PE, JB, JD, SP, JSN-V-T, and SK contributed substantially to subsequent drafts of the Article. All authors critically revised the manuscript. CCB, PL, and FDRH had final responsibility for the decision to submit for publication. CCB and L-MY had full access to and verified all study data.

Declaration of interests

JSN-V-T was seconded to the Department of Health and Social Care, England from October, 2017, to March, 2022, and reports lecture fees from Gilead and fees for participation on an advisory board for F Hoffmann-La Roche. KH is a member of the Health Technology Assessment General Committee and Funding Strategy Group, and Research Professors Funding Committee at the UK National Institute for Health and Care Research (NIHR), received a grant from AstraZeneca (paid to their institution) to support a trial of Evusheld for the prevention of COVID-19 in high-risk individuals, and is an independent member of the independent data monitoring committee for the OCTAVE-DUO trial of vaccines in individuals at high risk of COVID-19. DML has received grants or contracts from LifeArc, the UK Medical Research Council, Bristol Myers Squibb, GlaxoSmithKline, the British Society for Antimicrobial Chemotherapy, and Blood Cancer UK, personal fees or honoraria from Biotest UK, Gilead, and Merck, consulting fees from GlaxoSmithKline (paid to their institution), and conference support from Octapharma. DBR has received consulting fees from OMASS Therapeutics and has a leadership and fiduciary role in the Heal-COVID trial TMG. BRS, JM, MAD, CTS, NSB, and MF report grant money paid to their employer from the University of Oxford for the statistical design and analyses of the PANORAMIC trial. JM has also participated on data and safety monitoring boards as part of his employment with Berry Consultants. ML is a member of the data monitoring and ethics committee of RAPIS-TEST (NIHR efficacy and mechanism evaluation). SK reports grants from GlaxoSmithKline, ViiV, Ridgeback Biotherapeutics, Vir, Merck, the UK Medical Research Council, and the Wellcome Trust (all paid to his institution), speaker's honoraria from ViiV, and donations of drugs for clinical studies from ViiV Healthcare, Toyama, and GlaxoSmithKline. JFS has participated on a data safety monitoring board for GlaxoSmithKline. MA has received grants from the Blood and Transplant Research Unit, Janssen, Pfizer, Prenetics, Dunhill Medical Trust, the BMA Trust (Kathleen Harper Fund), and Antibiotic Research UK (all of which were paid to their institution), and consultancy fees from Prenetics and OxDx. MA reports a planned patent for Ramanomics, has participated on data safety monitoring boards or advisory boards for Prenetics, and has an unpaid leadership or fiduciary role in the E3 Initiative. NPBT has received payment for participation on an advisory board from MSD (before any knowledge or planning of this trial). OvH has received consulting fees from MindGap (fees paid to Oxford University Innovation), has participated on data safety monitoring boards or advisory boards for the CHICO trial, and has an unpaid leadership or fiduciary role in the British Society of Antimicrobial Chemotherapy. AU has received consulting fees and payment or honoraria from MSD, GlaxoSmithKline, and Gilead. NF has received consulting fees from Abbott Diagnostics and GlaxoSmithKline, is a member of the PRINCIPLE trial data safety monitoring board and the NIHR Health Technology Assessment General Funding Committee, and has stocks in Synairgen. JB has received consulting fees from GlaxoSmithKline (paid to her institution). All other authors declare no competing interests.

Data sharing

Qualifying researchers who wish to access our data should submit a proposal with a valuable research question. Proposals will be assessed by a committee formed from the trial management group, including senior statistical and clinical representation. Data will be shared in accordance with the data sharing policy of Nuffield Department of Primary Care Health Sciences.

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