Health outcomes 3 months and 6 months after molnupiravir treatment for COVID-19 for people at higher risk in the community (PANORAMIC): a randomised controlled trial

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Summary

Background No randomised controlled trials have yet reported on the effectiveness of molnupiravir on longer term outcomes for COVID-19. The PANORAMIC trial found molnupiravir reduced time to recovery in acute COVID-19 over 28 days. We aimed to report the effect of molnupiravir treatment for COVID-19 on wellbeing, severe and persistent symptoms, new infections, health care and social service use, medication use, and time off work at 3 months and 6 months post-randomisation.

Methods This study is a follow-up to the main analysis, which was based on the first 28 days of follow-up and has been previously reported. For this multicentre, primary care, open-label, multi-arm, prospective randomised controlled trial conducted in the UK, participants were eligible if aged at least 50 years, or at least 18 years with a comorbidity, and unwell 5 days or less with confirmed COVID-19 in the community. Participants were randomly assigned to the usual care group or molnupiravir group plus usual care (800 mg twice a day for 5 days), which was stratified by age (<50 years or ≥50 years) and vaccination status (at least one dose: yes or no). The primary outcome was hospitalisation or death (or both) at 28 days; all longer term outcomes were considered to be secondary outcomes and included self-reported ratings of wellness (on a scale of 0–10), experiencing any symptom (fever, cough, shortness of breath, fatigue, muscle ache, nausea and vomiting, diarrhoea, loss of smell or taste, headache, dizziness, abdominal pain, and generally feeling unwell) rated as severe (moderately bad or major problem) or persistent, any health and social care use, health-related quality of life (measured by the EQ-5D-5L), time off work or school, new infections, and hospitalisation.

Findings Between Dec 8, 2021, and April 27, 2022, 25 783 participants were randomly assigned to the molnupiravir plus usual care group (n=12 821) or usual care group (n=12 962). Long-term follow-up data were available for 23 008 (89·2%) of 25 784 participants with 11 778 (91·9%) of 12 821 participants in the molnupiravir plus usual care group and 11 230 (86·6%) of 12 963 in the usual care group. 22 806 (99·1%) of 23 008 had at least one previous dose of a SARS-CoV-2 vaccine. Any severe (3 months: adjusted risk difference –1·6% [–2·6% to –0·6%]; probability superiority [p(sup)]>0·99; number needed to treat [NNT] 62·5; 6 months: –1·9% [–2·9% to –0·9%]; p(sup)>0·99, NNT 52·6) or persistent symptoms (3 months: adjusted risk difference –2·1% [–2·9% to –1·5%]; p(sup)>0·99; NNT 47·6; 6 months: –2·5% [–3·3% to –1·6%]; p(sup)>0·99; NNT 40) were reduced in severity, and health-related quality of life (measured by the EQ-5D-5L) improved in the molnupiravir plus usual care group at 3 months and 6 months (3 months: adjusted mean difference 1·08 [0·65 to 1·53]; p(sup)>0·99; 6 months: 1·09 [0·63 to 1·55]; p(sup)>0·99). Ratings of wellness (3 months: adjusted mean difference 0·15 (0·11 to 0·19); p(sup)>0·99; 6 months: 0·12 (0·07 to 0·16); p(sup)>0·99), experiencing any more severe symptom (3 months; adjusted risk difference –1·6% [–2·6% to –0·6%]; p(sup)=0·99; 6 months: –1·9% [–2·9% to –0·9%]; p(sup)>0·99), and health-care use (3 months: adjusted risk difference –1·4% [–2·3% to –0·4%]; p(sup)>0·99; NNT 71·4; 6 months: –0·5% [–1·5% to 0·4%]; p(sup)>0·99; NNT 200) had high probabilities of superiority with molnupiravir treatment. There were significant differences in persistence of any symptom (910 [8·9%] of 10 190 *vs* 1027 [11%] of 9332, NNT 67) at 6 months, and reported time off work at 3 months (2017 [17·9%] of 11 274 *vs* 2385 [22·4%] of 10 628) and 6 months (460 [4·4%] of 10 562 *vs* 527 [5·4%] of 9846; NNT 100). There were no differences in hospitalisations at long-term follow-up.

Interpretation In a vaccinated population, people treated with molnupiravir for acute COVID-19 felt better, experienced fewer and less severe COVID-19 associated symptoms, accessed health care less often, and took less time off work at 6 months. However, the absolute differences in this open-label design are small with high numbers needed to treat.

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Introduction

Although hospitalisation and death from COVID-19 are currently rare, acute SARS-CoV-2 infection remains common with longer term symptoms representing a major public health burden.[1] The US Household Pulse Survey has estimated that about 10% of adults infected with SARS-CoV-2 continue to experience and have the many symptoms grouped together under the terms post-COVID-19 condition (also known as long COVID), defined as symptoms originating or exacerbated by COVID-19 persisting beyond 12 weeks and not explainable by other disease. The UK Office for National Statistics has estimated that 1·9 million people (2·9% of the UK population) were experiencing self-reported long COVID, which adversely affected the day-to-day activities of 1·5 million people, 20% of whom reported that their ability to undertake their day-to-day activities had been limited "a lot".[3] Identifying treatments for acute SARS-CoV-2 infection that reduce associated symptoms during the longer term could have considerable reach and impact.

Randomised controlled trials have shown that treatment of the acute infection with novel antiviral drugs (nirmatrelvir–ritonavir and molnupiravir) can reduce hospital admission, time taken for recovery, viral detection, and viral load more than placebo over 28 days of follow up in unvaccinated patients.[4,5] The Platform Adaptive Trial of Novel Antivirals for Early Treatment of COVID-19 in the Community (PANORAMIC) trial, which is to our knowledge the largest randomised evaluation of antivirals in the community, has found that molnupiravir did not reduce the already low risk of hospital admission by 28 days from randomisation in vaccinated people with COVID-19 aged at least 18 years and who had a comorbidity, or who were aged at least 50 years with or without a comorbidity. Molnupiravir did help them recover more quickly, and once well, it helped people stay well more often, reduced consulting in primary care, and reduced detection of the SARS-CoV-2 virus during the first 7 days.[6] However, although the initial viral load decrease was faster with molnupiravir versus usual care, 5 days of molnupiravir treatment

Research in context

Evidence before this study

The molnupiravir for oral treatment of COVID-19 in non-hospitalised patients (MOVe-OUT) trial found molnupiravir for SARS-CoV-2 infection reduced hospital admission in a largely unvaccinated population, whereas the Platform Adaptive Trial of Novel Antivirals for Early Treatment of COVID-19 in the Community (PANORAMIC) trial in a vaccinated population found that during 28 days, molnupiravir did not affect hospitalisation or death rates from COVID-19 but self-reported recovery was faster by at least 4 days. However, the affect of treating acute SARS-CoV-2 infection with antiviral drugs on longer term outcomes is unclear. We searched PubMed on April 24, 2024, using the search terms "Molnupiravir" AND "Long term" OR "Long COVID". We searched for clinical trials and observational studies published between database inception and April 24, 2024, with no language restrictions, and identified two retrospective observational studies using routinely collected data. We identified no randomised controlled trials of specific antiviral treatment for acute SARS-Cov-2 infection on wellbeing, severe and persistent symptoms, new infections, health care and social service use and medication use, and time off work during the longer term.

Added value of this study

The previous studies on longer term effect of molnupiravir for acute SARS-CoV-2 infection have not used prospective randomised controlled designs, relying on ascertaining diagnostic codes from medical records of conditions associated with post-COVID-19 condition (also known as long COVID). These studies identified a modest association with antiviral treatment and COVID-19 associated conditions during the longer term, without directly ascertaining the effect on health-related quality of life, well-being, or work and education status from those affected, and thus are prone to confounding and consultation bias. We have now completed our pre-specified 6-month follow-up of 23 008 (89·2%) of 25 783 trial participants, and found evidence of long-term benefit on symptoms (ie, fever, cough, shortness of breath, fatigue [tiredness], muscle ache, nausea and vomiting, diarrhoea, loss of smell or taste [or both], headache, dizziness, abdominal pain, and generally feeling unwell), quality of life, health-care and occupation-related outcomes, but with small effect sizes.

Implications of all the available evidence

Follow-up of participants in this study found that individuals taking molnupiravir for acute SARS-CoV-2 infection felt better, experienced fewer and less severe COVID-19 associated symptoms, accessed health care less often, and took less time off work at 6 months, but with high numbers needed to treat, which adds to previous findings of modest associations between molnupiravir treatment for SARS-CoV-2 infection and potentially related, subsequent diagnoses. There was conflicting evidence surrounding new infections in the household with fewer in the molnupiravir plus usual care group at 3 months but a higher number at 6 months.

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See Online for appendix

mostly failed to clear the virus in some cases, resulting in substantial viral mutagenesis and greater persistence at day 14 in addition to blunting the infection associated boost to anti-SARS-CoV-2 spike antibody concentrations.[7] WHO guidelines suggest the use of molnupiravir when nirmatrelvir–ritonavir is not available. By contrast, the molnupiravir for oral treatment of COVID-19 in non-hospitalised patients (MOVe-OUT) trial[8] found that molnupiravir reduced hospital admissions and or death (difference, −3·0% percentage points, 95% CI −5·9% to −0·1%), but the study population differed meaningfully from the PANORAMIC trial in that participants were mostly unvaccinated.

Retrospective observational studies have found a modest effect on post-COVID-19 conditions and associated symptoms from treatment of SARS-CoV-2 infection with molnupiravir. These studies have relied on ascertaining diagnostic codes from medical records of conditions associated with post-COVID-19 condition, and have not directly ascertained the effect on health-related quality of life, wellbeing, or work and education status from those affected, and are prone to confounding and consultation bias.[9,10] Evidence from randomised controlled trials is ideally needed to answer this question,[11] but no randomised controlled trials have yet reported the effect of molnupiravir treatment on longer term outcomes. We aimed to report on the effect of molnupiravir treatment for COVID-19 on wellbeing, severe and persistent symptoms, new infections, health care and social service use, medication use, and time off work at 3 months and 6 months post-randomisation.

Methods

Study design

For this multicentre, primary care, open-label, multi-arm, prospective randomised controlled trial conducted in the UK, we assessed the effectiveness of molnupiravir in the treatment of acute COVID-19, according to our published protocol.[12] The platform trial is ongoing. The primary analysis during 28 days of the molnupiravir intervention was previously published;[6] we now present results from the longer term follow-up.

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee approved the trial protocol. Patients were not involved in the design, conduct, reporting, or dissemination plans of our research. The authors vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent Trial Steering Committee and Data Monitoring and Safety Committee provided trial oversight.

Participants

People in the community were eligible if they were aged at least 50 years, or at least 18 years with at least one comorbidity (appendix p 4) and had ongoing symptoms from COVID-19 that had started within the previous 5 days, and a positive PCR or rapid antigen SARS-CoV-2 test within the past 7 days. The exclusion criteria were being currently admitted to hospital (inpatient), previous randomisation into the trial, and participation in a clinical trial of a therapeutic agent for acute COVID-19. Online informed consent was obtained from all participants. We collected self-reported sex assigned at birth as male, female, or other.

Randomisation and masking

Participants were randomly assigned to either usual care plus molnupiravir, or usual care without a specific antiviral drug between Dec 8, 2021, and April 27, 2022. Eligible, consenting participants were randomly assigned by a suitably qualified medical or research professional (CCB and many other health-care professionals) in equal allocation between molnupiravir and usual care using a secure, web-based randomisation system called Spinnaker (version custom built for the PANORAMIC trial; Spiral Software, Wellington, New Zealand). Randomisation was stratified by age (<50 years or ≥50 years) and vaccination status (at least one dose: yes or no). The trial is open label; thus, participants and members of the trial team responsible for recruitment, follow-up, and monitoring of participants were aware of the assignment of the groups. However, individuals managing the data were masked to the allocation of participants.

Procedures and outcomes

Participants received usual care plus molnupiravir 800 mg twice a day for 5 days, or usual care alone. Participants who were randomly assigned to molnupiravir were urgently couriered a participant pack containing molnupiravir, dosing, and safety information, and a pregnancy test (only for use by participants of child-bearing potential). Safety calls were carried out 2 days post-randomisation for participants in the molnupiravir plus usual care group. Usual care participants were emailed or posted a trial information booklet. The primary outcome was hospitalisation or death (or both) at 28 days; all longer term outcomes were considered as secondary outcomes.

Participants or their trial partner were contacted and asked to complete online questionnaires at 3 months and 6 months post-randomisation. If the participant did not complete the follow-up, or for those participants who did not have internet access, a telephone call was carried out at 4 months and 6 months and the participant was given the opportunity to answer questions over the telephone. Three attempts were made to contact the participant to minimise the amount of missing data. At these follow-up timepoints, participants were asked the following: to rate how well they were feeling on a scale of 0 to 10 (0 being the worst one can imagine and 10 being the best one can imagine); to rate 12 symptoms (fever, cough, shortness of breath, fatigue [tiredness],

muscle ache, nausea or vomiting, diarrhoea, loss of smell or taste [or both], headache, dizziness, abdominal pain, and generally feeling unwell) on a four point ordinal scale (no problem, mild problem, moderate problem, or major problem); if the participant had any contact with health and social services; whether they had any time off work or study; and whether they had been hospitalised. Other outcomes included whether the participant had taken over-the-counter or prescribed medication, if there had been additional cases of COVID-19 in the household, and the EQ-5D-5L visual analogue scale to assess their health-related quality of life, which was measured on a scale of 0 to 100 (0 representing the worst health state the participant could imagine and 100 being the best).

Statistical analysis

The sample size calculation and statistical analysis are detailed in the appendix (p 106). Statistical analyses were carried out in STATA (version 18) and R (version 4.3.0). Bayesian mixed-effects models were fitted using the brms package (version 2.19.0) in R. Priors were non-informative and are detailed in the appendix (pp 106, 186).

The primary analysis population was defined as all eligible participants concurrently randomly assigned to the molnupiravir plus usual care group or usual care (alone) group, according to the group they were allocated to regardless of deviation from the protocol. We analysed self-reported symptoms both individually and all symptoms together based on more severe symptoms, defined as any symptom rated as a moderate or major problem, and persistent symptoms defined as symptoms rated a moderate or major problem at 3 months or 6 months (regardless of outcome at 3 months for the 6 month timepoint) in addition to not feeling recovered at day 28 post study enrolment. Long-term outcomes pre-specified in the protocol include longer term effects including proportion with ongoing symptoms commonly associated with long COVID symptoms, health-care use, and wellness. We did not ascertain formal diagnoses of long COVID explicitly, but instead ascertained the presence of symptoms at the given timepoint. A scoping review found five definitions for long COVID in use, which differ by duration and nature of eligible symptoms.[13]

Adherence was assessed via self-reporting in participant daily diaries or telephone calls during the first 28 days post-randomisation, and those who took molnupiravir medication as prescribed for 4 days or 5 days were considered adherent.

Outcomes were analysed using a longitudinal Bayesian mixed-effects logistic or linear regression, adjusted for baseline characteristics of comorbidity, vaccination status, and age. Fixed effects for time (3 months and 6 months follow-up), randomised group, and a group by time interaction were fitted to estimate the timepoint-specific treatment effect. A random effect was fitted to allow for clustering of timepoints within participant.

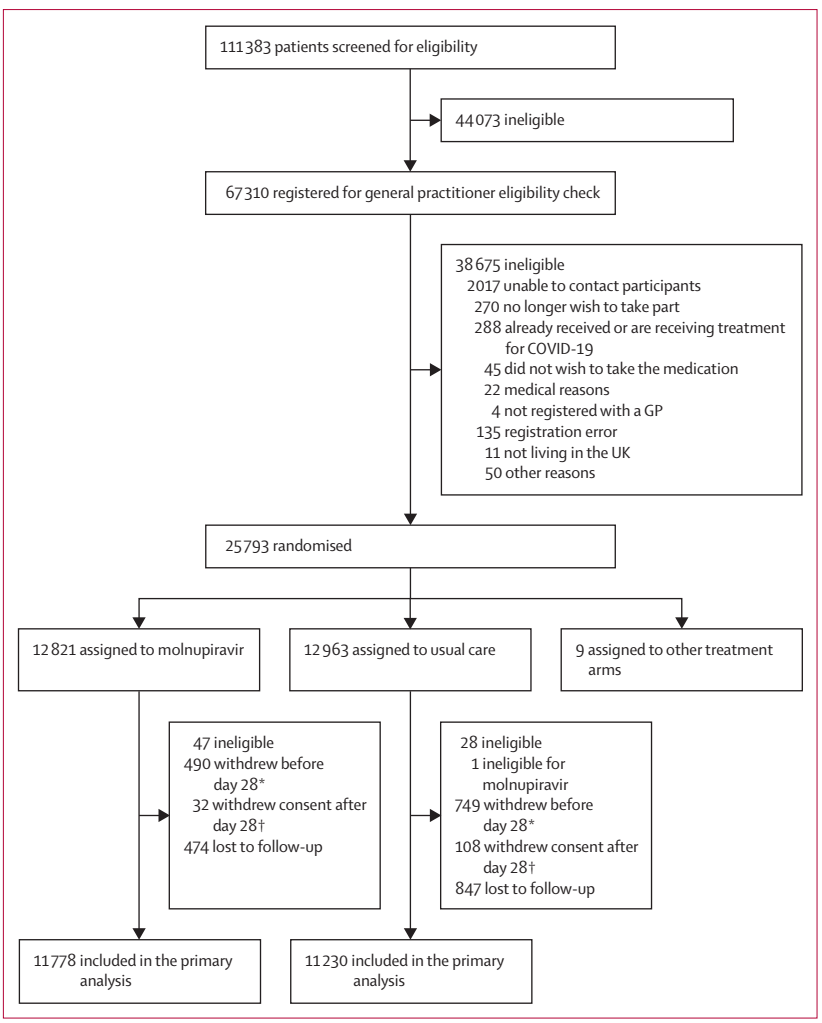

Figure: **Trial profile**
*Participants who did not withdraw due to ineligibility but withdrew before day 28 and have no follow-up data.
†Participants withdrew from long-term follow-up and had previous long-term data.

Bayesian prior distributions have been specified in the appendix (pp 106, 186).

To assess the robustness of the results to different missing at random assumptions, multiple imputation was carried out on all participants in the analysis population regardless of whether they had completed any follow-up measures for several key outcomes (appendix p 182).

Role of the funding source

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

Results

The first participant was randomly assigned on Dec 8, 2021, and randomisation to the molnupiravir plus usual care group was stopped on April 27, 2022, by which time 25 783 participants who were eligible for

	All molnupiravir (N=12 774)	Molnupiravir long term* (n=11 778)	All usual care (n=12 934)	Usual care long term* (n=11 230)	All overall (N=25 708)	Overall long term* (N=23 008)
Age, years	56·7 (12·5; 18·0–99·0)	57·1 (12·2; 18·0–99·0)	56·5 (12·7; 18·0–98·0)	57·2 (12·2; 18·0–98·0)	56·6 (12·6; 18·0–99·0)	57·2 (12·2; 18·0–99·0)
Sex						
Female	7422 (58·1%)	6807 (57·8%)	7631 (59·0%)	6630 (59·0%)	15053 (58·6%)	13 438 (58·4%)
Male	5349 (41·9%)	4968 (42·2%)	5299 (41·0%)	4597 (40·9%)	10 648 (41·4%)	9565 (41·6%)
Other	3 (<1%)	3 (<1%)	4 (<1%)	3 (<1%)	7 (<1%)	6 (<1%)
Strata						
≥50 unvaccinated	80 (0·6%)	70 (0·6%)	70 (0·5%)	48 (0·4%)	150 (0·6%)	118 (0·5%)
≥50 vaccinated	9941 (77·8%)	9345 (79·3%)	9975 (77·1%)	8971 (79·9%)	19916 (77·5%)	18 317 (79·6%)
<50 unvaccinated	62 (0·5%)	46 (0·4%)	61 (0·5%)	39 (0·3%)	123 (0·5%)	85 (0·4%)
<50 vaccinated	2691 (21·1%)	2317 (19·7%)	2828 (21·9%)	2172 (19·3%)	5519 (21·5%)	4489 (19·5%)
Days since symptom onset	2·4 (1·2; 0–6)	2·4 (1·2; 0–6)	2·4 (1·2; 0–6)	2·4 (1·2; 0–6)	2·4 (1·2; 0–6)	2·4 (1·2; 0–6)
Days since symptom onset	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)	2 (1–3)
Days from randomisation to reporting receipt of medication	1 (1–1)	2 (2–2)	..	..	..	..
Missing	266 (2·1%)	94 (0·8%)	..	..	..	..
Days from start of symptoms to taking medication	3 (3–5)	3 (3–5)	..	..	..	..
Missing	288 (2·2%)	101 (0·9%)	..	..	..	..
Ethnicity category						
White	12 043 (94·3%)	11 152 (94·7%)	12 155 (94·0%)	10 640 (94·7%)	24 198 (94·1%)	21 793 (94·7%)
Asian	365 (2·9%)	311 (2·6%)	434 (3·4%)	321 (2·9%)	799 (3·1%)	632 (2·7%)
Mixed Race	202 (1·6%)	182 (1·5%)	189 (1·5%)	157 (1·4%)	391 (1·5%)	339 (1·5%)
Black	78 (0·6%)	68 (0·6%)	77 (0·6%)	53 (0·5%)	155 (0·6%)	121 (0·5%)
Other	86 (0·7%)	65 (0·6%)	79 (0·6%)	59 (0·5%)	165 (0·6%)	124 (0·5%)
National Health Service priority category by age, years						
≥80	256 (2·0%)	228 (1·9%)	271 (2·1%)	201 (1·8%)	527 (2·0%)	429 (1·9%)
≥75 and <80	537 (4·2%)	510 (4·3%)	574 (4·4%)	510 (4·5%)	1111 (4·3%)	1020 (4·4%)
≥70 and <75, or ≥18 and <70 and in an at-risk group†	1116 (8·7%)	1078 (9·2%)	1111 (8·6%)	1016 (9·0%)	2227 (8·7%)	2094 (9·1%)
≥65 and <70 and not in an at-risk group†	1493 (11·7%)	1427 (12·1%)	1464 (11·3%)	1369 (12·2%)	2957 (11·5%)	2796 (12·2%)
≥18 and <65 in an at-risk group†	6514 (51·0%)	5854 (49·7%)	6576 (50·8%)	5438 (48·4%)	13090 (50·9%)	11 292 (49·1%)
≥60 and <65 and not in an at-risk group†	745 (5·8%)	706 (6·0%)	766 (5·9%)	720 (6·4%)	1511 (5·9%)	1426 (6·2%)
≥55 and <60 and not in an at-risk group†	994 (7·8%)	951 (8·1%)	1060 (8·2%)	976 (8·7%)	2054 (8·0%)	1927 (8·4%)
≥50 and <55 and not in an at-risk group†	1119 (8·8%)	1024 (8·7%)	1112 (8·6%)	1000 (8·9%)	2231 (8·7%)	2025 (8·8%)
Predicted risk quintile						
1 (lowest risk)	2483 (19·4%)	2361 (20·0%)	2553 (19·7%)	2382 (21·2%)	5036 (19·6%)	4743 (20·6%)
2	2672 (20·9%)	2510 (21·3%)	2632 (20·3%)	2395 (21·3%)	5304 (20·6%)	4906 (21·3%)
3	2511 (19·7%)	2327 (19·8%)	2656 (20·5%)	2364 (21·1%)	5167 (20·1%)	4691 (20·4%)
4	2774 (21·7%)	2540 (21·6%)	2760 (21·3%)	2308 (20·6%)	5534 (21·5%)	4848 (21·1%)
5 (highest risk)	2334 (18·3%)	2040 (17·3%)	2333 (18·0%)	1781 (15·9%)	4667 (18·2%)	3821 (16·6%)
Confirmed PCR positive	5936 (46·5%)	5358 (45·5%)	5882 (45·5%)	4985 (44·4%)	11818 (46·0%)	10 343 (45·0%)
Index of multiple deprivation quintile‡						
1 (most deprived)	1231 (9·6%)	1091 (9·3%)	1180 (9·1%)	922 (8·2%)	2411 (9·4%)	2013 (8·7%)
2	1907 (14·9%)	1729 (14·7%)	1952 (15·1%)	1646 (14·7%)	3859 (15·0%)	3375 (14·7%)
3	2563 (20·1%)	2352 (20·0%)	2587 (20·0%)	2242 (20·0%)	5150 (20·0%)	4594 (20·0%)
4	3203 (25·1%)	2989 (25·4%)	3207 (24·8%)	2851 (25·4%)	6410 (24·9%)	5841 (25·4%)
5 (least deprived)	3821 (29·9%)	3577 (30·4%)	3949 (30·5%)	3520 (31·3%)	7770 (30·2%)	7097 (30·8%)
Data unavailable	49 (0·4%)	40 (0·3%)	59 (0·5%)	49 (0·4%)	108 (0·4%)	89 (0·4%)

(Table 1 continues on next page)

	All molnupiravir (N=12 774)	Molnupiravir long term* (n=11 778)	All usual care (n=12 934)	Usual care long term* (n=11 230)	All overall (N=25 708)	Overall long term* (N=23 008)
(Continued from previous page)						
Took at least 4 days of molnupiravir§	11795 (92·3%)	11 337 (96·3%)	..	..	..	..
Received vaccination	12632 (98·9%)	11 662 (99·0%)	12803 (99·0%)	11 143 (99·2%)	25435 (98·9%)	22 806 (99·1%)
Number of vaccine doses						
1	86 (0·7%)	64 (0·5%)	87 (0·7%)	67 (0·6%)	173 (0·7%)	131 (0·6%)
2	518 (4·1%)	400 (3·4%)	454 (3·5%)	325 (2·9%)	972 (3·8%)	725 (3·2%)
3	11795 (92·3%)	10 982 (93·2%)	12022 (92·9%)	10 540 (93·9%)	23817 (92·6%)	21 523 (93·5%)
4	233 (1·8%)	216 (1·8%)	240 (1·9%)	211 (1·9%)	473 (1·8%)	427 (1·9%)
Missing	142 (1·1%)	116 (1·0%)	131 (1·0%)	87 (0·8%)	273 (1·1%)	203 (0·9%)
Smoker	789 (6·2%)	663 (5·6%)	804 (6·2%)	621 (5·5%)	1593 (6·2%)	1284 (5·6%)
Wellness score	5·1 (1·7; 0–10)	5·2 (1·7; 0–10)	5·2 (1·7; 0–10·0)	5·2 (1·7; 0–10)	5·1 (1·7; 0–10)	5·2 (1·7; 0–10)
People in household						
0	1651 (12·9%)	1523 (12·9%)	1658 (12·8%)	1437 (12·8%)	3309 (12·9%)	2960 (12·9%)
1	6090 (47·7%)	5714 (48·5%)	6006 (46·4%)	5373 (47·8%)	12096 (47·1%)	11 087 (48·2%)
2	2122 (16·6%)	1947 (16·5%)	2171 (16·8%)	1854 (16·5%)	4293 (16·7%)	3802 (16·5%)
3	1760 (13·8%)	1589 (13·5%)	1973 (15·3%)	1668 (14·9%)	3733 (14·5%)	3257 (14·2%)
4	805 (6·3%)	713 (6·1%)	771 (6·0%)	631 (5·6%)	1576 (6·1%)	1344 (5·8%)
≥5	346 (2·7%)	292 (2·5%)	355 (2·7%)	267 (2·4%)	701 (2·7%)	559 (2·4%)
Taking inhaled corticosteroids	2978 (23·3%)	2712 (23·0%)	3150 (24·4%)	2636 (23·5%)	6128 (23·8%)	5348 (23·2%)
Taking inhaled corticosteroids for COVID-19	182 (1·4%)	167 (1·4%)	158 (1·2%)	134 (1·2%)	340 (1·3%)	301 (1·3%)
Monoclonal antibodies for COVID-19	26 (0·2%)	23 (0·2%)	18 (0·1%)	17 (0·2%)	44 (0·2%)	40 (0·2%)
Comorbidities						
Lung disease	3000 (23·5%)	2709 (23·0%)	3169 (24·5%)	2613 (23·3%)	6169 (24·0%)	5322 (23·1%)
Heart disease	996 (7·8%)	931 (7·9%)	955 (7·4%)	837 (7·5%)	1951 (7·6%)	1768 (7·7%)
Kidney disease	225 (1·8%)	206 (1·7%)	253 (2·0%)	209 (1·9%)	478 (1·9%)	415 (1·8%)
Liver disease	159 (1·2%)	141 (1·2%)	143 (1·1%)	116 (1·0%)	302 (1·2%)	257 (1·1%)
Neurological disease	426 (3·3%)	383 (3·3%)	436 (3·4%)	351 (3·1%)	862 (3·4%)	734 (3·2%)
Learning disability	36 (0·3%)	30 (0·3%)	27 (0·2%)	25 (0·2%)	63 (0·2%)	55 (0·2%)
Down's syndrome	24 (0·2%)	23 (0·2%)	29 (0·2%)	27 (0·2%)	53 (0·2%)	50 (0·2%)
Diabetes	1478 (11·6%)	1349 (11·5%)	1510 (11·7%)	1258 (11·2%)	2988 (11·6%)	2607 (11·3%)
Weakened immune system	1119 (8·8%)	998 (8·5%)	1062 (8·2%)	859 (7·6%)	2181 (8·5%)	1857 (8·1%)
Transplant recipient	55 (0·4%)	51 (0·4%)	70 (0·5%)	54 (0·5%)	125 (0·5%)	105 (0·5%)
Obesity	1964 (15·4%)	1793 (15·2%)	1935 (15·0%)	1595 (14·2%)	3899 (15·2%)	3388 (14·7%)
Mental illness	198 (1·6%)	155 (1·3%)	220 (1·7%)	164 (1·5%)	418 (1·6%)	319 (1·4%)
Hypertension	2864 (22·4%)	2692 (22·9%)	2897 (22·4%)	2561 (22·8%)	5761 (22·4%)	5253 (22·8%)
Other vulnerability	2281 (17·9%)	2068 (17·6%)	2334 (18·0%)	1878 (16·7%)	4615 (18·0%)	3946 (17·1%)

Data are n (%), median (IQR), or mean (SD; range). *Long-term follow-up population defined as those contributing at least one diary data at 3 months, telephone call data at 4 months, diary data at 6 months, or telephone call data at 6 months. †The at-risk group is defined as having any of the comorbidities listed. ‡The index of multiple deprivation is a measure of relative deprivation across each of the constituent nations of the UK based on postcode and is ranked from most deprived to least deprived. §Data taken from participants' daily diaries and telephone calls. A participant is considered to have taken molnupiravir for 4 days if they have reported taking the prescribed dose each day for at least 4 days either in their diaries or during telephone calls on day 7, 14 or 28, or reported finishing the course.

Table 1: **Baseline characteristics of participants by treatment group**

randomisation to the molnupiravir plus usual care group had been enrolled. 12 821 participants were randomly assigned to the molnupiravir plus usual care group and 12 962 participants to usual care alone (figure). In total 23 008 (89·2%) of 25 783 participants, 11 778 (91·9%) participants in the molnupiravir plus usual care group and 11 230 (86·6%) in the usual care group, provided follow-up information for at least one long-term time-point. Participants who provided long-term follow-up data were similar to the full sample: mean age was 57·2 years (SD 12·2) versus 56·6 years (12·6); 13 438 (58·4%) of 23 008 participants were female versus 15 053 (58·6%) of 25 708 participants; 21 793 (94·7%) participants were White versus 24 198 (94·1%); and 22 806 (99·1%) participants versus 25 435 (98·9%) participants had received at least one dose of vaccination. Use of other medicines was rare with 40 (0·2%) of 23 008 participants reporting treatment with monoclonal

antibodies, 301 (1·3%) participants reporting taking corticosteroids for COVID-19, and no participants being randomly assigned to the usual care group reporting taking molnupiravir. More participants who adhered to the intervention have completed at least one long-term follow-up timepoint, compared with those originally randomised to molnupiravir plus usual care: 11 337 of 11 778 (96·3%) participants versus 11 795 of 12 774 (92·3%) participants (table 1). The number of serious adverse events within the first 28 days were 50 (0·4%) of 12 821 participants in the molnupiravir plus usual care group and 45 (0·3%) of 12 962 participants in the usual care group, and have been reported elsewhere.[6] An additional serious adverse event (non-COVID-19 hospitalisation due to gallstones) was recorded in the molnupiravir plus usual care group after 28 days follow-up and was deemed to be unrelated to the intervention. There were 17 deaths in the molnupiravir plus usual care group and ten deaths in the usual care group that occurred after day 28 but before 6 months, and represent a higher rate in molnupiravir but absolute numbers were small: 0·1% of those randomly assigned to the molnupiravir plus usual care group and less than 0·1% of those randomly assigned to the usual care group.

There was a small difference in participant rating of wellness between participants randomly assigned to the molnupiravir plus usual care group versus the usual care group at 3 months (adjusted mean difference 0·15, Bayesian credible interval (BCrI) 0·11–0·19; probability superiority [p(sup)]>0·999) and 6 months (0·12, 0·07–0·16; >0·999) favouring the treatment group (table 2).

Fewer participants originally randomised to the molnupiravir plus usual care group reported any symptoms that were rated moderately bad or worse at 3 months (1907 [16·9%] of 11 271 *vs* 1948 [18·3%] of 10 619, adjusted risk difference –1·6%, BCrI –2·6% to –0·6%; p(sup)>0·999; number needed to treat (NNT) 62·5) and 6 months (1746 [16·5%] of 10 554 *vs* 1796 [18·3%] of 9840, –1·9%, BCrI –2·9% to –0·9%; p(sup)>0·999; NNT 52·6). Fewer participants originally randomised to molnupiravir reported any persistent symptom at 3 months (910 [8·9%] of 10 190 *vs* 1027 [11·0%] of 9332, adjusted risk difference –2·1%, BCrI –2·9% to –1·5%; p(sup)>0·999; NNT=47·6) and at 6 months (817 [8·5%] of 9592 *vs* 946 [11·0%] of 8634, adjusted risk difference –2·5%, BCrI –3·3% to –1·6%; p(sup)>0·999; NNT=40; table 2; appendix pp 187–88).

Use of any health care or social service was lower in participants randomised to molnupiravir: at 3 months (1282 [14·1%] of 9092 *vs* 1298 [15·5%] of 8377, adjusted risk difference –1·4%, BCrI –2·3% to –0·4%; p(sup)>0·999; NNT 71·4), and there was a trend in the same direction at 6 months (818 [8·9%] of 9222 *vs* 777 [9·2%] of 8468, adjusted risk difference –0·5%, BCrI –1·5% to 0·4%; p(sup) 0·86; NNT 200; table 2; appendix p 189). There was a trend favouring usual care at 6 months for any contact with a social worker or respiratory outpatient unit but the numbers of participants having contact with each service was small at 6 months (<1% for a social worker and around 1% for a respiratory outpatient unit; appendix p 189).

Fewer participants in the molnupiravir plus usual care group reported having any time off work or study at 3 months (2017 [17·9%] of 11 274 *vs* 2385 [22·4%] of 10 628, adjusted risk difference –5·3%, BCrI –6·2% to –4·4%; p(sup)>0·999; NNT 18·9) and at 6 months (460 [4·4%] of 10 562 *vs* 527 [5·4%] of 9846, –1·1%, –2·0% to –0·2%; p(sup)>0·99; 90·9; table 2).

There was no difference in COVID-19 related hospitalisations (11 [0·1%] of 10 801 *vs* 11 [0·1%] of 10 173 at 3 months and 11 [0·1%] of 10 001 *vs* 11 [0·1%] of 9254 at 6 months) or all-cause hospitalisations at 3 months (654 [5·8%] of 11 274 *vs* 626 [5·9%] of 10 628, adjusted risk difference –0·2%, BCrI –0·8% to 0·5%; p(sup)=0·72; NNT 500) and 6 months (823 [7·8%] of 10 562 *vs* 802 [8·1%] of 9846, –0·4%, –1·1% to 0·3%; p(sup) 0·89; 250; table 2).

Fewer participants randomly assigned to the molnupiravir plus usual care group reported new cases of COVID-19 in their household from the end of their 28-day follow-up at 3 months (1114 [13·8%] of 8074 *vs* 1193 [15·7%] of 7602, adjusted risk difference –1·9%, BCrI –3·0% to –0·8%; p(sup)>0·999; NNT 52·6) but there was low probability of superiority on any new cases in the household between 3 months and 6 months (1066 [11·6%] of 9162 *vs* 893 [10·5%] of 8533, 1·2% (0·2% to 2·2%); p(sup)=0·006; 83·3). Proportions of the household with a new infection (defined as number of new infections divided by household size) was slightly lower at 3 months (mean [SD] 0·1 [0·3] *vs* 0·1 [0·3], adjusted mean difference –0·02, BCrI (–0·02 to –0·01); p(sup)>0·99) and at 6 months (0·1 [0·3] *vs* 0·1 [0·2], 0·01, <0·01 to 0·02; p(sup) 0·011; table 2).

Use of medication was lower at 3 months (1423 [12·6%] of 11 274 *vs* 1626 [15·3%] of 10 628, adjusted risk difference –2·8%, BCrI –3·6% to –1·9%; p(sup)>0·999; NNT 35·7) in the treated group but not at 6 months (481 [7·9%] of 6099 *vs* 432 [8·0%] of 5418, –0·3%, –1·4% to 0·9%; p(sup)=0·61; NNT 333·2). There was a difference in EQ-5D-5L visual analogue scale score in favour of molnupiravir at 3 months (mean [SD] 81·5 (17·5) *vs* mean (SD) 80·5 (17·8), adjusted mean difference 1·08, BCrI 0·65 to 1·53; p(sup)>0·999) and at 6 months (table 2).

The multiple imputation model was based on chained equations with a logit link for binary variables and identity link function for continuous variables. The imputation model for each imputed outcome included the main outcomes (ie, severe symptoms, health care and social service use, time off work and study, cases in the household, all-cause hospitalisation, any use of medication, participant rating of wellness, and EQ-5D-5L visual analogue scale score) at 3 months and 6 months, and included all covariates present in

	Molnupiravir (n=11778)	Usual care (n=11230)	Median estimate, 95% credible interval	Risk difference (95% credible interval)	Probability superiority
Participant rating of wellness*					
1–3 months	8·3 (1·6; n=11274)	8·2 (1·6; n=10 628)	0·15 (0·11 to 0·19)†	..	>0·99
3–6 months	8·3 (1·6; n=10562)	8·2 (1·6; n=9846)	0·12 (0·07 to 0·16)†	..	>0·99
Any severe symptom					
1–3 months	1907/11 271 (16·9%)	1948/10 619 (18·3%)	0·83 (0·73 to 0·93)‡	–1·6% (–2·6% to –0·6%)	0·99
3–6 months	1746/10 554 (16·5%)	1796/9840 (18·3%)	0·80 (0·70 to 0·90)‡	–1·9% (–2·9% to –0·9%)	>0·99
Any persistent symptom					
1–3 months	910/10 190 (8·9%)	1027/9332 (11·0%)	0·78 (0·71 to 0·85)§	–2·1% (–2·9% to –1·5%)	>0·99
3–6 months	817/9592 (8·5%)	946/8634 (11·0%)	0·74 (0·67 to 0·82)§	–2·5% (–3·3% to –1·6%)	>0·99
Any health or social care service					
1–3 months	1282/9092 (14·1%)	1298/8377 (15·5%)	0·85 (0·76 to 0·96)‡	–1·4% (–2·3% to –0·4%)	>0·99
3–6 months	818/9222 (8·9%)	777/8468 (9·2%)	0·92 (0·80 to 1·07)‡	–0·5%, (–1·5% to 0·4%)	0·86
Any time off work					
1–3 months	2017/11 274 (17·9%)	2385/10 628 (22·4%)	0·64 (0·58 to 0·71)‡	–5·3% (–6·2% to –4·4%)	>0·99
3–6 months	460/10 562 (4·4%)	527/9846 (5·4%)	0·75 (0·64 to 0·88)‡	–1·1% (–2·0% to –0·2%)	>0·99
Number of days off work					
1–3 months	2·6 (10·4; n=11 122)	3·2 (11·2; n=10435)	–0·58 (–0·88 to –0·29)†	..	>0·99
3–6 months	1·2 (11·1; n=10 519)	1·3 (11·1; n=9803)	–0·16 (–0·46 to 0·14)†	..	0·85
COVID-19 related hospitalisation					
1–3 months	11/10 801 (0·1%)	11/10 173 (0·1%)	..¶	..	..
3–6 months	11/10 001 (0·1%)	11/9254 (0·1%)	..¶	..	..
All-cause hospitalisation					
1–3 months	654/11 274 (5·8%)	626/10 628 (5·9%)	0·96 (0·83 to 1·11)‡	–0·2% (–0·8% to 0·5%)	0·72
3–6 months	823/10 562 (7·8%)	802/9846 (8·1%)	0·92 (0·81 to 1·05)‡	–0·4%, (–1·1% to0·3%)	0·89
Over the counter medication					
1–3 months	1317/11 274 (11·7%)	1517/10 628 (14·3%)	0·72 (0·64 to 0·80)‡	–2·7% (–3·5% to –1·8%)	>0·99
3–6 months	456/6099 (7·5%)	397/5418 (7·3%)	1·02 (0·85 to 1·22)‡	–0·0% (–1·1% to1·1%)	0·43
Prescribed medication					
1–3 months	193/11 274 (1·7%)	233/10 628 (2·2%)	0·68 (0·52 to 0·90)‡	–0·5% (–0·8% to –0·2%)	>0·99
3–6 months	50/6099 (0·8%)	66/5418 (1·2%)	0·57 (0·35 to 0·91)‡	–0·4% (–0·1% to0·0%)	>0·99
All medication					
1–3 months	1423/11 274 (12·6%)	1626/10 628 (15·3%)	0·72 (0·64 to 0·80)‡	–2·8% (–3·6% to –1·9%)	>0·99
3–6 months	481/6099 (7·9%)	432/5418 (8·0%)	0·97 (0·81 to 1·17)‡	–0·3% (–1·4% to0·9%)	0·61
Any new infection within the household					
1–3 months	1114/8074 (13·8%)	1193/7602 (15·7%)	0·85 (0·77 to 0·93)‡	–1·9% (–3·0% to –0·8%)	>0·99
3–6 months	1066/9162 (11·6%)	893/8533 (10·5%)	1·14 (1·03 to 1·26)‡	1·2% (0·2% to 2·2%)	0·006
Proportion of household with new infection||					
1–3 months	0·1 (0·3; n=8074)	0·1 (0·3; n=7602)	–0·02 (–0·02 to –0·01)†	..	>0·99
3–6 months	0·1 (0·3; n=9162)	0·1 (0·2; n=8533)	0·01 (<0·01 to 0·02)†	..	0·011
EQ–5D–5L VAS score					
1–3 months	81·5 (17·5; n=11257)	80·5 (17·8; n=10 613)	1·08 (0·65 to 1·53)†	..	>0·99
3–6 months	81·2 (16·6; n=10 558)	80·3 (17·3; n=9835)	1·09 (0·63 to 1·55)†	..	>0·99

Data are n (%), mean (SD; n=X), or n/N (%). VAS= Visual Analog Scale. *0 was the worst score and 10 was the best score. †Bayesian linear mixed-effects model adjusted for vaccination status, comorbidity, and age. ‡Bayesian logistic mixed-effects model adjusted for vaccination status, comorbidity, and age. §Models fitted as separate timepoints due to convergence issues: Bayesian logistic model adjusted for vaccination status, comorbidity, and age. ¶Presented descriptively only due to low event rate. ||Proportion of household infections calculated as number of new infections in the household divided by number of people in the household.

Table 2: **Outcomes**

the analysis model (ie, vaccination status, age at baseline, and presence of comorbidities). Imputation was carried out separately for each treatment group to allow for differential effects. A single set of imputations was carried out for all outcomes simultaneously, resulting in a total of 100 imputed datasets. In addition to all variables included in the analysis model, additional baseline characteristics, adherence to medication treatment regime, and recovery at day 28 were tested for any association with missingness status. The following variables

	Effect (95% CI)*	p value
Any severe symptom		
3 months	0·73 (0·65–0·83)	<0·0001
6 months	0·71 (0·62–0·81)	<0·0001
Any health or social care use		
3 months	0·78 (0·69–0·88)	<0·0001
6 months	0·89 (0·77–1·03)	0·11
Any time off work and study		
3 months	0·61 (0·55–0·68)	<0·0001
6 months	0·67 (0·56–0·78)	<0·0001
Any cases in the household		
3 months	0·85 (0·77–0·93)	0·00047
6 months	1·12 (1·01–1·24)	0·0294
Any hospitalisation use		
3 months	0·92 (0·79–1·07)	0·27
6 months	0·91 (0·80–1·05)	0·20
Any medication use		
3 months	0·67 (0·59–0·75)	<0·0001
6 months	0·89 (0·71–1·12)	0·31
Participant rating of wellness		
3 months	0·19 (0·15–0·24)	<0·0001
6 months	0·16 (0·11–0·20)	<0·0001
EQ-5D-5L VAS score		
3 months	1·43 (0·97–1·89)	<0·0001
6 months	1·51 (1·05–1·97)	<0·0001

VAS=Visual Analog Scale. *Linear mixed-effects model adjusted for age, vaccination status and comorbidity with 100 imputations. The following variables found to be predictive of missingness were included in the imputation model: ethnicity, other comorbidity, using inhaled corticosteroid at baseline, smoking status, vaccine doses at baseline, baseline symptoms (generally unwell, fever, cough, nausea and vomiting, diarrhoea, loss of smell and taste, headache, dizziness, abdominal pain, shortness of breath, fatigue, and muscle ache) and recovery by day 28, baseline rating of wellness, and compliance with the intervention for those randomly assigned to molnupiravir.

Table 3: **Sensitivity analysis—multiple imputation with predictors of missingness**

found to be predictive of missingness were included in the imputation model: ethnicity, other comorbidity, using inhaled corticosteroid at baseline, smoking status, vaccine doses at baseline, baseline symptoms (generally unwell, fever, cough, nausea or vomiting, diarrhoea, loss of smell or taste, headache, dizziness, abdominal pain, shortness of breath, fatigue, and muscle ache), recovery by day 28, baseline rating of wellness, and compliance with the intervention for participants randomly assigned to molnupiravir plus usual care. Sensitivity analysis results did not substantially differ from the main analysis (table 3).

Discussion

To our knowledge, this is the first large scale, multicentre, primary care, open-label, multi-arm, prospective randomised controlled trial to report on the longer term effect of early treatment with molnupiravir for SARS-CoV-2 infection in the community.

Participant rating of wellness, any symptom rated moderately bad or worse, any persistent symptom, and health or social care use and time off work were all statistically superior in the molnupiravir plus usual care group at 3 months and 6 months but with small absolute effects. Cough, shortness of breath, fatigue, muscle aches, and being generally unwell were less prevalent in the molnupiravir plus usual care group at 3 months and 6 months. Very few participants were hospitalised due to COVID-19 during the longer term and there was no difference in all-cause hospitalisations.

Use of over-the-counter medication was lower in the molnupiravir plus usual care group compared with usual care at 3 months and use of any medication was also lower at 3 months in the molnupiravir plus usual care group. Numbers needed to treat ranged from 18 to 500.

New cases reported by participants within the household were lower in the molnupiravir plus usual care group compared to usual care alone at 3 months but not at 6 months. The odds ratio at 6 months favoured the usual care group, which could be a chance finding but there could also be biologically plausible mechanisms (ie, for the blunted infection associated boost to anti-SARS-CoV-2 spike).[7]

Health-related quality of life as measured by the EQ-5D-5L visual analogue scale score was higher at 3 months and 6 months among those treated with molnupiravir compared with those receiving usual care alone, but with small absolute effects.

Participants were generally treated for their acute illness within 5 days of symptom onset; adherence was more than 90% (defined as taking the medication on at least 4 days) and nearly 90% of the 25 783 participants who were randomised provided follow-up information for at least one long-term timepoint. Our prospective randomised controlled trial design overcomes risk of bias inherent in retrospective analysis of routine data. Wellbeing and quality of life are subjective phenomena and we were able to ascertain these directly from trial participants. However, participants were not asked whether their symptoms had persisted since their original infection and participants could have recovered after day 28 and re-developed symptoms during follow-up.

This study was a secondary long-term analysis, and although we did not correct for multiplicity, the number of statistically superior outcomes make chance a very unlikely explanation of the results. The trial design was pragmatic and open-label; therefore, participants were not masked and recovery and wellbeing outcomes were ascertained by self-reporting. In contrast to efficacy trials, in trials of effectiveness that ask what would happen if an intervention was deployed in the course of routine clinical care, which does not include the use of placebos, an open-label trial is most suited to answering a pragmatic question.[14–16] In such studies, the control condition should reflect best care without the drug in question, reflecting

what would happen under usual circumstances.[16] The trial therefore assesses whether there is added value to adding a new drug over and above usual care. An open-label design does not allow one to estimate the contribution of either placebo or nocebo effects to any observed differences between the randomised groups.[17,18] Knowing whether one is taking a treatment with proven efficacy or not can affect help seeking behaviour. Subjective measures such as symptom scores and participant rating of wellbeing are at potential risk from reporting bias due to the open-label trial design. However, although for many conditions, clearly there can be substantial placebo effects for acute respiratory infections, and even where beliefs in medication are high, the estimates from open-label trials with self-report outcomes (eg, sore throat,[19] acute bronchitis,[20] and otitis[21]) suggest either no placebo effects or minimal effects when compared with placebo controlled trials in Cochrane reviews.[22–25] We have found similar evidence for COVID-19 therapeutics: the PRINCIPLE trial, using a similar open-label design, found no clinically meaningful benefit from treatment for COVID-19 with azithromycin, doxycycline, and ivermectin,[26–28] a trend for harm from treatment with colchicine,[29] and of benefit form treatment with inhaled budesionide.[30] Effect sizes in open trials are generally similar to those of placebo controlled trials.[31] Small, absolute differences could be statistically significant but not necessary clinically meaningful.[32]

Although we cannot discount bias in favour of the usual care group, it is more plausible that any bias would be in favour of the intervention, which could account for some of the effects favouring molnupiravir. Health-care service use was obtained from routine clinical records and was not at the same risk of reporting bias.

The amount of missing data differed between both groups, with participants in the usual care group more likely not to complete follow-up surveys. Multiple imputation was used to compensate for this finding; however, this approach assumes data were missing at random, which might not have been the case. The loss to follow-up rate was higher among participants randomly assigned to the usual care group alone. This difference in attrition rate could have resulted from the open-label design, with participants randomly assigned to the usual care group alone being less committed to providing follow-up data. If we assume participants lost to follow-up had substantially poorer outcomes than found in the observed data, effect sizes would favour molnupiravir more strongly, whereas if the outcomes in those lost to follow-up were better, the effects were attenuated or reversed in favour of control.

Evidence from this study applies to a vaccinated community-based population at higher risk of more severe outcome from COVID-19 compared with the general population while the omicron variant circulated. Individuals deemed extremely vulnerable and at highest risk while participants could have been included in the PANORAMIC platform trial had direct access to antiviral treatment from the National Health Service.

The MOVe-OUT trial[8] found significant effects on adverse outcomes for unvaccinated patients in the acute phase of COVID-19, but did not report longer term effects. We have not been able to identify evidence from randomsied controlled trials on treating acute COVID-19 with molnupiravir during the longer term, but observational studies have been done. In a US Department of Veterans Affairs observational cohort study, 229 286 participants who were mostly men tested positive for SARS-CoV-2 between Jan 5, 2022, and Jan 15, 2023, with a risk factor for progression to severe COVID-19.[10] Molnupiravir within 5 days of COVID-19 onset was prescribed for 11 472 participants and was associated with a relative risk of post-acute consequences of COVID-19 of 0·86 (95% CI 0·83–0·89, absolute risk reduction 2·79% [95% CI 2·31–3·60%]).

A US observational study of 2 975 690 Medicare enrolees aged 65 years and older between January and September, 2022, of which 2·6% had received molnupiravir, used ICD diagnoses in routine medical records to ascertain evidence of post COVID-19 conditions.[9] The prevalence was 13·7% for molnupiravir and 14·5% for individuals who had received neither molnupiravir nor nirmatrelvir and ritonavir, with an absolute risk reduction of 0·8% (hazard ratio [HR] 0·92, 95% CI 0·90–0·94).

Three retrospective target trial emulation studies used routinely collected US Veterans Health Administration data to compare matched cohorts of nirmatrelvir and ritonavir versus no treatment, molnupiravir versus no treatment, and nirmatrelvir and ritonavir versus molnupiravir in non-hospitalised veterans who were at risk for severe COVID-19 and tested positive for SARS-CoV-2 from January to July, 2022, with follow-up for 180 days.[8] Molnupiravir-treated participants (n=3504) had lower 30-day and 31-day to 180-day risks for death (3·14 *vs* 13·56 per 1000 participants at 30 days, risk difference –10·42 [95% CI –13·49 to –7·35] per 1000 participants, relative risk 0·23 [95% CI 0·13 to 0·43]; 11·05 *vs* 16·39 per 1000 participants at 31–180 days; HR 31–180 days, 0·67 [95% CI 0·48–0·95]) but not hospitalisation. A difference in 30-day or 31-day to 180-day risk for hospitalisation or death was not observed between matched nirmatrelvir and ritonavir or molnupiravir-treated participants.[8]

The studies mentioned used observational and retrospective data so the comparison groups may not have been similar for unknown potential confounders and not all known confounders will have been recorded and taken into account. Our randomised trial showed no effect of molnupiravir on hospitalisation and death in contrast to the dramatic effects found by the trial emulation studies. Furthermore, these studies were not able to report on health-related quality of life, employment, and wellbeing. The small effect sizes from these studies reflect formal diagnoses that can potentially be related to

COVID-19 consequences, whereas this study captures participant reporting on wellbeing, work, and study. Health care use, however, was ascertained in our study from routine clinical records in a similar way to the observational cohorts. Results for household infections were conflicting with lower incidence in the molnupiravir plus usual care group compared with usual care alone at 3 months but higher incidence at 6 months.

The few unvaccinated participants in the PANORAMIC study do not allow for a formal subgroup analysis, so we did not test whether there was a differential effect for unvaccinated participants in the longer term.

Treatment with molnupiravir needs to be balanced against the risk of viral mutagenesis and blunting of the antibody boost from infection in those receiving molnupiravir, although the clinical implication of these findings is unclear. Longer duration of treatment with molnupiravir might have shown a greater benefit, as was suggested by the separate virology study that found culturable virus isolated from some molnupiravir-treated patients.[7]

In a vaccinated population, people treated with molnupiravir for acute COVID-19 felt better, experienced significantly fewer and less severe COVID-19 associated symptoms, accessed health care less often, and took less time off work at 6 months. However, the absolute differences were small with high estimated numbers needed to treat.

Contributors

CCB and JSN-V-T conceived the study. CCB was the chief investigator to PL and FDRH who were the co-chief investigators, and all three authors made the decision to publish the study. BRS, L-MY, JH, MD, CCB, FDRH, PL, GH, OG-T, JD, NMR, DBR, SP, DML, JFS, and KH provided input into the trial design. PE, LC, MC, CB, JCD, IR-W, AC-S, HA, and DB were responsible for the implementation of the study and acquisition of data. CCB and VH drafted the manuscript. L-MY, BRS, JH, and VH contributed to the statistical analysis. SK, DBR, GH, NMR, and MD provided input to the safety evaluations and drug interactions. MGP was the national pharmacy and inclusion and diversity lead for the trial. SP and MEP ran the economic assessments. SP provided oversight of the economic evaluation. MP led the data management and MP and VH accessed and verified the data. CCB, PL, OG-T, NMR, SP, DBR, KH, MGP, BRS, JCD, DML, SK, NF, NPBT, PE, JFS, JB, MD, MEP, GH, BDJ, NDH, LC, MA, OvH, AU, L-MY, and FDRH are members of the Trial Management Group. VH and CCB produced the first draft of the manuscript. All authors critically revised the manuscript. All authors have contributed to the conduct of the trial. VH had full access to all the data in the study (other members of the trial team did not have access to the data because recruitment was ongoing into other groups of the trial) and the corresponding author (CCB) had final responsibility for the decision to submit for publication.

Declaration of interests

JSN-V-T was seconded to the Department of Health and Social Care, England from Oct 1, 2017, to March 31, 2022. On June 15, 2023, JSN-V-T completed one 3-h paid consultancy assignment for Merck Sharp & Dohme on a subject unrelated to COVID-19, and has given two paid lectures for Gilead who have manufactured COVID-19 treatments in 2022–23, and one paid lecture for AstraZeneca in 2022, who manufacture COVID-19 vaccines. JSN-V-T has consulted occasionally for Moderna (May 1, 2023 onwards) who manufacture COVID-19 vaccines. DML has received personal fees from Gilead for an educational video and from Merck for a roundtable discussion, speaker fees from Biotest, Takeda, and Astra Zeneca, and support to attend a conference from Octapharma. DML holds research grants from GlaxoSmithKline and Bristol Myers Squibb, has received consultancy fees from GlaxoSmithKline paid to his institution, all outside the current work, and reports giving lectures for Biotest, Takeda, and AstraZeneca. JFS has participated in a Data and Safety Monitoring Committee for the sotrovimab paediatric programme for GlaxoSmithKline (fee paid to the institution). JB reports being the Principle Investigator on The Medicines and Healthcare products Regulatory Agency commissioned study with GlaxoSmithKline to look at the evolution of variants in sotrovimab treated patients, and consulting fees from GlaxoSmithKline, hVIVO, Moderna, and Symbios (donated to UCL). SK has been a speaker for Pfizer and ViiV Healthcare. KH reports a grant to Cardiff University (via University of Oxford), and was on the National Institute for Health and Care Research (NIHR) Health Technology Assessment General Committee and Health Technology Assessment Funding Strategy Group until November, 2022, and is currently Deputy Chair of the Research Professors panel. BRS reports consulting fees were paid to his former employer (Berry Consultants) for tiral design and implementation. NPBT reports being on a single advisory board in July, 2021, with Merck & Co. OvH reports consulting fees from MindGap. AU reports honoria from Merck & Co, Gilead Sciences, Pfizer, and Astra Zeneca in relation to this disease area and manuscript. All other authors declare no competing interests.

Data sharing

Qualifying researchers who wish to access our data should submit a proposal to primarycarectu@phc.ox.ac.uk 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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