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

Christopher C Butler, FMedSci[1†]; F.D. Richard Hobbs, FMedSci[1†]; Oghenekome A Gbinigie, DPhil[1]; Najib M Rahman, DPhil[2,3,4]; Gail Hayward, DPhil[1]; Duncan B Richards, DM[5]; Jienchi Dorward, MBChB[1,6]; David M Lowe, PhD[7]; Joseph F Standing, PhD[8,9]; Judith Breuer, MD[8]; Saye Khoo, FRCP[10]; Stavros Petrou, PhD[1]; Kerenza Hood, PhD[11]; Jonathan S Nguyen-Van-Tam, FMedSci[12]; Mahendra G Patel, PhD[1]; Benjamin R Saville, PhD[13,14]; Joe Marion, PhD[13]; Emma Ogburn, PhD[1]; Julie Allen, BA(Hons)[1]; Heather Rutter, BSc[1]; Nick Francis, PhD[15]; Nicholas P B Thomas, FRCGP[16,17,18]; Philip Evans, FRCGP[19,20]; Melissa Dobson, BSc(Hons) [2]; Tracie-Ann Madden, PhD[11]; Jane Holmes, PhD[1]; Victoria Harris, PhD[1]; May Ee Png, PhD[1]; Mark Lown, PhD[15]; Oliver van Hecke, DPhil[1]; Michelle A Detry, PhD[13]; Christina T Saunders, PhD[13]; Mark Fitzgerald, PhD[13]; Nicholas S Berry, PhD[13]; Lazaro Mwandigha, PhD[1]; Ushma Galal, MSc[1]; Bhautesh Jani, PhD[21]; Nigel D Hart, MD[22]; Daniel Butler, MBChB(Hons)[22]; Jem Chalk, PhD[1]; Layla Lavallee, MPH[1]; Elizabeth Hadley, MSc[1]; Lucy Cureton, BSc[1]; Magdalena Benysek, MSc[1]; Monique Andersson, MD[23]; Maria Coates;[1] Sarah Barrett[1]; Clare Bateman, BA(Hons)[1]; Jennifer C Davies, PhD[1]; Ivy Raymundo-Wood, BSc[1]; Andrew Ustianowski, PhD[24]; Andrew Carson-Stevens, PhD[11]; Ly-Mee Yu, DPhil[1]*; Paul Little, FMedSci.[15]*

For the PANORAMIC Trial Collaborative Group¶

Author affiliations
1. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK
2. Oxford Respiratory Trials Unit, Nuffield Department of Medicine, University of Oxford, UK
3. Oxford NIHR Biomedical Research Centre, UK
4. Chinese Academy of Medicine Oxford Institute, University of Oxford, UK
5. Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK
6. Centre for the AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu–Natal, Durban, South Africa
7. Institute of Immunity and Transplantation, University College London, London, UK
8. Infection Inflammation and Immunology, UCL Great Ormond Street Institute of Child Health, London, UK
9. Department of Pharmacy, Great Ormond Street Hospital for Children, London, UK
10. Department of Pharmacology, University of Liverpool, Liverpool, UK
11. Centre for Trials Research, Cardiff University, UK
12. Lifespan and Population Health Unit, University of Nottingham School of Medicine, Nottingham, UK
13. Berry Consultants, Austin, Texas, USA
14. Department of Biostatistics, Vanderbilt University School of Medicine, Tennessee, USA
15. Primary Care Research Centre, University of Southampton, Southampton, UK
16. Windrush Medical Practice, Witney, UK
17. National Institute for Health and Care Research, Thames Valley and South Midlands Clinical Research Network, UK
18. Royal College of General Practitioners, London, UK
19. Faculty of Health and Life Sciences, University of Exeter, UK
20. National Institute for Health and Care Research Clinical Research Network, UK
21. General Practice and Primary Care, School of Health and Wellbeing, MVLS, University of Glasgow, UK
22. School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland, UK

23. Department of Microbiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
24. Regional Infectious Diseases Unit, North Manchester General Hospital, Manchester, UK

†Profs Butler and Hobbs contributed equally to this article

*Profs Little and Yu contributed equally to this article

Corresponding author: Christopher C Butler

christopher.butler@phc.ox.ac.uk

Abstract

Background The safety, effectiveness and cost-effectiveness of molnupiravir, an oral antiviral medication for SARS-CoV-2, in patients in the community who are multiply-vaccinated and at increased risk of morbidity and mortality from COVID-19, has not been established. We aimed to determine whether molnupiravir added to usual care reduced hospital admissions/deaths among people at higher risk from COVID-19, and here report our preliminary analyses.

Methods Participants in this UK multicentre, open-label, adaptive, multi-arm, platform, randomised controlled trial were aged ≥50, or ≥18 years with comorbidities, and unwell ≤5 days with confirmed COVID-19 in the community, and were randomised to usual care or usual care plus molnupiravir (800mg twice daily for 5 days). The primary outcome measure was all-cause hospitalisation/death within 28 days, analysed using Bayesian models. The main secondary outcome measure was time to first self-reported recovery. A sub-set of participants in each group were assessed for the virology primary outcome measure of day seven SARS-CoV-2 viral load. Trial registration: ISRCTN30448031

Findings Between December 8, 2021 and April 27, 2022, 25783 participants were randomised to molnupiravir plus usual care (n=12821) or usual care alone (n=12962). Mean (range) age of participants was 56·6 years (18 to 99), 58·6% were female, and 99% had at least one dose of a SARS-CoV-2 vaccine. The median duration of symptoms prior to randomisation was two days (IQR 1 – 3), the median number of days from symptom onset to starting to take the medication was three days (IQR 3 – 4), 87% (11109/11997) received their medication within five days of symptom onset, and 95·4% (n=11857) of participants

randomised to molnupiravir reported taking molnupiravir for five days. Primary outcome measure data were available in 25000 (97%) participants and included in this analysis. 103/12516 (0·8%) hospitalisations/deaths occurred in the molnupiravir group versus 96/12484 (0·8%) in usual care alone with a posterior probability of superiority of 0·34 (adjusted odds ratio 1·061 (95% Bayesian credible interval [BCI]) 0·80 to 1·40). Estimates were similar for all subgroups. The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4·2 (95% BCI: 3·8 – 4·6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0·999 (estimated median TTR 10·3 [10·2 – 10·6] days vs 14·5 [14·2 – 14·9] days respectively; hazard ratio [95% BCI], 1·36 [1·3–1·4] days), which met the pre-specified superiority threshold. On day 7, SARS-CoV-2 virus was below detection levels in 7/34 (21%) of the molnupiravir group, versus 1/39 (3%) in the usual care group (p=0.039), and mean viral load was lower in the molnupiravir group compared with those receiving usual care [(SD) of $\log_{10}$(viral load) 3·82 (1·40) in the molnupiravir group and 4.93 (1·38) in the usual care group, (P<0·001)]. 59 (0·4%) participants experienced serious adverse events in the molnupiravir group and 52 (0·4%) in usual care.

Interpretation In this preliminary analysis, we found that molnupiravir did not reduce already low hospitalisations/deaths among higher risk, vaccinated adults with COVID-19 in the community, but resulted in faster time to recovery, and reduced viral detection and load.

Funding: This project is funded by the NIHR (NIHR135366). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Research in context (box)

Evidence before this study

A search of PubMed on 5 September 2022 with no date or language restrictions using the following search terms (randomised OR trial) AND (molnupiravir) AND (COVID* OR SARS-CoV-2 OR SARS-CoV) AND (systematic review) 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. The reviews suggest that molnupiravir reduces hospital admissions in patients with mild-moderate COVID-19, with the World Health Organisation (WHO) living guideline recommending use of molnupiravir in outpatients with mild-moderate COVID-19 at the highest risk of hospital admission. The largest randomised clinical trial identified by the evidence syntheses was the randomised, placebo-controlled, phase 3 MOVe-OUT trial. In this trial of 1433 unvaccinated COVID-19 outpatients, there was a relative reduction in the primary outcome measure of hospitalisations and deaths of approximately 30% up to day 29 post randomisation in people receiving molnupiravir, versus placebo. Of note, this reduction was closer to 50% with molnupiravir compared with placebo when the MOVe-OUT trial published their interim results, after recruiting 762 participants. The reason for this difference is unclear. A number of trials of molnupiravir have been conducted in India; to date, the full peer-reviewed findings have not been made publicly available. The ACE2 trial among 180 participants (both vaccinated and unvaccinated) demonstrated faster time to a negative PCR test with molnupiravir compared with placebo (8 days versus 11 days).

Added value of this study

In this preliminary analysis, we found that molnupiravir did not reduce hospitalisations/deaths among a multiply-vaccinated adult population with COVID-19 in the

community at higher risk of an adverse outcome, with similar estimates for all subgroups, during a time when the proportion of people with COVID-19 requiring hospital admission was low. However, molnupiravir resulted in earlier recovery across a wide range of measures including: time to recovery; sustained recovery overall as well as for key individual symptoms; reduced health care seeking in primary care in some services; and, reduced viral detection and load in a sub-group on Day 7. Molnupiravir was safe, but adverse effects were cited as a reason for withdrawing from the study drug in 1·1% (142/12821) randomised to receive it. Trials of molnupiravir have, thus far, been conducted in largely unvaccinated participants and prior to the emergence of the omicron SARS-CoV-2 variant. PANORAMIC provides an estimate of the effectiveness of molnupiravir in a multiply-vaccinated population whilst the omicron SARS-CoV-2 strain is dominant. The large sample size of PANORAMIC (>25,000 participants) allows for more precision around subgroup analyses estimates, to help determine the populations that may, or may not, derive benefit from molnupiravir. PANORAMIC additionally incorporates virological and cost-effectiveness analyses; such analyses have not been published (in detail) in other trials of molnupiravir.

Implications of all the available evidence

This preliminary analysis involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admission, but that molnupiravir resulted in faster time to recovery, earlier sustained recovery, reduced contact with GP services, and reduced viral detection and viral load.

INTRODUCTION

Early treatment of COVID-19 with directly acting antiviral drugs in the community may: prevent deterioration; speed recovery; reduce healthcare utilisation in the community; reduce viral shedding; and, reduce the need for hospital admission.

Molnupiravir is an oral antiviral that was initially developed for treatment of influenza,[1] but has subsequently been evaluated for treatment of COVID-19.[2] It is a prodrug; the ribonucleoside analogue β-d-N4 -hydroxycytidine (NHC) is metabolised to NHC-triphosphate in cells, which competes with naturally occurring nucleotides, especially cytidine triphosphate.[3] Once incorporated into viral RNA, the errant nucleotide induces 'viral error catastrophe,' impeding viral fitness and inhibiting replication.[3] Molnupiravir has demonstrated anti-SARS-CoV-2 activity in animal models,[4-6] and has been found to be safe and well tolerated at doses of 800mg twice daily in phase 1 trials [7,8] and phase 2/3 outpatient trials.[2,9,10]

The largest trial of molnupiravir to date has been the MOVe-OUT trial, a phase 3 industry-funded trial among unvaccinated, non-hospitalized patients at high risk of adverse outcomes.[10] Interim results after recruiting 762 participants showed a nearly 50% decrease in hospitalisations and deaths with molnupiravir compared to placebo, resulting in molnupiravir authorisation for use by several regulatory bodies.[11,12] However, the final results demonstrated a smaller effect (30% reduction in hospitalisations and deaths).[10] The reason for this difference has been debated.[13] Several Phase 3 trials have been conducted in India among non-hospitalized patients with reportedly mixed findings,[14] but to date the full peer-reviewed results have not been published. The AGILE CST-2 trial conducted in 180 vaccinated and

unvaccinated participants showed that molnupiravir resulted in a faster time to a negative PCR test compared with placebo (8 days versus 11 days).[15]

The effectiveness of molnupiravir in patients in the community who are multiply-vaccinated and at increased risk of morbidity and mortality from COVID-19 has not yet been established. We therefore aimed to determine the effectiveness of molnupiravir in reducing all-cause, non-elective hospital admissions and/or death within 28 days of randomisation in test-positive COVID-19 outpatients at higher risk of an adverse outcome in a UK population with high levels of SARS-CoV-2 vaccination. Ahead of a possible increase in COVID-19 incidence over the coming winter months, important decisions need to be taken urgently about possible deployment of antiviral drugs, and awareness of the scope of forthcoming analyses and inviting early scrutiny and discussion may be helpful. We therefore report a preliminary analysis here; outstanding data linkage and site queries are ongoing pending data lock and final analysis.

METHODS

Study design and oversight

We assessed the effectiveness of molnupiravir in the UK national, multi-centre, primary care, open-label, multi-arm, prospective, Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community (PANORAMIC), which opened on December 8, 2021, and is ongoing. The protocol is available on the trial website (https://www.panoramictrial.org). A "platform trial" allows 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.[16] Interventions evaluated in PANORAMIC include molnupiravir and nirmatrelvir/ritonavir.

The UK Medicines and Healthcare products Regulatory Agency and the South Central-Berkshire Research Ethics Committee approved the trial protocol. Online informed consent is obtained from all participants. The authors vouch for the accuracy and completeness of the data and for fidelity to the protocol. An independent Trial Steering Committee (TSC), and Data and Safety Monitoring Committee (DSMC) provide trial oversight.

Participants

People in the community were eligible if they were aged ≥50 years, or ≥18 years with comorbidities (supplementary appendix 1), had ongoing symptoms from COVID-19 that had started within the previous five days, and a positive polymerase chain reaction (PCR) or rapid antigen SARS-CoV-2 test within the past seven days. People were ineligible to be randomised to molnupiravir if they were pregnant or breastfeeding, were of childbearing potential and unwilling to use effective contraception, were already taking molnupiravir, or were allergic to molnupiravir. Patients at the highest risk of adverse outcomes with COVID in the UK have been advised to seek medical advice from special regional COVID specialist clinics to provide access to COVID antivirals or monoclonal antibodies, and were not the target population for PANORAMIC, although they were eligible. Potentially eligible people were screened, recruited, and enrolled in participating general practices, or online and telephonically with central trial teams across the UK.

Randomisation and masking

Eligible, consenting participants were randomised by a suitably qualified and trained medical or research professional in equal allocation between molnupiravir and usual care using a secure, web-based randomisation system (Spinnaker). Randomisation was stratified by age (</≥ 50 years) and vaccination status (yes/no). Participants and members of the trial team responsible for recruitment/follow-up/monitoring of participants were aware of group assignment. The trial investigators and recruiting clinicians were kept blind to emerging results, with only unblinded statisticians and the independent members of the DSMC granted access to unblinded results until the decision was made to close recruitment to molnupiravir.

Procedures

Participants received usual care plus molnupiravir 800mg twice daily for 5 days, or usual care alone. Participants randomised 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). Usual care participants were emailed/posted a trial information booklet. Usual care in the UK National Health Service for COVID-19 in the community is largely focused on managing symptoms with antipyretics.[17] However, patients at very highest risk (very impaired immunity or extremely clinically vulnerable) are eligible for monoclonal antibodies (sotrovimab), intravenous antivirals (remdesivir), or oral antivirals (molnupiravir or nirmatrelvir/ritonavir) through the NHS.[18] Prescriptions of monoclonal antibodies and antiviral agents other than a study drug in the course of usual care was permitted, and monoclonal antibody use was recorded in an online diary. Participants randomised to molnupiravir would not have received additional molnupiravir through the NHS; however, those randomised to usual care may have received molnupiravir through the NHS and this was recorded in the online diary.

Participants were followed up through an online, daily diary for 28 days after randomisation, supplemented with telephone calls to non-responders on days 7, 14 and 28. Participants were asked: to rate a variety of symptoms (e.g. fever, cough and breathlessness) on an ordinal scale (‘no problem,’ ‘mild problem,’ ‘moderate problem’ or ‘major problem’); whether they had been hospitalised or required contact with health and social services; how they were feeling on a scale of zero to ten (zero being the worst one can imagine, and ten being the best one can imagine); whether they felt fully recovered; whether they were taking over-the-counter medication; whether the number of people in the household with COVID-19 had changed; to confirm whether they had taken the antiviral agent (if applicable); and, at fortnightly intervals the EQ-5D-5L to assess their health-related quality of life. Participants could nominate a trial partner to help provide follow up data. We obtained consent to ascertain healthcare use outcome measure data from general practice and hospital records. Additional questions regarding longer term symptoms and healthcare use are asked at three and six months after randomisation; these results are not reported in this manuscript.

Virology sub-study

Between March 23, 2022 and April 27, 2022, enrolling participants were offered participation in an intensively and non-intensively sampled virology cohort. Those who took part were couriered European In-Vitro Diagnostic Devices Directive (CE-IVD) approved sampling kits and instructions for nasopharyngeal and dried blood spot self-sampling, with pre-paid postage and packaging, to post samples to the virology processing site. In the intensive sampling cohort, participants were asked to provide daily nasopharyngeal swabs for the first seven days, and on day fourteen (+/- 1 day). In the non-intensive sampling cohort, participants were asked to provide nasopharyngeal swabs on days one, five (+/- 1 day) and fourteen (+/- 1 day). Participants were asked to take the first sample on the day following randomization (usual

care group) or before the first dose of molnupiravir (molnupiravir group). All virology sampling participants were asked to take three finger-prick dried blood spot samples on days one, five (+/- 1 day) and fourteen (+/- 1 day).

Outcomes

The primary outcome measure was all-cause, non-elective hospital admission and/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 after hospital assessment. Spending time during the course of a day in a hospital accident and emergency (A&E) unit that did not extend overnight was classified as an A&E attendance. An overnight stay in A&E was counted as an admission. Hospitalisation for a pre-existing condition, including elective procedures planned prior to trial entry, which had not worsened, did not contribute to our primary outcome measure.

Secondary outcome measures included: time to self-reported recovery (TTR) defined as the first instance that a participant reported feeling fully recovered from the illness; time to early sustained recovery (recovered by day 14 and remained recovered until day 28); time to sustained recovery (date participant first reported recovery and subsequently remained well until 28 days); rating from 0-10 of how well participants felt; time to initial alleviation of symptoms (date symptoms first reported as minor or none); time to sustained alleviation of symptoms (date symptoms first reported as minor or none and subsequently remained minor or none until 28 days); time to initial reduction of severity of symptoms; contacts with health and social services; hospital assessment without admission; oxygen administration; new household COVID-19 infections; and, safety outcome measures.

Statistical analysis

The sample size calculation and statistical analysis are detailed in the Adaptive Design Report and the Master Statistical Analysis Plan. The sample size was initially calculated based on a 3% event rate in usual care and an intervention was expected to lower the hospitalization/death rate to 2% (i.e., 33% relative reduction); 5300 participants per group would be required with 5% level of significance and 90% power. However, the proportion of participants admitted to hospital was lower than anticipated so the sample size calculation was revised to 16578 per group (90% power) and 12534 per group (80% power), assuming event rates of 1% and 0·67% in the usual care and treatment groups, respectively.

The primary analysis population was defined as all eligible participants concurrently randomised to the intervention and usual care, according to the group they were allocated to regardless of deviation from the protocol.

The primary outcome measure was analysed using a Bayesian logistic regression model, with weakly-informative Cauchy priors, regressed on treatment group, comorbidity, and stratification covariates (age, vaccination status). The success thresholds at final and interim analysis were pre-specified in the Adaptive Design Report and were dependent on the number of interims performed, which was a function of the speed of enrolment. If no interim analyses are performed (in the case of very fast enrolment) the success threshold at the final analysis is 0.975.

The sample size for the virology sub-study was based on simulations from a viral dynamic model from early 2020,[19] which suggested that 30 patients per arm would detect a 2·5-fold increase in viral clearance (undetectable viral load at day seven, the primary outcome

measure for this sub-study) in patients who started therapy within five days of symptom onset (90% power; alpha 0·05). Clinical improvement may 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.[20] 300 patients would provide a 95% probability of seeing at least one example of a SARS-CoV-2 mutation occurring in at least 1% of participants.

Secondary time to event outcome measures were modelled using a Bayesian piecewise exponential model with weakly-informative normal priors and four time segments to estimate the hazard ratio for a treatment arm versus control, adjusting for age, vaccination status, and comorbidity status. For binary outcome measures with a low event rate, results were reported descriptively by treatment group and a Chi-square test or Fisher's exact test used. Early sustained recovery was analysed using a Bayesian logistic regression model, with randomised group, age, vaccination status, and comorbidity status included as covariates.

Missing data of primary outcome measure was 3%, which was less than 5%, therefore no pre-specified imputation of missing data was carried out.

Given that this is a pragmatic trial of a licensed medicine in its licensed population, we adopted a pharmacovigilance strategy and standard adverse event data were not routinely captured. Our strategy was to comprehensively capture safety data on serious adverse events and adverse events for which there is currently limited information (e.g., pregnancy). There was, however, a robust mechanism in place for participants to seek advice on the management of troublesome adverse events.

Role of the funding source

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

RESULTS

Population

The first participant was randomised on December 8, 2021, and randomization to molnupiravir was completed on April 27, 2022, by which time 25783 participants had been enrolled. 12821 were allocated to molnupiravir plus usual care, and 12962 to usual care alone (Figure 1). Data were extracted on August 17 2022 and the 504 randomised nirmatrelvir/ritonavir plus usual care and usual care alone are not included in the analyses presented here.

The mean age (range) of participants was 56·6 (18 to 99) years, and 17759/25783 (68·9%) had co-morbidities. 98·9% had at least one dose of a SARS-CoV-2 vaccine, and 94·4% had received at least three doses. Baseline characteristics were similar between groups (Table 1).

Of 12432 participants randomised to molnupiravir who provided medication use information, 95·4% (n=11857) reported taking molnupiravir for 5 days. 0·001% (n=19/12962) of usual care participants recorded receiving monoclonal antibody treatment out with PANORAMIC.

The median duration of symptoms prior to randomisation was 2 days (IQR 1 – 3), the median number of days from symptom onset to starting to take the medication was 3 days (IQR 3 –

4), and 87% (11109/11997) received their medication within first 5 days from start of symptoms.

Primary Outcomes

The proportion experiencing primary outcome measure events was less than 1% overall, and there was no evidence of a beneficial difference in hospitalisation/death between the groups (Table 2). There were 103/12516 (0·8%) hospitalisations/deaths in the molnupiravir group versus 96/12484 (0·8%) in usual care [adjusted odds ratio 1·06; 95% Bayesian credible interval (BCI) 0·80 – 1·40, probability of superiority 0·336]. Estimates were similar for all subgroups.

Secondary outcomes

The observed median (IQR) time-to-first-recovery from randomisation was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4·2 (95% BCI: 3·8 – 4·6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0.999 (estimated median TTR (10·3 [10·2 – 10·6] days vs 14·5 [14·2 – 14·9] days respectively; hazard ratio [95% BCI], 1·36 [1·3–1·4] days), which met the pre-specified superiority threshold (Table 2). Subgroup analysis demonstrated that this benefit was consistent across all studied groups.

Compared to the usual care group, participants receiving molnupiravir more often reported: early sustained recovery (31·8% vs 22·6%; adjusted odds ratio 1·62 [95% BCI: 1·53 – 1·72]); higher self-rating of wellness on a score of 0 to 10 at days 7, 14 and 28; reduced time to sustained recovery; reduced time to sustained alleviation of all symptoms; reduced time to reduction of symptom severity; fewer moderate or severe symptoms at day 7, 14 and 28 (e.g.

cough, shortness of breath, loss of smell/taste and fatigue); and, there was generally less health care seeking in primary care in the molnupiravir group (e.g., any contact with GP services: 19·6% vs 23·7%, respectively), although A&E attendances were similar (Table 2). The number of new infections over 28 days in the households of participants was similar in both groups (35·9% for molnupiravir, 36·7% for usual care).

In the intensively sampled virology cohort, on Day 7, the SARS-CoV-2 virus was below detection levels in 7/34 (21%) in the molnupiravir group, and in 1/39 (3%) in the usual care group (p=0·039), and mean (SD) of $\log_{10}$(Viral load) was 3·82 (1·40) in the molnupiravir group and 4·93 (1·38) in the usual are group (p<0·001). This was similar in the less intensively sampled virology cohort at Day 7, but the viral loads detected at Day 14, although low in both groups, were on average slightly higher in the molnupiravir group.

Regarding safety, 59 (0·4%) participants experienced serious adverse events in the molnupiravir group and 52 (0·4%) in usual care, with no serious adverse event definitely related to the intervention. 142 (1.1%) participants in the molnupiravir group withdrew due to adverse effects attributed to the medication. There were no adverse events of special interest.

DISCUSSION

This analysis from the largest randomised trial involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admissions, but that participants provided with molnupiravir recovered by a median of six days sooner. Molnupiravir resulted in an improvement in early sustained recovery in about one in ten

participants and reduced GP consultations. Faster patient reported recovery was consistent with a reduction in detectable virus and viral load in the studied subgroup on day seven among those who received molnupiravir.

Two living reviews of treatments for COVID-19; a World Health organisation (WHO) living guideline[21] and a living review and network analysis that informs the WHO on drug treatments;[22] identified six trials of molnupiravir. Of these trials, one was phase 1,[7] another was phase 2a,[2] one was the phase 3 MOVe-Out trial, [10] and three trials disclosed their data to the WHO (data were accessible to the review authors) but have not made their full findings publicly available. Concern has been raised regarding the lack of public sharing or formal publication of the findings of these three trials, along with nine others, all of which were conducted in India.[23] The reviews found that molnupiravir probably reduces: hospitalisation (odds ratio 0·54; 95% CI: 0·30 to 0·90; n=5 trials); and, time to symptom resolution (-3·3 days; 95% CI: - 4·8 days to -1·6 days; n=3 trials). The WHO therefore advises that molnupiravir may be of benefit in outpatients with mild-moderate COVID-19 at the highest risk of an adverse outcome. [21]

Prior to PANORAMIC, MOVe-OUT was the largest randomised trial of molnupiravir.[10] MOVe-OUT recruited 1,433 COVID-19 outpatients in over 20 countries to molnupiravir or placebo, with a primary outcome measure of all-cause hospitalisation or death within 29 days of enrolment.[10] The median age of participants was 43 years (range 18-90 years), which is younger than the average of 56·6 years for participants in PANORAMIC. Similar to PANORAMIC, all participants had at least one risk factor for progression to serious illness (obesity – 73·7%, age > 60 years – 17·2%, Diabetes – 15·9%), and the same dose and duration of molnupiravir was used. However, participants in MOVe-OUT were unvaccinated,

whilst most UK adults are now multiply-vaccinated (primary course plus one or two boosters).[24] Furthermore, Delta, Gamma and Mu SARS-CoV-2 variants were most commonly seen in the MOVe-OUT trial,[25] whereas the predominant variant in circulation in the UK has been Omicron since recruitment to PANORAMIC commenced in December 2021. [26]

In contrast to PANORAMIC, the MOVe-OUT trial investigators found that molnupiravir statistically significantly reduced the risk of hospitalisation or death compared with placebo (risk difference, −3·0 %; 95% CI: −5·9 % to −0·1%).[10] Of note, the observed benefit on hospitalisations/deaths in MOVe-OUT was reduced in the analysis from full trial dataset compared with the initial interim results, and analysis of the post-interim data in isolation did not suggest a beneficial impact of molnupiravir on this outcome measure.[13] The MOVe-Out investigators have considered many possible explanations, including: changes in the prevailing pandemic conditions and circulating SARS-CoV-2 variants; recruitment from sites in new regions with different hospitalisation policies; and, recruitment of participants with less severe illness. [10]

In the placebo-controlled MOVe-OUT trial, molnupiravir statistically significantly increased sustained recovery from anosmia (hazard ratio 1·20; 95% CI: 1·01 to 1·43) and fatigue (hazard ratio 1·15; 95% CI: 1·01 to 1·31), but not other symptoms.[10] In PANORAMIC, molnupiravir helped alleviate all of symptoms measured, including fever, cough, fatigue, muscle ache, diarrhoea, headache, loss of taste and smell, dizziness and feeling generally unwell, and shortened the time to self-reported. Molnupiravir may have shortened the time to resumption of normal activities, since the time that normal activities are affected is closely related to the duration of feeling unwell, but we did not measure this outcome directly.[27,28]

Differences in recovery outcomes between MOVe-OUT and PANORAMIC may have arisen from the open design of PANORAMIC. The proportion experiencing adverse events was similar in PANORAMIC and MOVe-OUT.

Exploratory analyses from MOVe-OUT found that molnupiravir was associated with a greater reduction in mean viral load from baseline to days three, five and ten, compared with placebo. Furthermore, the AGILE CST 2 placebo-controlled trial of 180 participants (both vaccinated and unvaccinated) demonstrated a faster time to a negative PCR test (8 days versus 11 days) with molnupiravir.[15] These findings are consistent with the findings from PANORAMIC of a reduction in viral detection and load in a subgroup of the trial cohort with molnupiravir compared with usual care at day 7.

PANORAMIC is the largest randomised trial of novel antiviral agents to date, recruiting over 26,000 participants by 4 October 2022 with test-positive SARS-CoV-2 early on in their illness. We achieved ascertainment of 97% for the primary outcome measure. Due to the large sample size, we have been able to conduct subgroup analyses with good precision around effect size estimates to determine populations in which molnupiravir is most likely to have benefit. Participants were randomised a mean of 2 days after symptom onset, and nearly 90% reported beginning their treatment course within 5 days of symptoms onset.

While it is critical to ensure that patients who are likely to benefit receive treatment with antiviral agents, using these precious medicines for patients who are unlikely to benefit carries the risk of driving resistance, wasting resources, and exposing people unnecessarily to harm. Due to the potential mutagenic properties of molnupiravir, there is a theoretical risk that administering this drug on a large scale could lead to new SARS-CoV-2 variants. This is

being evaluated through the PANORAMIC trial's virology sub-study. However, animal studies suggest that viral mutations induced by molnupiravir are likely to lead to reduced viral viability, and that there is low susceptibility to development of resistance.[29,30] Analysis of mutation frequency and the infectivity of persisting strains after molnupiravir use is ongoing and will be reported separately.

Theoretical risks have been raised regarding the potential for molnupiravir to cause mutagenesis in human cells.[31] Evidence of bone and cartilage toxicity was found in an animal study in which molnupiravir was administered for three months and at five times the dose; however, this effect was not replicated in other animal studies in which molnupiravir was administered at even higher doses (up to 19 times the normal human dose) for up to a month.[32] No impairment of fertility was identified when molnupiravir was administered to rats at up to six times the usual dose that would be given to humans.[32] On the basis of all available evidence, the risk of human genotoxicity was deemed low by the Medicines and Healthcare products Regulatory Agency (MHRA).[33] Nonetheless, we incorporated safety measures in the trial, including: inclusion of adult participants only; exclusion of breastfeeding patients and those with known/suspected pregnancy; exclusion of participants of childbearing potential who were not willing to use effective contraception for the following 28 days; a pregnancy test to confirm non-pregnancy of participants of child-bearing potential; and, confirmation of a negative pregnancy through a safety call to the participant shortly after enrolment. We additionally would have recorded pregnancies occurring within 28 days of enrolment as adverse events of special interest with any such participants followed up until the outcome of their pregnancy was known. The numbers citing drug side effects as a reason for discontinuation was recorded; a small proportion stopped the drug and an even

smaller proportion (just over 1%) did so because of side effects. We found few serious adverse events, with none definitely related to molnupiravir.

Molnupiravir is an orally administered drug with no known important drug interactions, and therefore, if effective, has potential for widespread distribution and use. Patients with COVID-19 who were extremely clinically vulnerable, whilst eligible for participation in PANORAMIC, were able to access monoclonal antibody and antiviral treatment directly from the NHS: our findings may therefore be less applicable to patients in this highest risk category. Our health economics analysis is ongoing, and we are continuing to evaluate the longer-term economic implications of molnupiravir administration through collection of outcome measure data at three and six months.

We are also studying the effect of COVID-19 on longer-term symptoms, namely long COVID. Long COVID syndrome may affect up to 43% of people who experience acute COVID-19,[34] and typically causes a range of physical and psychological symptoms.[35] There is limited research evaluating the effect of treatments given during acute COVID-19 illness on longer term outcomes,[36] and to date, no published data on the effect of molnupiravir administration on long-term outcomes. Given the demonstrated improvement in time to recovery of all symptoms, we await with interest the analysis of long COVID comparing those treated with molnupiravir and usual care.

The design of PANORAMIC breaks with the traditional trial paradigm in which the "participant comes to the research." The molnupiravir comparison in PANORAMIC allowed "research to be taken to the patient," with remote recruitment of participants possible from all four UK nations, irrespective of where people live or receive their healthcare. This is

important, as research suggests that the low representation of people from diverse and ethnic minority backgrounds is because their access to research is more difficult.[37] The ability of participants to be recruited, enrolled and followed up without having to leave their homes reduces the burden of trial procedures on participants and reduces spread. PANORAMIC strives to be a 'democratic' trial, with a proactive outreach strategy, led by the trial's national pharmacy, and inclusion and diversity lead, with the support of UK-wide pharmacy networks, to actively promote the trial UK-wide and to people from all backgrounds. This includes people from ethnic minority background and people residing in areas of higher deprivation, who may be disproportionately affected by COVID-19, yet also traditionally poorly represented in clinical trials. Participants living in areas with the most deprived quintile of the Index of Multiple Deprivation was around 10%, and about 30% lived the least deprived areas; this may be explained by large numbers being recruited after self-screening and follow up online. The proportion of participants from ethnic minority origin was nearly 6%; the mean age of our participants was 56.6 years and as there are proportionally fewer people of ethnic minority origin in older age groups in the UK, [38] this is largely representative of the general population.

The open-label design means that we cannot estimate the proportion of the positive effect of molnupiravir on symptoms resulting from any placebo effect. However, the objective primary outcome measure in PANORAMIC (non-elective hospitalisation and/or death) is unlikely to be affected by a placebo effect. Furthermore, the virology sub-study found reduced duration of viral RNA detection in nasal swabs with molnupiravir at day 7, which is in line with self-reported reduction in illness duration. In keeping with pragmatic trial design, PANORAMIC is designed to be more closely reflective of real-world practice; [39] our results are more likely to reflect what would happen if molnupiravir were introduced into routine clinical practice [39] and facilitate a more realistic cost-effectiveness and cost utility assessment. Of note, findings

from our open label PRINCIPLE trial of repurposed drugs for community treatment of COVID-19 has found no difference in outcome measures relying on participants' self-reported recovery for several treatments. [40-42]

This preliminary analysis involving people vaccinated against SARS-CoV-2 infection at increased risk of an adverse outcome in the community and unwell with COVID-19 found that molnupiravir did not reduce already low hospital admission, but that molnupiravir resulted in faster time to recovery, earlier sustained recovery, reduced contact with GP services, and reduced viral detection and viral load. These benefits need to be considered in the context of the prevailing disease, burden on healthcare services, social circumstances, cost-effectiveness, and opportunity costs.

Contributors

Declaration of interests

JSN-V-T was seconded to the Department of Health and Social Care, England (DHSC) from October 2017 to March 2022. The views expressed in this paper are those of its authors and not necessarily those of DHSC. Berry statisticians are paid by the University of Oxford for their statistical work on the unblinded analyses for PANORAMIC, but their compensation is not dependent on the outcomes of arms in the study. SK has received research support from ViiV, Merck, Ridgeback, GSK and Vir and honoraria from Pfizer unrelated to this work. UW has received speaker/advisory board fees from AZ, Gilead, GSK/ViiV and MSD/Merck.

Data sharing

Data can be shared with qualifying researchers who submit a proposal with a valuable research question as assessed by a committee formed from the trial management group, including senior statistical and clinical representation. A contract should be signed.

Acknowledgements

The authors would like to especially thank all participants in the study and acknowledge the work and support of all participating general practices, NHS COVID-19 treatment services and other health and social care organisations supporting the trial. We would also like to thank our PPI contributors, the Trial Steering Committee, the Data Monitoring and Safety Committee, primary care colleagues in the National Institute of Health and Care Research Clinical Research Network (lead network – Thames Valley and South Midlands CRN), Health and Care Research Wales, NHS Research Scotland, the Health and Social Care Board in Northern Ireland, the National Institute of Health and Care Research, and the Therapeutics

Task Force. NHS DigiTrials, the Intensive Care National Audit and Research Centre, Public Health Scotland, National Records Service of Scotland, the Secure Anonymised Information Linkage (SAIL) at University of Swansea, Health and Social Care Northern Ireland (HSC Business Services Organisation/HSC Trusts).

This project is funded by the NIHR (NIHR135366). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. CCB acknowledges part support as Senior Investigator of the National Institute of Health Research, the NIHR Community Healthcare Medtech and In-Vitro Diagnostics Co-operative (MIC), and the NIHR Health Protection Research Unit on Health Care Associated Infections and Antimicrobial Resistance. FDRH acknowledges his part-funding from the NIHR Applied Research Collaboration (ARC OxTV) and the NIHR Community Healthcare Medtech and In-Vitro Diagnostics Co-operative (MIC). GH is funded by an NIHR Advanced Fellowship and by the NIHR Community Healthcare Medtech and In-Vitro Diagnostics Co-operative (MIC). JD is funded by the Wellcome Trust PhD Programme for Primary Care Clinicians (216421/Z/19/Z). SP receives support as a NIHR Senior Investigator (NF-SI-0616-10103) and from the UK NIHR Applied Research Collaboration Oxford and Thames Valley. OAG receives funding from ECRAID-Prime, project number 101046109. JB receives supports as an NIHR Senior Investigator and from the UCL/UCLH NIHR Biomedical Research Centre.

Data Monitoring and Safety Committee Independent members:

Prof Deborah Ashby (Chair)

Prof Benjamin Fisher

Prof Simon Gates

Prof Gordon Taylor

Prof Martin Underwood

Trial Steering Committee Independent members

Philip Hannaford Chair

Ms Corina Cheeks

Prof Ranjit Lall

Prof Alastair Hay

Prof William Hollingworth

Prof Matthew Sydes: Independent observer

Prof Mike Moore: Independent observer

Recruiting sites

Abbeywell Surgery; AGILE Lighthouse Laboratory - UK Health Security Agency; Ashton Medical Group; Babylon Healthcare Services Limited; Ballygomartin Group Practice; Banbury Cross Health Centre; Barlow Medical Centre; Barnet Federated GPs; Beaconsfield Medical Centre; Bicester Health Centre; Brierley Park Medical Centre, Sherwood Forest Hospitals NHS Foundation Trust; Budbrooke Medical Centre; Carlisle Healthcare; Central London Healthcare CIC; Chesterfield Royal Hospital NHS Foundation Trust; Danes Camp Medical Centre; Derwentside Federation; Dorking Healthcare Federation; Duncairn Medical Practice; Fellview Healthcare; Fife Health Board; GP Direct; Granta Medical Practices; Guy's and St Thomas' NHS Foundation Trust; Hammersmith and Fulham Partnership; Hartlepool & Stockton Health Ltd ; Highcliffe Medical Centre; Highland Health Board; Honiton Surgery; Hounslow Medical Centre; Humber Teaching NHS Foundation Trust; James Alexander Family Practice; K & W Healthcare Ltd; Lancaster Medical Practice; Little Horton Lane Medical Centre; LMA West London GP Federation; Lothian Health Board; Marshalls Cross

Medical Centre; Mathukia Surgery; Medicus Health Partners; Middlewood Partnership; Millview Surgery c/o East Staffordshire PCN; Newquay Health Centre; Newton Place Surgery; North West North Tyneside PCN; Northern Ireland Clinical Research Network; One Norwich Practices; Primary Care Sheffield Ltd (Clover Research Cluster); Public Health Wales NHS Trust; Rowden Surgery; Shifa Surgery; Sovereign Health Partnership, The Highlands Practice; St Bartholomew's Medical Centre; Stourport Medical Centre; Summertown Medical Centre; Symphony Healthcare Services Ltd; The Adam Practice; The Confederation, Hillingdon CIC; The University of Nottingham Health Service; The White House Surgery; Vauxhall Primary Health Care; Wansford and Kings Cliffe Practice; Waterloo Medical Centre; Whiteladies Medical Group; Willows Health; Windrush Medical Practice; Woodbridge Hill Surgery.

Authors' contributions

CCB and JSN-V-T conceived the study. CCB is the Chief Investigator. PL, FDRH are co-Chief Investigators. CCB, PL, and FDRH decided to publish the paper. BRS, L-MY, JH, MD, CCB, FDRH, PL, GH, OAG, JD, NMR, DBR, SP, DML, JFS, KH, PE, OvH and ML provided input to the trial design. EO, JA, PE, LL, EH, LC, MB, MC, SB, CB, JCD, IR-W, AC-S and DB are responsible for study implementation and acquisition of data. CCB, OAG, L-MY, PL, FDRH, GH, NMR, DBR, MGP, DML, JFS, PE, JB, JD, SP, JSN-V-T and SK drafted the manuscript. HR leads the clinical team. L-MY, BRS, JH, VH, UG, JM, MAD, CTS, MF and NSB contribute to statistical analysis. SK, DBR, GH, NMR and MD provide input to safety evaluations, monitoring, and drug interactions. MGP is the National Pharmacy, and Inclusion and Diversity Lead for the trial. SP and MEP run the economic evaluation. JFS, DML and JB lead the virology sub-study. GH leads on patient and public

involvement. JC leads on the information systems. MB leads 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, BJ, NDH, JC, EH, LC, MB, MA, OvH, AU, L-MY and FDRH are members of the Trial Management Group supporting site recruitment, activity and delivery. OAG and CCB produced the first draft of the manuscript. All authors critically revised the manuscript. All authors are contributing to the conduct of the trial.

References

1. Toots M, Yoon JJ, Cox RM, et al. Characterization of orally efficacious influenza drug with high resistance barrier in ferrets and human airway epithelia. *Sci Transl Med* 2019; **11**(515).
2. Fischer WA, 2nd, Eron JJ, Jr., Holman W, et al. A phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2 RNA clearance and elimination of infectious virus. *Sci Transl Med* 2022; **14**(628): eabl7430.
3. Malone B, Campbell EA. Molnupiravir: Coding for catastrophe. *Nature Structural & Molecular Biology* 2021; **28**(9): 706-8.
4. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nature Microbiology* 2021; **6**(1): 11-8.
5. Wahl A, Gralinski LE, Johnson CE, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature* 2021; **591**(7850): 451-7.
6. Rosenke K, Hansen F, Schwarz B, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. *Nat Commun* 2021; **12**(1): 2295.
7. Khoo SH, Fitzgerald R, Fletcher T, et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomized controlled study. *Journal of Antimicrobial Chemotherapy* 2021; **76**(12): 3286-95.
8. Painter WP, Holman W, Bush JA, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. *Antimicrob Agents Chemother* 2021; **65**(5): e02428-20.
9. Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 Trial of Molnupiravir for Treatment of Covid-19 in Nonhospitalized Adults. *NEJM Evidence*; **0**(0): EVIDoa2100043.
10. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med* 2022; **386**(6): 509-20.
11. Medicines and Healthcare products Regulatory Agency. First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA 2021.
12. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Authorizes Additional Oral Antiviral for Treatment of COVID-19 in Certain Adults. 2021.
13. Thorlund K, Sheldrick K, Meyerowitz-Katz G, Singh S, Hill A. Making Statistical Sense of the Molnupiravir MOVe-OUT Clinical Trial. *Am J Trop Med Hyg* 2022: tpmd211339.
14. Singh S, Kumar Mitra A, Arora N. Two Indian drugmakers to end trials of generic Merck pill for moderate COVID-19. Reuters, 2021.
15. Khoo SH, FitzGerald R, Saunders G, et al. A Randomised-Controlled Phase 2 trial of Molnupiravir in Unvaccinated and Vaccinated Individuals with Early SARS-CoV-2. *medRxiv* 2022.
16. Woodcock J, LaVange LM. Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *N Engl J Med* 2017; **377**(1): 62-70.
17. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing COVID-19: National Institute for Health and Care Excellence (NICE), 2021.
18. NHS England. Interim clinical commissioning policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. 14th June 2022 2022. https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-neutralising-monoclonal-antibodies-or-antivirals-for-non-hospitalised-patients-with-covid-19/ (accessed 4th October 2022 2022).
19. Gastine S, Pang J, Boshier FA, et al. Systematic review and patient-level meta-analysis of SARS-CoV-2 viral dynamics to model response to antiviral therapies. *Clinical Pharmacology & Therapeutics* 2021; **110**(2): 321-33.
20. Laouénan C, Guedj J, Mentré F. Clinical trial simulation to evaluate power to compare the antiviral effectiveness of two hepatitis C protease inhibitors using nonlinear mixed effect models: a viral kinetic approach. *BMC Medical Research Methodology* 2013; **13**(1): 1-10.

21. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for covid-19. *bmj* 2020; **370**.
22. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *Bmj* 2020; **370**.
23. Lawrence J, Mirchandani M, Hill A. Evaluation of publication bias for 12 clinical trials of molnupiravir to treat SARS-CoV-2 infection in 13,694 patients. *Research Square* 2022.
24. GOV.UK. Vaccinations in the United Kingdom. 2022. https://coronavirus.data.gov.uk/details/vaccinations (accessed 10th May 2022 2022).
25. Merck. Merck and Ridgeback's Investigational Oral Antiviral Molnupiravir Reduced the Risk of Hospitalization or Death by Approximately 50 Percent Compared to Placebo for Patients with Mild or Moderate COVID-19 in Positive Interim Analysis of Phase 3 Study. 2021. https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/ (accessed 4th May 2022 2022).
26. Burki TK. Omicron variant and booster COVID-19 vaccines. *The Lancet Respiratory Medicine* 2022; **10**(2): e17.
27. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *The Lancet Infectious Diseases* 2013; **13**(2): 123-9.
28. Little P, Rumsby K, Kelly J, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomized controlled trial. *Jama* 2005; **293**(24): 3029-35.
29. Abdelnabi R, Foo CS, Kaptein SJ, et al. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. *EBioMedicine* 2021; **72**: 103595.
30. Urakova N, Kuznetsova V, Crossman DK, et al. β-d-N 4-hydroxycytidine is a potent anti-alphavirus compound that induces a high level of mutations in the viral genome. *Journal of virology* 2018; **92**(3): e01965-17.
31. Zhou S, Hill CS, Sarkar S, et al. β-d-N 4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. *The Journal of infectious diseases* 2021; **224**(3): 415-9.
32. Merck Sharp & Dohme (UK) Limited. Lagevrio 200 mg hard capsules. 2022. https://www.medicines.org.uk/emc/product/13044#gref (accessed 7th September 2022 2022).
33. Medicine & Healthcare products Regulatory Agency. Summary of Product Characteristics for Lagevrio. 2021. https://www.gov.uk/government/publications/regulatory-approval-of-lagevrio-molnupiravir/summary-of-product-characteristics-for-lagevrio (accessed 7th September 2022 2022).
34. Cirulli E, Barrett KMS, Riffle S, et al. Long-term COVID-19 symptoms in a large unselected population. *medrxiv* 2020.
35. National Institute for Health and Care Excellence. COVID 19: Scenario: Managing long-term effects [Online]. November 2021 2021. https://cks.nice.org.uk/topics/coronavirus-covid-19/management/managing-long-term-effects/.
36. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *The Lancet Respiratory Medicine* 2021; **9**(11): 1275-87.
37. Wendler D, Kington R, Madans J, et al. Are racial and ethnic minorities less willing to participate in health research? *PLoS Med* 2005; **3**(2): e19.
38. GOV.UK. Ethnicity facts and figures - Population of England and Wales. 7th August 2020 2018. https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest (accessed 26th September 2022 2022).
39. MacPherson H. Pragmatic clinical trials. *Complementary therapies in medicine* 2004; **12**(2-3): 136-40.

40. Hayward G, Butler CC, Yu LM, et al. Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE): protocol for a randomised, controlled, open-label, adaptive platform, trial of community treatment of COVID-19 syndromic illness in people at higher risk. *BMJ Open* 2021; **11**(6): e046799.
41. Butler CC, Yu LM, Dorward J, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *Lancet Respir Med* 2021; **9**(9): 1010-20.
42. Dorward J, Yu LM, Hayward G, et al. Colchicine for COVID-19 in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial. *Br J Gen Pract* 2022; **72**(720): e446-e55.

Figure 1 Participant flow diagram

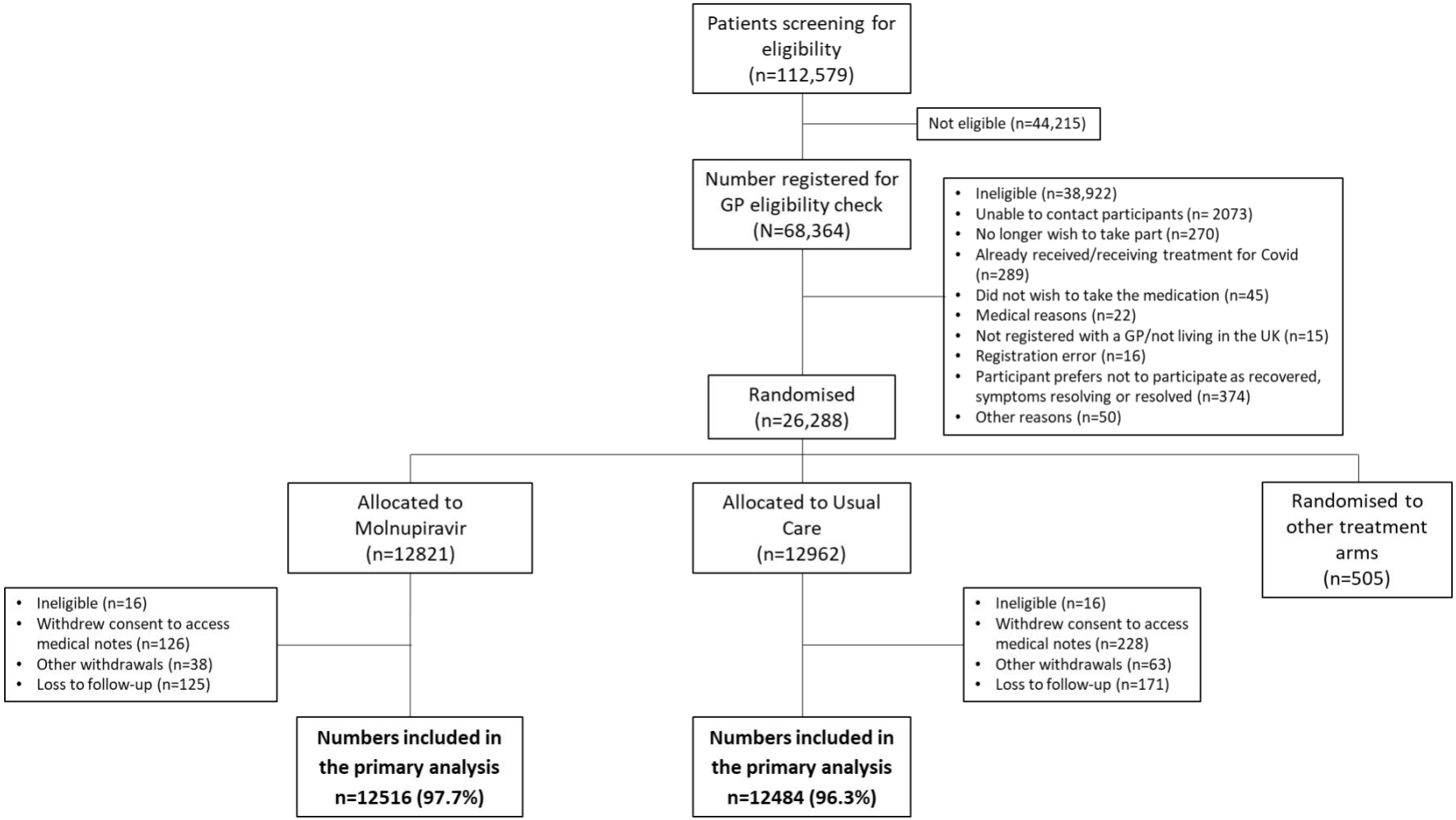
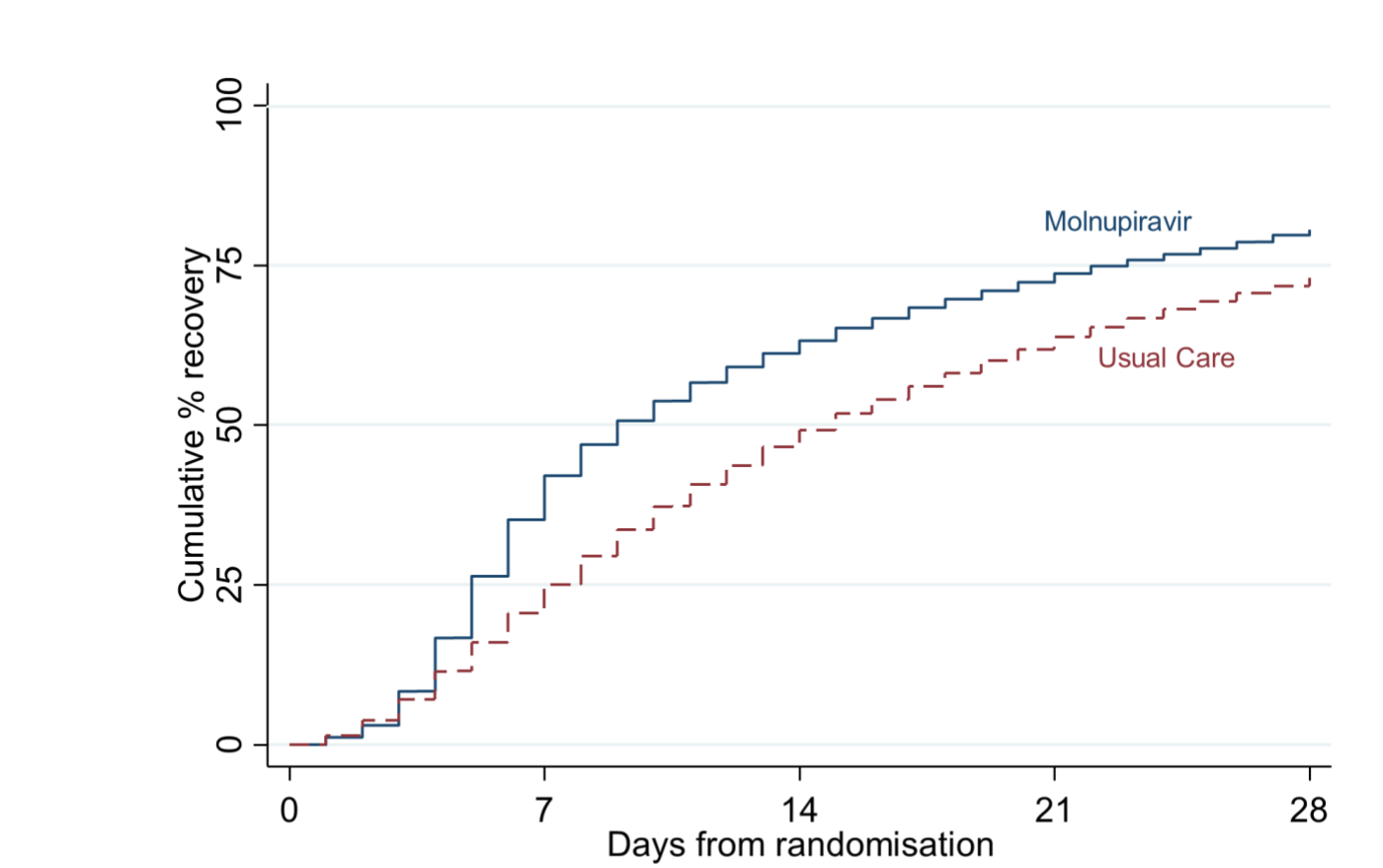


Figure 2 Time to first reported recovery



Cumulative number not yet recovered (recovered)					
Molnupiravir	12432 (0)	7948 (5179)	4670 (7734)	3228 (8966)	2173 (9741)
Usual Care	12151 (0)	9415 (2993)	6124 (5788)	4177 (7393)	2776 (8376)

Figure 3 Forest plot of subgroup analysis of hospitalization/death

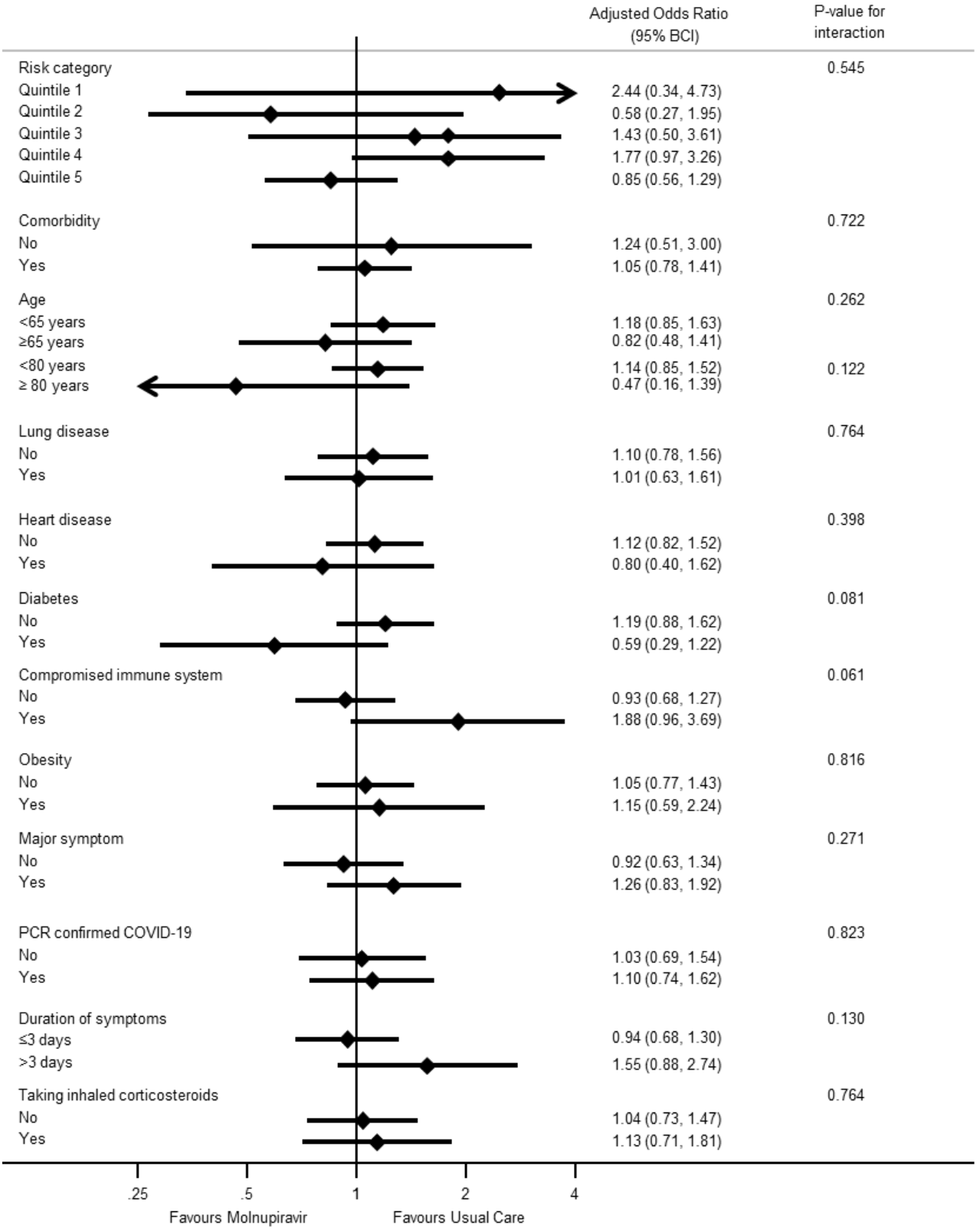


Figure 4 Forest plot of subgroup analysis of time to recovery

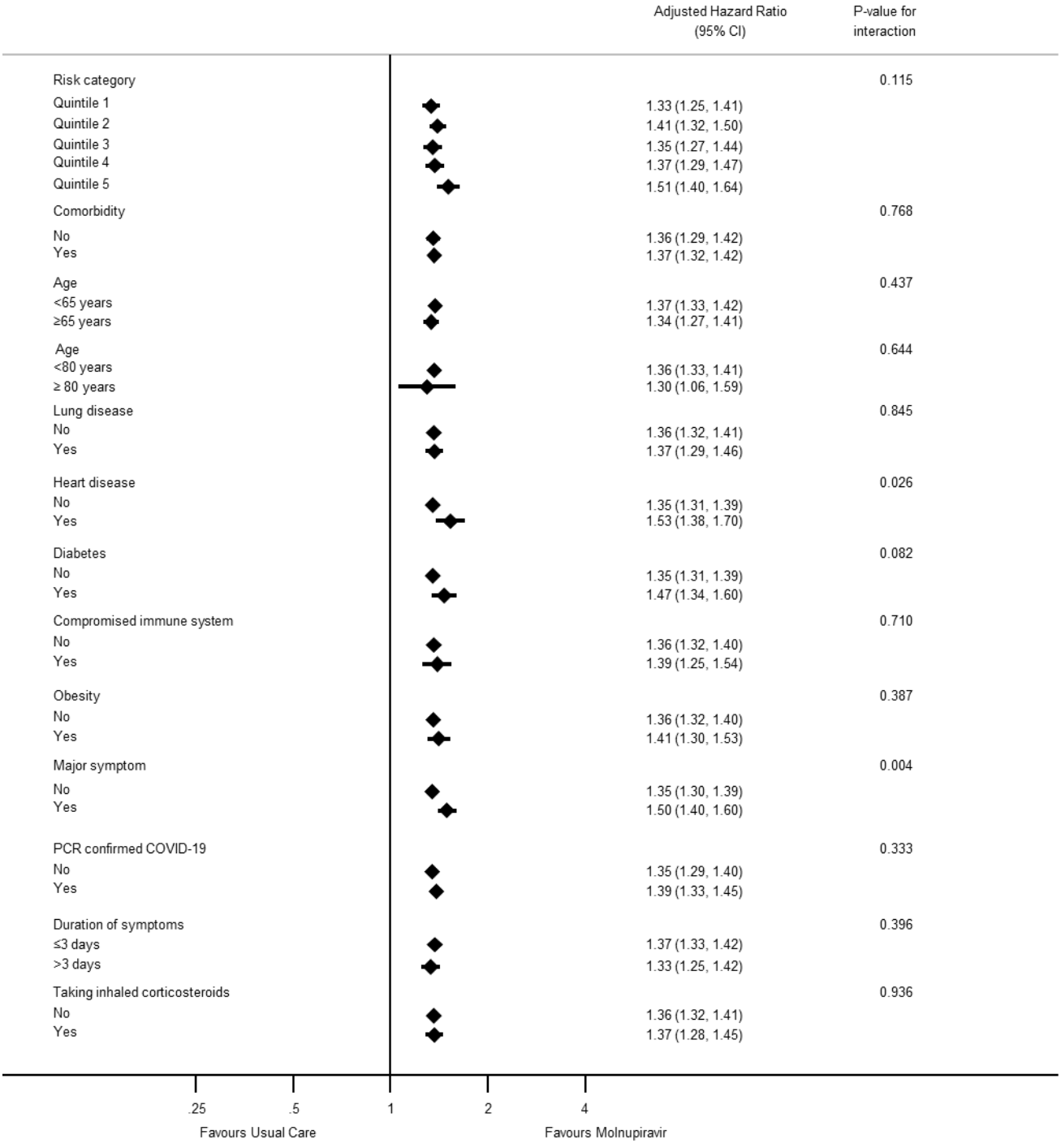


Table 1 Baseline characteristics of participants by treatment group

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Age, mean(SD)	56·7 (12·5)	56·5 (12·7)	56·6 (12·6)
Sex, n(%)			
Female	7451 (58%)	7650 (59%)	15101 (59%)
Male	5367 (42%)	5308 (41%)	10675 (41%)
Other	3 (<1%)	4 (<1%)	7 (<1%)
Days from randomisation to reporting receipt of medication for those with day 1 to 7 diaries*, median(IQR)	1.0 (1.0 to 2.0)		1.0 (1.0 to 2.0)
Days from start of symptoms to taking medication for those with day 1 to 7 diaries*, median(IQR)	3·0 (3·0 to 4·0)		3·0 (3·0 to 4·0)
Missing, n(%)	824 (3%)		
Ethnicity category, n(%)			
White	12088 (94%)	12182 (94%)	24270 (94%)
Asian	366 (3%)	434 (3%)	800 (3%)
Mixed Race	203 (2%)	189 (2%)	392 (2%)
Black	78 (<1%)	77 (<1%)	155 (<1%)
Other	86 (<1%)	80 (<1%)	166 (<1%)
NHS priority category, n(%)			
Aged ≥80	259 (2·%)	272 (2%)	531 (2%)
Aged ≥75 and <80	539 (4%)	577 (5%)	1116 (4%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1117 (9%)	1114 (9%)	2231 (9%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1496 (12%)	1464 (11%)	2960 (12%)
Aged ≥18 and <65 in an at-risk group	6541 (51%)	6591 (51%)	13132 (51%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at-risk group	746 (6%)	768 (6%)	1514 (6%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at-risk group	997 (8%)	1063 (8%)	2060 (8%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at-risk group	1126 (9%)	1113 (9%)	2239 (9%)
Predicted risk quintile, n(%)			
1 (lowest risk)	2491 (19%)	2558 (20%)	5049 (20%)
2	2679 (21%)	2636 (20%)	5315 (21%)
3	2524 (20%)	2660 (21%)	5184 (20%)
4	2784 (22%)	2767 (21%)	5551 (22%)
5 (highest risk)	2343 (18%)	2341 (18%)	4684 (18%)
Confirmed PCR positive, n(%)	5965 (46%)	5902 (46%)	11867 (46%)
IMD quintile, n(%)			
(Most deprived) 1	1234 (10%)	1182 (9%)	2416 (9%)
2	1913 (15%)	1956 (15%)	3869 (15%)
3	2569 (20%)	2592 (20%)	5161 (20%)
4	3216 (25%)	3213 (25%)	6429 (25%)
(Least deprived) 5	3839 (30%)	3960 (31%)	7799 (30%)
Missing, n(%)	50 (<1%)	59 (<1%)	109 (<1%)
Received vaccination, n(%)	12678 (99%)	12830 (99%)	25508 (99%)
Number of vaccine doses, n(%)			
1	87 (<1%)	88 (<1%)	175 (0<1%)
2	519 (4%)	458 (4%)	977 (4%)
3	11836 (92%)	12044 (93%)	23880 (93%)
4	236 (2%)	240 (2%)	476 (2%)
Missing, n(%)	143 (1%)	132 (1%)	275 (1%)

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Smoker, n(%)	795 (6%)	805 (6%)	1600 (6%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	6111 (48%)	6125 (47%)	12236 (48%)
Minor problem	4514 (35%)	4684 (36%)	9198 (36%)
Moderate problem	1936 (15%)	1896 (15%)	3832 (15%)
Major problem	260 (2%)	257 (2%)	517 (2%)
Fatigue, n(%)			
No problem	1251 (10%)	1216 (9%)	2467 (10%)
Minor problem	4721 (37%)	4853 (37%)	9574 (37%)
Moderate problem	5083 (40%)	5127 (40%)	10210 (40%)
Major problem	1766 (14%)	1766 (14%)	3532 (14%)
Muscle ache, n(%)			
No problem	3479 (27%)	3425 (26%)	6904 (27%)
Minor problem	4504 (35%)	4791 (37%)	9295 (36%)
Moderate problem	3763 (29%)	3684 (28%)	7447 (29%)
Major problem	1075 (8%)	1062 (8%)	2137 (8%)
Vomiting, n(%)			
No problem	10440 (81%)	10503 (81%)	20943 (81%)
Minor problem	1847 (14%)	1913 (15%)	3760 (15%)
Moderate problem	478 (4%)	477 (4%)	955 (4%)
Major problem	56 (<1%)	69 (<1%)	125 (<1%)
Diarrhoea, n(%)			
No problem	10600 (83%)	10732 (83%)	21332 (83%)
Minor problem	1649 (13%)	1681 (13%)	3330 (13%)
Moderate problem	471 (4%)	457 (4%)	928 (4%)
Major problem	101 (<1%)	92 (<1%)	193 (<1%)
Loss of smell or taste, n(%)			
No problem	9066 (71%)	9402 (73%)	18468 (72%)
Minor problem	2484 (19%)	2368 (18%)	4852 (19%)
Moderate problem	825 (6%)	800 (6%)	1625 (6%)
Major problem	446 (4%)	392 (3%)	838 (3%)
Headache, n(%)			
No problem	2702 (21%)	2820 (22%)	5522 (21%)
Minor problem	5194 (41%)	5215 (40%)	10409 (40%)
Moderate problem	3783 (30%)	3838 (30%)	7621 (30%)
Major problem	1142 (9%)	1089 (8%)	2231 (9%)
Dizziness, n(%)			
No problem	8446 (66%)	8382 (65%)	16828 (65%)
Minor problem	3087 (24%)	3295 (25%)	6382 (25%)
Moderate problem	1096 (9%)	1087 (8%)	2183 (9%)
Major problem	192 (2%)	198 (2%)	390 (2%)
Abdominal pain, n(%)			
No problem	10391 (81%)	10440 (81%)	20831 (81%)
Minor problem	1834 (14%)	1920 (15%)	3754 (15%)
Moderate problem	524 (4%)	542 (4%)	1066 (4%)
Major problem	72 (<1%)	60 (<1%)	132 (<1%)
Generally unwell, n(%)			
No problem	525 (4%)	535 (4%)	1060 (4%)
Minor problem	5028 (39%)	5145 (40%)	10173 (40%)
Moderate problem	5789 (45%)	5838 (45%)	11627 (45%)
Major problem	1479 (12%)	1444 (11%)	2923 (11%)
Fever, n(%)			
No problem	5670 (44%)	5765 (45%)	11435 (44%)

	Molnupiravir (N=12821)	Usual Care (N=12962)	OVERALL (N=25783)
Minor problem	4813 (38%)	4955 (38%)	9768 (38%)
Moderate problem	2107 (16%)	2042 (16%)	4149 (16%)
Major problem	231 (2%)	200 (2%)	431 (2%)
Cough, n(%)			
No problem	1410 (11%)	1343 (10%)	2753 (11%)
Minor problem	6153 (48%)	6384 (49%)	12537 (49%)
Moderate problem	4502 (35%)	4509 (35%)	9011 (35%)
Major problem	756 (6%)	726 (6%)	1482 (6%)
Wellness score, mean(SD)	5·1 (1·7)	5·2 (1·7)	5·1 (1·7)
People in household, n(%)			
0	1660 (13%)	1660 (13%)	3320 (13%)
1	6113 (48%)	6019 (46%)	12132 (47%)
2	2129 (17%)	2176 (17%)	4305 (17%)
3	1765 (14%)	1979 (15%)	3744 (15%)
4	808 (6%)	772 (6%)	1580 (6%)
Taking inhaled corticosteroids, n(%)	2990 (23%)	3152 (24%)	6142 (24%)
Taking inhaled corticosteroids for COVID, n(%)	183 (1%)	158 (1%)	341 (1%)
Monoclonal antibodies for COVID, n(%)	26 (<1%)	19 (<1%)	45 (<1%)
Comorbidities			
Lung disease, n(%)	3014 (24%)	3171 (25%)	6185 (24%)
Heart disease, n(%)	1000 (8%)	957 (7%)	1957 (8%)
Kidney disease, n(%)	227 (2%)	253 (2%)	480 (2%)
Liver disease, n(%)	159 (1%)	144 (1%)	303 (1%)
Neurological disease, n(%)	430 (3%)	438 (3%)	868 (3%)
Learning disability, n(%)	36 (<1%)	27 (<1%)	63 (<1%)
Down's syndrome', n(%)	24 (<1%)	30 (<1%)	54 (<1%)
Diabetes, n(%)	1483 (12%)	1512 (12%)	2995 (12%)
Weakened immune system, n(%)	1125 (9%)	1070 (8%)	2195 (9%)
Transplant recipient, n(%)	57 (<1%)	71 (<1%)	128 (<1%)
Obesity, n(%)	1968 (15%)	1944 (15%)	3912 (15%)
Mental illness, n(%)	198 (2%)	220 (2%)	418 (2%)
Hypertension, n(%)	2880 (23%)	2902 (22%)	5782 (22%)
Other vulnerability, n(%)	2295 (18%)	2341 (18%)	4636 (18%)

*Median and interquartile range presented for non-normally distributed variables.

Table 2: Primary and Secondary Outcomes

	Molnupiravir	Usual Care	Estimated treatment effect (95% BCI/CI)	Estimated benefit (95% BCI)	Pr(Superiority)/ P-value
Primary outcomes					
Number of hospitalisation	102	93			
Number of death	2	5			
Hospitalisation/death at 28 days, n (%)	103/12516 (0·8%)	96/12484 (0·8%)	1·06 (0·80 to 1·40)*		0·34*
Secondary outcomes					
First reported recovery, n/N (%)	9741/12432 (78%)	8376/12151 (69%)			
Time to first reported recovery (days), median (IQR)	9 (5 to 23)	15 (7 to not reached)	1·36 (1·32 to 1·40)†	4·17 (3·78 to 4·58)†	>0·999†
Early sustained recovery, n/N (%)	3631/11411 (32%)	2446/10826 (23%)	1·62 (1·53 to 1·72)‡		>0·999‡
Sustained recovery, n/N (%)	8558/12432 (69%)	7304/12151 (60%)			
Time to sustained recovery (days), median (IQR)	21 (10 to not reached)	24 (14 to not reached)	1·24 (1·21 to 1·28)†	3·80 (3·25, 4·31)†	>0·999†
Alleviation of all symptoms, n/N (%)	9000/9689 (93%)	8352/9407 (89%)			
Time to alleviations of all symptoms (days), median (IQR)	4 (2 to 7)	4 (2 to 9)	1·18 (1·15 to 1·22)†	0·66 (0·54, 0·78)†	>0·999†
Sustained alleviation of all symptoms, n/N (%)	8134/9689 (84%)	7383/9407 (79%)			
Time to sustained alleviation of all symptoms (days), median (IQR)	9 (3 to 23)	12 (4 to 25)	1·16 (1·13 to 1·20)†	2·01 (1·58, 2·45)†	>0·999†
Initial reduction of severity of symptoms, n/N (%)	10073/11954 (84%)	8862/11555 (77%)			
Time to initial reduction of severity of symptoms (days), median (IQR)	8 (5 to 18)	12 (7 to 24)	1·30 (1·26 to 1·34)†	2.35 (2.02 to 2.69) †	>0·999†
Rating of how well participant feels (0 worst, 10 best), mean (SD) [n]					
Day 7	7·3 (1·7) [11857]	6·8 (1·8) [11233]	0·5 (0·5 to 0·6)§		<0·001§
Day 14	7·9 (1·7) [11524]	7·6 (1·7) [10740]	0·3 (0·2 to 0·3)§		<0·001§
Day 21	8·2 (1·6) [10761]	8·0 (1·7) [9698]	0·2 (0·1 to 0·2)§		<0·001§
Day 28	8·4 (1·5) [10658]	8·3 (1·6) [9777]	0·2 (0·1 to 0·2)§		<0·001§
New infections in household	3890/10823 (36%)	3874/10557 (37%)	0·96 (0·91 to 1·02)*		0·90*
Any contact with NHS 111, n/N (%)	584/12431 (5%)	778/12145 (6%)	0·72 (0·64 to 0·80)*		>0·999*
Any contact with GP, n/N (%)	2432/12431 (20%)	2879/12146 (24%)	0·77 (0·73 to 0·82)*		>0·999*
Any contact with ambulance service (not hospitalised), n/N (%)	344/12426 (3%)	331/12131 (3%)	1·02 (0·87 to 1·180) *		0·43*
Any contact with community nurse, n/N (%)	42/550 (8)	53/543 (10)	0·78 (0·53 to 1·15)*		0·76*
Any contact with physiotherapist, n/N (%)	22/786 (3)	22/797 (3)	1·01 (0·57 to 1·82)*		0·0004*
Any contact with counsellor, n/N (%)	50/774 (7)	73/785 (9)	0·69 (0·49 to 0·98)*		0·89*
Any contact with social worker	27/12431 (<1%)	32/12142 (<1%)	0·84 (0·49 to 1·36)*		0·79*
Any contact with home carer	89/12430 (<1%)	95/12140 (<1%)	0·91 (0·67 to 1·20)*		0·77*
Any contact with occupational therapist	261/12430 (2%)	240/12142 (2%)	1·07 (0·89 to 1·27)*		0·25*
Any contact with hospital A&E	708/12431 (6%)	674/12143 (6%)	1·03 (0·92 to 1·14)*		0·32*
Any contact with respiratory outpatient clinic	234/12431 (2%)	252/12141 (2%)	0·90 (0·75 to 1·07)*		0·88*
Any contact with hospital at home for COVID-19	352/12431 (3%)	431/12142 (4%)	0·79 (0·68 to 0·90)*		>0·999*
Any contact with other services	584/12431 (5%)	647/12141 (5%)	0·87 (0·77 to 0·97)*		0·99*
Virology outcomes					
Intensive Samples					
Viral load below detection level, n/N (%)					

	Molnupiravir	Usual Care	Estimated treatment effect (95% BCI/CI)	Estimated benefit (95% BCI)	Pr(Superiority)/ P-value
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¶
log10Viral load, mean(SD)					
Day 2	6·66 (1·59)	7·11 (1·04)	-0·48 (-0·98 to 0·01)**		0·056**
Day 3	6·07 (1·48)	6·47 (1·07)	-0·42 (-0·92 to 0·07)**		0·092**
Day 4	5·32 (1·61)	5·87 (1·21)	-0·56 (-1·04 to -0·07)**		0·026**
Day 5	4·45 (1·52)	5·82 (1·08)	-1·41 (-1·91 to -0·92)**		<0·001**
Day 6	4·12 (1·50)	5·32 (1·28)	-1·23 (-1·72 to -0·73)**		<0·001**
Day 7	3·82 (1·40)	4·93 (1·38)	-1·11 (-1·60 to -0·63)**		<0·001**
All Samples					
Viral load below detection level, n/N (%)					
Day 5	20/238 (8%)	8/280 (3%)	5·78 (1·70 to 19·62) ††		0·005††
Day 7 ll	7/35 (20%)	2/40 (5%)	14·01 (1·06 to 184·75) ††		0·045††
Day 14	96/203 (47%)	134/241 (56%)	0·60 (0·31 to 1·14) ††		0·12††
log10Viral load, mean(SD)					
Day 5	4·88 (1·51)	5·89 (1·41)	-1·06 (-1·27 to -0·85)**		<0·001**
Day 7	3·86 (1·40)	4·85 (1·45)	-1·11 (-1·65 to -0·57)**		<0·001**
Day 14	2·72 (1·33)	2·41 (1·05)	0·27 (0·06 to 0·52)**		0·015**

* Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline, with 95% Bayesian credible interval. Odds Ration < 1 favours molnupiravir. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0·975 versus usual care.

†Estimated benefit in median time to recovery derived from a Bayesian piecewise exponential model adjusted for age and comorbidity at baseline, with 95% Bayesian credible interval. A positive value in estimated benefit in median time to recovery (or HR > 1) corresponds to a reduction in time to recovery in days in molnupiravir compared to Usual Care. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0.975 versus usual care.

‡ Bayesian logistic regression model adjusted for age, vaccination status, and comorbidity at baseline, with 95% Bayesian credible interval. Odds Ration > 1 favours molnupiravir. Pr(Superiority) is the probability of superiority and treatment superiority is declared if Pr(superiority) ≥ 0·975 versus usual care.

§ Linear mixed effect model adjusted for age, comorbidity and vaccination status· Participant fitted as a random effect. Estimated mean difference > 0 favours molnupiravir. Frequentist model estimates display P-value rather than a probability, P < 0.05 indicates statistical significance versus usual care.

ll Virology primary outcome

¶ Firth logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load)· Adjusted OR > 1 favours molnupiravir. Frequentist model estimates display P-value rather than a probability. P < 0.05 indicates statistical significance versus usual care.

**Mixed effect model adjusting for sex, age, and baseline $\log_{10}$(viral load); adjusted difference < 0 favours molnupiravir. Frequentist model estimates display P-value rather than a probability. P < 0.05 indicates statistical significance versus usual care.

†† Mixed effect logistic regression model adjusting for sex, age, and baseline log10(viral load); adjusted OR > 1 favours molnupiravir