STATISTICAL ANALYSIS PART 1 REPORT

Platform **A**daptive trial of **NO**vel antivi**R**als for e**A**rly treat**M**ent of covid-19 **I**n the **C**ommunity

Reference Number / Short title: PANORAMIC

MONUPIRAVIR

Ethics Ref: 21/SC/0393

IRAS Project ID: 1004274

EudraCT Number: 2021-005748-31

Based on protocol version 5.0 9th May 2022

Version 2.0 Date: 9th October 2023

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2 CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 BACKGROUND

The Center for Outcomes Research and Economic Evaluation for Health (C2H) is currently conducting a cost-effectiveness evaluation of molnupiravir as a part of the Japanese health technology assessment (HTA) process. The data from the PANORAMIC study(Butler CC, et al. Lancet. 2023:28;401:281-293) could potentially be the source to assess the additional benefit of molnupiravir in the Japanese setting. However, there are several differences between the study design of the PANORAMIC and the indication for molnupiravir in Japan. For example, molnupiravir is approved in Japan for the treatment of COVID-19 in adults with risk factors for severe COVID-19 whereas the PANORAMIC study included adults without these risk factors. Additionally, differences in the definition of standard of care also exist. In Japan, concomitant use of molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. Given these differences, the purpose of this report is to present the results of sub-group analysis of the PANORAMIC study in line with the indication and clinical practice of molnupiravir in Japan. The results are presented excluding both **A) participants without risk factors** and **B) participants using other COVID-19 medications at the prescription of molnupiravir**.

DISCLAIMER: Publication of the results presented in this report requires approval in writing to the Chief Investigators.

2 INTRODUCTION

This document details the analysis for the subgroup reporting results for the comparison of Molnupiravir with usual care from the PANORAMIC trial. The results reported in these papers follow the strategy set out in the statistical analysis plan. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

This report is based on the statistical analysis plan { **Subgroup analysis of PANORAMIC study in Japan_Plan2.docx**}. Any deviations from the statistical analysis plan will be described and justified in this report of the trial.

PANORAMIC-MOLNUPIRAVIR Statistical Analysis Part 2 Report Version 2.0

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2.1 SOFTWARE EMPLOYED

Analysis was carried out using STATA v18

3 METHODS

3.1 TRIAL OVERVIEW

Despite high uptake of vaccination against COVID-19, the disease remains prevalent in the UK and in many countries around the world, with many patients continuing to require hospital admission. COVID-19 causes considerable suffering, including loss of ability to perform activities of daily living, loss of educational and work opportunities, and inability to perform caring duties, with far reaching personal and societal consequences. Many go on to experience persisting and/or relapsing symptoms. People with underlying health conditions, unvaccinated people, and those in whom the vaccine is not effective are at increased risk of more severe disease. [11] New 'vaccine escaping' variants may yet emerge, and the impact of early antiviral treatment on long COVID syndromes is as yet unknown. Early treatment with antiviral agents may prevent progression to the later phase of COVID-19. Therefore, there is an urgent need to identify treatments for COVID-19 for use in the community early on in the illness that speeds recovery and prevents the need for hospital admission.

Antiviral agents may reduce viral shedding, and use of antiviral agents may lead to the emergence of resistance to novel antiviral agents, but the impact of novel antiviral agents on shedding and resistance is not yet known.

3.2 STUDY DESIGN

PANORAMIC is an open label, prospective, individually randomised, platform, adaptive, controlled clinical trial in community care. Trial arms will include:

Intervention arms: Novel antiviral agents (or combinations) targeting SARS-CoV-2, initially specified by The UK Antivirals National Taskforce (ATF) and with capacity for sequential introduction of each treatment regimen into the trial plus Usual Care. This report presents the primary and secondary analysis for the Molnupiravir arm.

Comparator arm: Usual Care, defined as the currently recommended treatment delivered by responsible clinicians. Usual Care was not mandated by the trial, as recommended treatments may change and be tailored to individual characteristics, and self-care will vary. Use of over the counter medication as well as key medications such as inhaled steroids and monoclonal antibodies was captured. In this report only usual care participants randomised concurrently and eligible to Molnupiravir were included.

3.3 Adaptive Design

The trial design allows for interim analysis and early stopping due to futility or efficacy and the addition or removal of interventions. The number and timing of interim analyses depends on the rate of recruitment. Full details of the design and decision criteria are given in the Adaptive Design Report. Due to rapid recruitment no interim analyses were carried out on the Molnupiravir arm. Paxlovid was added as an additional arm on 21st April 2022.

3.4 Objectives

Main Trial: The primary aim is to determine the effectiveness of selected antiviral agents in preventing hospitalisation and/or death in higher-risk patients with a confirmed positive PCR or LFT SARS-CoV-2 test result (see Inclusion/Exclusion Criteria, below).

Main Study	Objectives	Endpoint Measures	Timepoint (s)
Primary	To determine whether antiviral treatment in the community safely reduces non-elective hospitalisations/ deaths in higher risk, symptomatic patients with confirmed COVID-19	All cause, non-elective hospitalisation and/or death, within 28 days of randomisation	Within 28 days of randomisation Patient report, Study Partner report, HES/ONS/medical record data linkage
Secondary	To explore whether antiviral treatment affects 1) Time to recovery (defined as the first instance that a participant report of feeling recovered from the illness)	1-3) Participant reports symptoms daily for 28 days and at 3 and 6 months.	1-3) Daily online symptom scores. Telephone call or text on days 7, 14 and 28 if data is not obtained through the online diary.

	2) Participant reported illness severity, reported by daily rating of how well participant feels, enabling identification of sustained recovery. 3) Duration of severe symptoms and symptom recurrence, including time to alleviation of symptoms, time to initial reduction of severity of symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms and worsening of symptoms 4) Contacts with the health services	4) Contacts with health services reported by patients and/or captured by reports of patients' medical records	Also, at 3 and 6 months. 4) GP notes review if available through Oxford RCGP RSC network; otherwise, other sources of routinely collected data after 28 days. Medical notes review for up to 10 years.

	5) New infections in household	5) Reports of new infections in the household from daily diary	5) Daily online symptom scores or telephone call or text on days 7, 14 and 28
	6) To investigate the safety of antiviral agents	6) Evaluation of overall safety of drugs by the monitoring of adverse events (Aes as defined in the ISAs)	6) For the duration of the antiviral course and a defined period after the antiviral finishes (see ISAs)
	7) Longer term effects, including proportion with long covid, long covid symptoms, health care use and wellness	7) Well-being, symptoms and heath care utilisation	7) Patient contact at three and six months, electronic medical record search for up to one year
	8) Cost effectiveness	8) Resource use and cost data and EQ-5D-5L	8) Baseline and Day 28

3.5 TARGET POPULATION

The trial includes participants who test positive for SARS-CoV-2 infection and with ongoing symptoms consistent with COVID-19, not hospitalised, and who are aged 50 years and over, or 18-49 years and considered clinically vulnerable (see Inclusion Criteria below).

3.5.1 Inclusion Criteria

- Participant is able and willing to provide informed consent, or their legal representative is willing to provide informed consent
- Symptoms attributable to COVID-19 started within the past 5 days and ongoing
- A positive PCR or LFT SARS-CoV-2 test* Aged ≥50 years OR aged 18-49 years with one of the following known underlying chronic health condition considered to make them clinically vulnerable:
    - chronic respiratory disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis and asthma requiring at least daily use of preventative and/or reliever medication)
    - chronic heart or vascular disease
    - chronic kidney disease
    - chronic liver disease
    - chronic neurological disease (including dementia, stroke, epilepsy)
    - severe and profound learning disability
    - Down's syndrome
    - Diabetes mellitus (Type I or Type II)
    - immunosuppression: primary (e.g., inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood) or secondary due to disease or treatment (e.g., sickle cell, HIV, cancer, chemotherapy)
    - solid organ, bone marrow and stem cell transplant recipients
    - morbid obesity (BMI >35)
    - severe mental illness
    - care home resident
    - judged by recruiting clinician or research nurse (registered medical practitioner or trained study nurse) to be clinically vulnerable

* Any positive PCR test taken between two days before symptom onset and randomisation qualifies. A positive lateral flow test in a symptomatic person qualifies for randomisation and will be subject to pre-specified secondary analysis by type of diagnostic test.

3.5.2 EXCLUSION CRITERIA

- Patient currently admitted to hospital (inpatient)
- Previous randomisation in the PANORAMIC trial
- Currently participating in a clinical trial of a therapeutic agent for acute COVID-19
- Additional exclusions specific to each intervention arm, if any, as listed in the Intervention Specific Appendices (ISA's) of currently open trial arms

3.5.3 A RISK FACTORS

Risk factors for severe COVID-19 by the Ministry of Health, Labour and Welfare (MHLW) in Japan may not be available in the PANORAMIC study. Therefore, we propose the following 2 options to extract the data according to risk or modified risk factors that could be applicable to the Japanese setting.

1. Risk factors for severe COVID-19 defined by the Ministry of Health, Labour and Welfare (MHLW) is shown in Table 1.

TABLE 1 THE MHLW DEFINED RISK FACTORS FOR SEVERE COVID-19

Older adults aged ≥ 65 years	Hypertension	History of smoking
Malignant tumor	Dyslipidemia	Immunodeficiency after solid organ transplantation
Chronic respiratory disease (i.e., COPD)	Cardiovascular disease	Use of immunomodulatory agent or immunosuppressant
Chronic renal disease	Cerebrovascular disease	HIV infection (particularly CD4 < 200/μL)
Diabetes	Obesity (BMI ≥ 30 kg/m^2)	

Clinical Management of Patients with COVID-19 in Japan version 9.0 (In Japanese)

(https://www.mhlw.go.jp/content/000936655.pdf)

The diagnostic criteria for each risk factor have not been clearly indicated.

2. The modified definition of risk factors for severe COVID-19 is shown in Table 2. By reviewing the article of the PANORAMIC study, we believe that we could define the modified risk factors as follows:

TABLE 2 THE MODIFIED DEFINITION OF RISK FACTORS FOR SEVERE COVID-19

Risk factor	Details
Age	● Older adults aged ≥ 65 years
Asthma	
Cancer	● Hematologic malignancies
Cerebrovascular disease	
Chronic kidney disease	● People receiving dialysis
Chronic lung diseases limited to:	● Bronchiectasis ● COPD (Chronic obstructive pulmonary disease) ● Interstitial lung disease ● Pulmonary embolism ● Pulmonary hypertension
Chronic liver diseases limited to:	● Cirrhosis ● Non-alcoholic fatty liver disease ● Alcoholic liver disease ● Autoimmune hepatitis
Cystic fibrosis	
Diabetes mellitus, type 1	
Diabetes mellitus, type 2	
Down syndrome	
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	
HIV (Human immunodeficiency virus)	
Mental health conditions limited to:	● Mood disorders, including depression ● Schizophrenia spectrum disorders
Neurologic conditions limited to dementia	
Obesity	● BMI ≥ 30 kg/m^2
Physical inactivity	

Primary immunodeficiencies

Smoking, current and former

Solid organ or blood stem cell transplantation

Tuberculosis

Use of corticosteroids or other immunosuppressive medications

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Risk factors have been defined by CDC criteria(https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html). We only extracted factors categorized into "Higher Risk (conclusive)" from the CDC criteria.

Clinical Management of Patients with COVID-19 in Japan version 10.0 (001136687.pdf (mhlw.go.jp))(In Japanese).

Disabilities were excluded from a risk factor.

a: Obesity was originally defined as BMI ≥ 35 kg/m^2 in the PANORAMIC study.

TABLE 3 THE DIAGNOSTIC CRITERIA FOR EACH RISK FACTOR IN THE PANORAMIC STUDY

Risk factor	Diagnostic criteria or definition
Older adults aged ≥ 65 years	Aged ≥ 65 years
Asthma	From free text and collected under lung disease.
Cancer (Hematologic malignancies)	From free text only. Mentions "blood cancer".
Cerebrovascular disease	From free text, mentions "stroke" or "cerebral aneurysm"
Chronic kidney disease (People receiving dialysis)	Collected as "long term kidney disease", not clear if receiving dialysis. Have counted anyone who has this checked.
Bronchiectasis	Collect "long term lung disease (including chronic obstructive pulmonary disease (COPD), cystic fibrosis or asthma requiring at least daily use of inhalers)".
COPD (Chronic obstructive pulmonary disease)	Collected as lung disease
Interstitial lung disease	Collected as lung disease
Pulmonary embolism	Collected as lung disease
Pulmonary hypertension	Collected as lung disease
Cirrhosis	Collected as liver disease
Non-alcoholic fatty liver disease	Collected as liver disease
Alcoholic liver disease	Collected as liver disease
Autoimmune hepatitis	Collected as liver disease
Cystic fibrosis	Collected as lung disease
Diabetes mellitus, type 1	Collected as diabetes, not separated by type.
Diabetes mellitus, type 2	Collected as diabetes, not separated by type.
Down syndrome	Down syndrome
Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)	Defined as long term heart or vascular disease
HIV (Human immunodeficiency virus)	Comes under weakened immune system or free text mentions HIV
Mood disorders, including depression	Collected under severe mental health disorder
Schizophrenia spectrum disorders	Free text mentions "Schizoaffective disorder" or collected under severe mental health disorder
Neurologic conditions limited to dementia	Collected as long term neurological disease (including dementia, stroke, epilepsy).
Obesity (BMI ≥ 30 kg/m^2)	Defined as BMI≥ 35 kg/m^2
Physical inactivity	Not collected
Primary immunodeficiencies	Collected as weakened immune system due to a condition you were born with or due to disease or treatment (e.g. sickle cell, HIV, cancer, chemotherapy)
Smoking, current and former	Current only
Solid organ or blood stem cell transplantation	Collected as transplant
Tuberculosis	Not collected, no free text.
Use of corticosteroids or other immunosuppressive medications	Free text mentions "steroids" or "immunosuppressant"

3.5.4 CONCOMITANT USE OF OTHER COVID-19 MEDICATIONS

In Japan, concomitant use of molnupiravir with other COVID-19 medications (e.g., remdesivir) is not recommended. We would like to exclude adults taking the following medications at the prescription of molnupiravir (Table 4) from the dataset. On the other hand, we consider that adults using the following medications **after the completion of treatment with molnupiravir** should not be excluded from the analysis because they are most likely to have progressed to severe COVID-19 (e.g., adults prescribed the following medications 10 days after a prescription for molnupiravir, adults who stopped treatment with molnupiravir within 5 days and subsequently received the following medications).

TABLE 4 THE DEFINITION OF OTHER COVID-19 MEDICATIONS

Remdesivir	Tixagevimab/cilgavimab	Any other neutralizing antibody for COVID-19
Nirmatrelvir/ritonavir	Tocilizumab	Any other immunosuppressive medications for COVID-19
Ensitrelvir	Baricitinib	Favipiravir
Casirivimab/imdevimab	Dexamethasone	Ivermectin
Sotrovimab	Any other antiviral medications for COVID-19	

3.6 INTERVENTIONS

Based on version 5.0 of the Protocol, the main randomisation was between the following treatment arms (although not all treatments were available at all times and not all participants were eligible for all treatments). However, the trial design accommodates interventions being added and dropped as appropriate.

- Usual care
- Molnupiravir (recruitment between 8th December 2021 and 27th April 2022)
- PAXLOVID (recruitment started 21st April 2022)

3.7 OUTCOMES

3.7.1 PRIMARY OUTCOME

The primary outcome is all-cause, non-elective hospitalisation and/or death within 28 days of randomisation.

3.7.2 SECONDARY OUTCOMES

Secondary outcomes include time to self-reported recovery defined as the first instance that a participant reports feeling fully recovered from the illness; duration of symptoms; symptom recurrence; daily rating of feeling well reported by participants; healthcare service use; participant reported household infection rate; safety outcomes and cost-effectiveness outcomes; symptoms and well-being at three and six months (with determination of proportion with Long Covid) from randomisation.

3.7.2.1 TIME TO RECOVERY

Time to recovery from COVID-19 infection within 28 days from randomisation, where recovery is defined as the first instance that a participant reported feeling recovered.

3.7.2.2 PATIENT REPORTED ILLNESS SEVERITY

Participants are asked to rate how well they are feeling overall each day on a scale of 1-10 (1 being the worst and 10 being the best). This is captured on the patients' daily diaries and the Call CRF.

3.7.2.3 DURATION OF SEVERE SYMPTOMS AND SYMPTOM RECURRENCE

Participants are asked to rate their symptoms of fever, cough, shortness of breath, fatigue (tiredness), muscle ache, nausea / vomiting, diarrhoea, loss of smell and/or taste, headache, dizziness, abdominal pain and generally feeling unwell on a four point scale from 0=no problem, 1=mild problem, 2=moderate problem and 3=major problem.

This is captured on patients' daily diaries and Call CRF.

The outcomes to be analysed include time to alleviation of symptoms, time to initial reduction in severe symptoms, time to sustained recovery, time to sustained alleviation of symptoms, number of days of severe symptoms, number reporting severe symptoms at days 7, 14 and 28, symptom recurrence and worsening of symptoms.

3.7.2.4 CONTACTS WITH HEALTH SERVICES BETWEEN RANDOMISATION AND DAY 28 OF FOLLOW-UP (FU).

This is captured on patients' daily diaries and telephone call CRFs.

3.7.2.5 NEW INFECTIONS IN THE HOUSEHOLD

Number of new infections within the household are captured within the participant daily diaries and call CRF.

3.7.2.6 SAFETY OF ANTIVIRAL AGENTS

Common side effects, according to the SmPC, include dizziness, headache, diarrhoea, and nausea. These symptoms, potential medication side-effects and Serious Adverse Events (SAE) were collected from participant daily diaries, calls to participants/Study Partners, face-to-face visits with Hub clinicians, medical records, notes reviews, NHS Digital data extracts and RCGP data downloads.

Pregnancy was recorded as an AE of Special Interest and was monitored from the start of treatment for the 28-day trial duration.

3.7.2.7 LONGER TERM EFFECTS: SYMPTOMS AND WELL-BEING AT 3 AND 6 MONTHS

The primary analysis is based on data collected through 28 days from randomisation; however additional outcomes will be collected at 3 and 6 months follow-up to capture the

long term outcomes of participants. This report covers outcomes for the first 28 days follow-up. The long term follow-up analysis will be covered in a future report.

3.7.2.8 HEALTHCARE MEASURES (EQ-5D-5L)

The EQ-5D-5L is a questionnaire consisting of 5 items (crosswalk) and a scale from 0 to 100 (VAS) defining overall health. These were captured in participant's daily diaries and call CRF. Cost effectiveness outcomes will be reported in a separate health economic analysis report and the analysis of this outcome will be described in a separate health economic analysis plan.

3.8 SAMPLE SIZE

The sample size calculation as stated in the protocol:

An estimated maximum of approximately 5300 participants per arm will be required to provide approximately 90% power for detecting a 33% relative reduction in the hospitalisation/death in an experimental arm relative to Usual Care, based on the assumption of an underlying 3% combined hospitalisation/death rate in the Usual Care arm, and an intervention lowering the hospitalisation/death rate to 2%. We expect fewer participants will be needed to detect the same relative reduction if the event rate is larger than 3% in the Usual Care arm, or if there is a greater reduction in the relative risk of hospitalisation/death for a given intervention. However, should the event rate be lower than expected, then the target sample size will be increased to reflect this.

We recruited 25783 for the comparison of Molnupiravir with Usual Care.

3.9 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Participants were randomised using a secure, fully validated and compliant web-based randomisation system. Once deemed eligible, the medically qualified clinician or research nurse from the central clinical team or Hub (as documented on the delegation log) randomised the participant. Participants were randomised to one study arm using equal allocation ratios corresponding to the number of arms they were eligible for that were recruiting in the trial at that time. This started as 1:1 Molnupiravir:Usual Care, and once Paxlovid was introduced on 21st April 2022 changed to 1:1:1 Molnupiravir:Usual Care:Paxlovid. Patients had to be eligible for at least two arms (Usual Care and at least one novel antiviral intervention). Stratification was by age (< 50/ ≥ 50 years) and vaccination status (see 2.2.3).

The randomisation database automatically alerted the relevant IMP distributor and the participant, trial team and legal representative if applicable were notified electronically of the treatment allocation. If the participant did not have an email address, they were notified by telephone.

3.10 Definition of population for analysis

The analysis population will include participants as defined by the protocol eligibility criteria and having at least one of the vulnerabilities as listed in Table 3.

As per ICH E9 guidance the following participants will be excluded from the analysis population;

(a) Participants randomised but subsequently found to be not eligible for randomization

(b) Participants previously randomised to an arm in the PANORAMIC trial (subsequent randomisations will be excluded)

In addition, the following participants will be excluded;

(c) Participants who withdraw consent for data linkage and notes review and for whom no outcome data has been collected.

(d) Participants taking medications listed in Table 4

3.10.1.1 Primary analysis population

The primary analysis population is defined as participants who were randomised to Molnupiravir or usual care and were eligible for randomisation to Molnupiravir, during the same time frame when Molnupiravir was actively randomising (i.e. Concurrent Randomised and Eligible Analysis Population). That is, participants who were eligible for Molnupiravir and randomised to either Molnupiravir or usual care between 8th December 2021 and 27th April 2022.

This includes participants for whom data are available with participants analysed according to the groups they were randomly allocated to, regardless of deviation from protocol.

3.10.1.2 Secondary analysis population

Analysis of the secondary outcomes for a given intervention will be based on the same population as the primary analysis.

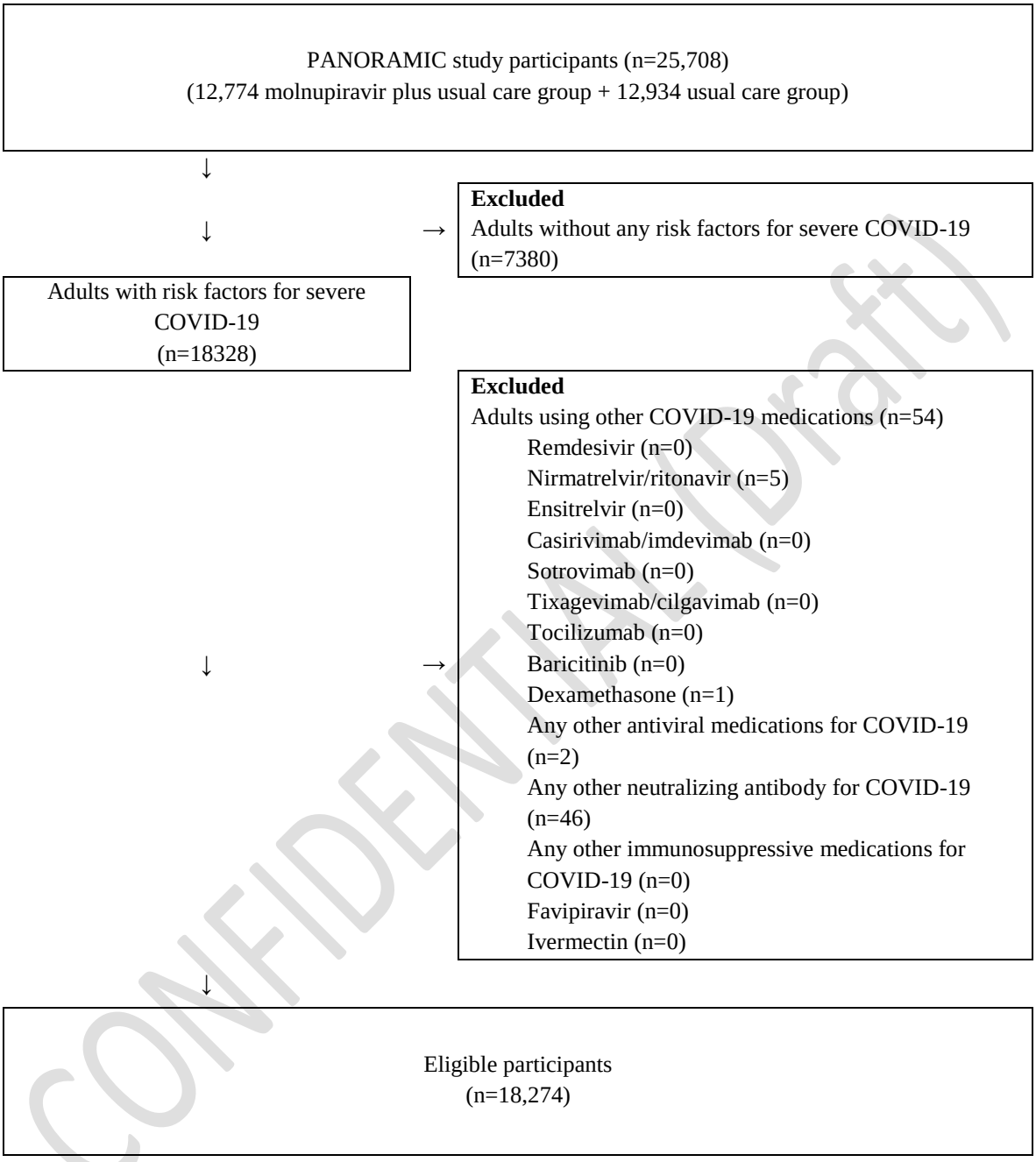
4 RESULTS

4.1 RECRUITMENT

Randomisation to the Molnupiravir arm was stopped on 27th April 2022. Participants randomised to the Molnupiravir arm and Usual Care between 8th December 2021 and 27th April 2022 (inclusive) are included in this report (see SAP for more details). During this time 111,383 participants were screened, 44,073 of whom were not eligible on screening and a further 41,517 were excluded after GP eligibility check (see CONSORT in appendix for reasons). 25,793 in total were randomised, of which 25,783 were randomised between Molnupiravir and Usual Care and were eligible for randomisation to Molnupiravir. 504 participants were randomised to other arms or randomised to Usual Care and not eligible for Molnupiravir. 75 participants were excluded from the analysis population as they were found to be ineligible after randomisation, leaving 25,708 participants in the analysis population.

Figure 2 shows the flow of participants for the subgroup analysis as presented in this report. 7380 participants were excluded as they did not have any risk factors for severe COVID-19 and a further 54 were excluded due to taking other medications. This leaves 18,274 in the subgroup analysis population.

FIGURE 1 FLOW DIAGRAM OF TRIAL PARTICIPANTS FOR THE SUBGROUP POPULATION



4.2 BASELINE CHARACTERISTICS OF PARTICIPANTS

Baseline characteristics by randomised group and overall are given in Table 5 for the concurrent and eligible population.

TABLE 5 BASELINE CHARACTERISTIC BY RANDOMISED GROUP

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Age, mean(SD) [min,max]	56.7 (12.5) [18.0 to 99.0]	56.5 (12.7) [18.0 to 98.0]	56.6 (12.6) [18.0 to 99.0]
Sex, n(%)			
Female	7451 (58.1%)	7650 (59.0%)	15101 (58.6%)
Male	5367 (41.9%)	5308 (41.0%)	10675 (41.4%)
Other	3 (0.0%)	4 (0.0%)	7 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0)	N/A	2.0 (2.0 to 2.0)
Days from start of symptoms to taking medication*, median(IQR)	5.0 (4.0 to 6.0)	N/A	5.0 (4.0 to 6.0)
Missing, n(%)	288 (1.1%)		
Ethnicity category, n(%)			
White	12088 (94.3%)	12182 (94.0%)	24270 (94.1%)
Asian	366 (2.9%)	434 (3.3%)	800 (3.1%)
Mixed Race	203 (1.6%)	189 (1.5%)	392 (1.5%)
Black	78 (0.6%)	77 (0.6%)	155 (0.6%)
Other	86 (0.7%)	80 (0.6%)	166 (0.6%)
NHS priority category, n(%)			
Aged ≥80	259 (2.0%)	272 (2.1%)	531 (2.1%)
Aged ≥75 and <80	539 (4.2%)	577 (4.5%)	1116 (4.3%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1117 (8.7%)	1114 (8.6%)	2231 (8.7%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1496 (11.7%)	1464 (11.3%)	2960 (11.5%)
Aged ≥18 and <65 in an at risk group	6541 (51.0%)	6591 (50.8%)	13132 (50.9%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	746 (5.8%)	768 (5.9%)	1514 (5.9%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	997 (7.8%)	1063 (8.2%)	2060 (8.0%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	1126 (8.8%)	1113 (8.6%)	2239 (8.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	2491 (19.4%)	2558 (19.7%)	5049 (19.6%)
2	2679 (20.9%)	2636 (20.3%)	5315 (20.6%)
3	2524 (19.7%)	2660 (20.5%)	5184 (20.1%)
4	2784 (21.7%)	2767 (21.3%)	5551 (21.5%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
5 (highest risk)	2343 (18.3%)	2341 (18.1%)	4684 (18.2%)
Confirmed PCR positive, n(%)	5965 (46.5%)	5902 (45.5%)	11867 (46.0%)
IMD quintile, n(%)			
(Most deprived) 1	1234 (9.6%)	1182 (9.1%)	2416 (9.4%)
2	1913 (14.9%)	1956 (15.1%)	3869 (15.0%)
3	2569 (20.0%)	2592 (20.0%)	5161 (20.0%)
4	3216 (25.1%)	3213 (24.8%)	6429 (24.9%)
(Least deprived) 5	3839 (29.9%)	3960 (30.6%)	7799 (30.2%)
Missing, n(%)	50 (0.4%)	59 (0.5%)	109 (0.4%)
Took at least 4 doses IMP, n(%)	11892 (92.8%)	N/A	11892 (46.1%)
Received vaccination, n(%)	12678 (98.9%)	12830 (99.0%)	25508 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	87 (0.7%)	88 (0.7%)	175 (0.7%)
2	519 (4.0%)	458 (3.5%)	977 (3.8%)
3	11836 (92.3%)	12044 (92.9%)	23880 (92.6%)
4	236 (1.8%)	240 (1.9%)	476 (1.8%)
Data unavailable, n(%)	143 (1.1%)	132 (1.0%)	275 (1.1%)
Smoker, n(%)	795 (6.2%)	805 (6.2%)	1600 (6.2%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	6111 (47.7%)	6125 (47.3%)	12236 (47.5%)
Minor problem	4514 (35.2%)	4684 (36.1%)	9198 (35.7%)
Moderate problem	1936 (15.1%)	1896 (14.6%)	3832 (14.9%)
Major problem	260 (2.0%)	257 (2.0%)	517 (2.0%)
Fatigue, n(%)			
No problem	1251 (9.8%)	1216 (9.4%)	2467 (9.6%)
Minor problem	4721 (36.8%)	4853 (37.4%)	9574 (37.1%)
Moderate problem	5083 (39.6%)	5127 (39.6%)	10210 (39.6%)
Major problem	1766 (13.8%)	1766 (13.6%)	3532 (13.7%)
Muscle ache, n(%)			
No problem	3479 (27.1%)	3425 (26.4%)	6904 (26.8%)
Minor problem	4504 (35.1%)	4791 (37.0%)	9295 (36.1%)
Moderate problem	3763 (29.4%)	3684 (28.4%)	7447 (28.9%)
Major problem	1075 (8.4%)	1062 (8.2%)	2137 (8.3%)
Vomiting, n(%)			
No problem	10440 (81.4%)	10503 (81.0%)	20943 (81.2%)
Minor problem	1847 (14.4%)	1913 (14.8%)	3760 (14.6%)
Moderate problem	478 (3.7%)	477 (3.7%)	955 (3.7%)
Major problem	56 (0.4%)	69 (0.5%)	125 (0.5%)
Diarrhoea, n(%)			
No problem	10600 (82.7%)	10732 (82.8%)	21332 (82.7%)
Minor problem	1649 (12.9%)	1681 (13.0%)	3330 (12.9%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
Moderate problem	471 (3.7%)	457 (3.5%)	928 (3.6%)
Major problem	101 (0.8%)	92 (0.7%)	193 (0.7%)
Loss of smell or taste, n(%)			
No problem	9066 (70.7%)	9402 (72.5%)	18468 (71.6%)
Minor problem	2484 (19.4%)	2368 (18.3%)	4852 (18.8%)
Moderate problem	825 (6.4%)	800 (6.2%)	1625 (6.3%)
Major problem	446 (3.5%)	392 (3.0%)	838 (3.3%)
Headache, n(%)			
No problem	2702 (21.1%)	2820 (21.8%)	5522 (21.4%)
Minor problem	5194 (40.5%)	5215 (40.2%)	10409 (40.4%)
Moderate problem	3783 (29.5%)	3838 (29.6%)	7621 (29.6%)
Major problem	1142 (8.9%)	1089 (8.4%)	2231 (8.7%)
Dizziness, n(%)			
No problem	8446 (65.9%)	8382 (64.7%)	16828 (65.3%)
Minor problem	3087 (24.1%)	3295 (25.4%)	6382 (24.8%)
Moderate problem	1096 (8.5%)	1087 (8.4%)	2183 (8.5%)
Major problem	192 (1.5%)	198 (1.5%)	390 (1.5%)
Abdominal pain, n(%)			
No problem	10391 (81.0%)	10440 (80.5%)	20831 (80.8%)
Minor problem	1834 (14.3%)	1920 (14.8%)	3754 (14.6%)
Moderate problem	524 (4.1%)	542 (4.2%)	1066 (4.1%)
Major problem	72 (0.6%)	60 (0.5%)	132 (0.5%)
Generally unwell, n(%)			
No problem	525 (4.1%)	535 (4.1%)	1060 (4.1%)
Minor problem	5028 (39.2%)	5145 (39.7%)	10173 (39.5%)
Moderate problem	5789 (45.2%)	5838 (45.0%)	11627 (45.1%)
Major problem	1479 (11.5%)	1444 (11.1%)	2923 (11.3%)
Fever, n(%)			
No problem	5670 (44.2%)	5765 (44.5%)	11435 (44.4%)
Minor problem	4813 (37.5%)	4955 (38.2%)	9768 (37.9%)
Moderate problem	2107 (16.4%)	2042 (15.8%)	4149 (16.1%)
Major problem	231 (1.8%)	200 (1.5%)	431 (1.7%)
Cough, n(%)			
No problem	1410 (11.0%)	1343 (10.4%)	2753 (10.7%)
Minor problem	6153 (48.0%)	6384 (49.3%)	12537 (48.6%)
Moderate problem	4502 (35.1%)	4509 (34.8%)	9011 (34.9%)
Major problem	756 (5.9%)	726 (5.6%)	1482 (5.7%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.2 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1660 (12.9%)	1660 (12.8%)	3320 (12.9%)
1	6113 (47.7%)	6019 (46.4%)	12132 (47.1%)

	Molnupiravir plus usual care (N=12821)	Usual Care (N=12962)	Overall (N=25783)
2	2129 (16.6%)	2176 (16.8%)	4305 (16.7%)
3	1765 (13.8%)	1979 (15.3%)	3744 (14.5%)
4	808 (6.3%)	772 (6.0%)	1580 (6.1%)
Taking inhaled corticosteroids, n(%)	2990 (23.3%)	3152 (24.3%)	6142 (23.8%)
Taking inhaled corticosteroids for COVID, n(%)	183 (1.4%)	158 (1.2%)	341 (1.3%)
Monoclonal antibodies for COVID, n(%)	26 (0.2%)	19 (0.1%)	45 (0.2%)
Comorbidities			
Lung disease	3014 (23.5%)	3171 (24.5%)	6185 (24.0%)
Heart disease	1000 (7.8%)	957 (7.4%)	1957 (7.6%)
Kidney disease	227 (1.8%)	253 (2.0%)	480 (1.9%)
Liver disease	159 (1.2%)	144 (1.1%)	303 (1.2%)
Neurological disease	430 (3.4%)	438 (3.4%)	868 (3.4%)
Learning disability	36 (0.3%)	27 (0.2%)	63 (0.2%)
Down's syndrome'	24 (0.2%)	30 (0.2%)	54 (0.2%)
Diabetes	1483 (11.6%)	1512 (11.7%)	2995 (11.6%)
Weakened immune system	1125 (8.8%)	1070 (8.3%)	2195 (8.5%)
Transplant recipient	57 (0.4%)	71 (0.5%)	128 (0.5%)
Obesity	1968 (15.3%)	1944 (15.0%)	3912 (15.2%)
Mental illness	198 (1.5%)	220 (1.7%)	418 (1.6%)
Hypertension	2880 (22.5%)	2902 (22.4%)	5782 (22.4%)
Other vulnerability	2295 (17.9%)	2341 (18.1%)	4636 (18.0%)

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

TABLE 6 BASELINE CHARACTERISTIC OF THE SUBGROUP POPULATION BY RANDOMISED GROUP

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Age, mean(SD) [min,max]	56.9 (14.4) [18.0 to 99.0]	56.7 (14.7) [18.0 to 98.0]	56.8 (14.5) [18.0 to 99.0]
Sex, n(%)			
Female	5267 (57.8%)	5319 (58.1%)	10586 (57.9%)
Male	3851 (42.2%)	3832 (41.9%)	7683 (42.0%)
Other	2 (0.0%)	3 (0.0%)	5 (0.0%)
Days from randomisation to reporting receipt of medication*, median(IQR)	2.0 (2.0 to 2.0) [0.0 to 7.0]	N/A	2.0 (2.0 to 2.0) [0.0 to 7.0]
Days from start of symptoms to taking medication*, median(IQR)	4.0 (3.0 to 5.0) [1.0 to 29.0]	N/A	4.0 (3.0 to 5.0) [1.0 to 29.0]
Data unavailable, n(%)	7163 (78.5%)	0 (0.0%)	7163 (39.2%)
Ethnicity category, n(%)			
White	8589 (94.2%)	8596 (93.9%)	17185 (94.0%)
Asian	257 (2.8%)	318 (3.5%)	575 (3.1%)
Mixed Race	150 (1.6%)	138 (1.5%)	288 (1.6%)
Black	54 (0.6%)	52 (0.6%)	106 (0.6%)
Other	70 (0.8%)	50 (0.5%)	120 (0.7%)
NHS priority category, n(%)			
Aged ≥80	256 (2.8%)	271 (3.0%)	527 (2.9%)
Aged ≥75 and <80	537 (5.9%)	573 (6.3%)	1110 (6.1%)
Aged ≥70 and <75 OR Aged ≥18 and <70 and clinically extremely vulnerable	1115 (12.2%)	1108 (12.1%)	2223 (12.2%)
Aged ≥65 and <70 and not clinically extremely vulnerable	1488 (16.3%)	1463 (16.0%)	2951 (16.1%)
Aged ≥18 and <65 in an at risk group	5577 (61.2%)	5582 (61.0%)	11159 (61.1%)
Aged ≥60 and <65 and not clinically extremely vulnerable or in an at risk group	37 (0.4%)	35 (0.4%)	72 (0.4%)
Aged ≥55 and <60 and not clinically extremely vulnerable or in an at risk group	43 (0.5%)	56 (0.6%)	99 (0.5%)
Aged ≥50 and <55 and not clinically extremely vulnerable or in an at risk group	67 (0.7%)	66 (0.7%)	133 (0.7%)
Predicted risk quintile, n(%)			
1 (lowest risk)	623 (6.8%)	633 (6.9%)	1256 (6.9%)
2	1810 (19.8%)	1780 (19.4%)	3590 (19.6%)
3	2108 (23.1%)	2157 (23.6%)	4265 (23.3%)
4	2442 (26.8%)	2439 (26.6%)	4881 (26.7%)
5 (highest risk)	2137 (23.4%)	2145 (23.4%)	4282 (23.4%)
Confirmed PCR positive, n(%)	4267 (46.8%)	4161 (45.5%)	8428 (46.1%)
IMD quintile, n(%)			
(Most deprived) 1	985 (10.8%)	930 (10.2%)	1915 (10.5%)
2	1427 (15.6%)	1466 (16.0%)	2893 (15.8%)
3	1838 (20.2%)	1833 (20.0%)	3671 (20.1%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
4	2248 (24.6%)	2238 (24.4%)	4486 (24.5%)
(Least deprived) 5	2590 (28.4%)	2640 (28.8%)	5230 (28.6%)
Data unavailable, n(%)	32 (0.4%)	47 (0.5%)	79 (0.4%)
Took at least 4 doses IMP, n(%)	8412 (92.2%)		8412 (46.0%)
Received vaccination, n(%)	9015 (98.8%)	9064 (99.0%)	18079 (98.9%)
Number of COVID-19 vaccine doses, n(%)			
1	67 (0.7%)	72 (0.8%)	139 (0.8%)
2	369 (4.0%)	329 (3.6%)	698 (3.8%)
3	8361 (91.7%)	8440 (92.2%)	16801 (91.9%)
4	218 (2.4%)	223 (2.4%)	441 (2.4%)
Data unavailable, n(%)	105 (1.2%)	90 (1.0%)	195 (1.1%)
Smoker, n(%)	787 (8.6%)	799 (8.7%)	1586 (8.7%)
Baseline Symptoms			
Shortness of breath, n(%)			
No problem	4011 (44.0%)	3948 (43.1%)	7959 (43.6%)
Minor problem	3289 (36.1%)	3393 (37.1%)	6682 (36.6%)
Moderate problem	1585 (17.4%)	1577 (17.2%)	3162 (17.3%)
Major problem	235 (2.6%)	236 (2.6%)	471 (2.6%)
Fatigue, n(%)			
No problem	853 (9.4%)	836 (9.1%)	1689 (9.2%)
Minor problem	3251 (35.6%)	3254 (35.5%)	6505 (35.6%)
Moderate problem	3672 (40.3%)	3694 (40.4%)	7366 (40.3%)
Major problem	1344 (14.7%)	1370 (15.0%)	2714 (14.9%)
Muscle ache, n(%)			
No problem	2501 (27.4%)	2384 (26.0%)	4885 (26.7%)
Minor problem	3051 (33.5%)	3295 (36.0%)	6346 (34.7%)
Moderate problem	2724 (29.9%)	2649 (28.9%)	5373 (29.4%)
Major problem	844 (9.3%)	826 (9.0%)	1670 (9.1%)
Vomiting, n(%)			
No problem	7361 (80.7%)	7340 (80.2%)	14701 (80.4%)
Minor problem	1339 (14.7%)	1381 (15.1%)	2720 (14.9%)
Moderate problem	380 (4.2%)	371 (4.1%)	751 (4.1%)
Major problem	40 (0.4%)	62 (0.7%)	102 (0.6%)
Diarrhoea, n(%)			
No problem	7414 (81.3%)	7476 (81.7%)	14890 (81.5%)
Minor problem	1237 (13.6%)	1249 (13.6%)	2486 (13.6%)
Moderate problem	380 (4.2%)	358 (3.9%)	738 (4.0%)
Major problem	89 (1.0%)	71 (0.8%)	160 (0.9%)
Loss of smell or taste, n(%)			
No problem	6379 (69.9%)	6567 (71.7%)	12946 (70.8%)
Minor problem	1791 (19.6%)	1686 (18.4%)	3477 (19.0%)
Moderate problem	614 (6.7%)	600 (6.6%)	1214 (6.6%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Major problem	336 (3.7%)	301 (3.3%)	637 (3.5%)
Headache, n(%)			
No problem	1912 (21.0%)	2015 (22.0%)	3927 (21.5%)
Minor problem	3630 (39.8%)	3570 (39.0%)	7200 (39.4%)
Moderate problem	2718 (29.8%)	2734 (29.9%)	5452 (29.8%)
Major problem	860 (9.4%)	835 (9.1%)	1695 (9.3%)
Dizziness, n(%)			
No problem	5820 (63.8%)	5748 (62.8%)	11568 (63.3%)
Minor problem	2286 (25.1%)	2373 (25.9%)	4659 (25.5%)
Moderate problem	855 (9.4%)	864 (9.4%)	1719 (9.4%)
Major problem	159 (1.7%)	169 (1.8%)	328 (1.8%)
Abdominal pain, n(%)			
No problem	7311 (80.2%)	7280 (79.5%)	14591 (79.8%)
Minor problem	1329 (14.6%)	1410 (15.4%)	2739 (15.0%)
Moderate problem	417 (4.6%)	417 (4.6%)	834 (4.6%)
Major problem	63 (0.7%)	47 (0.5%)	110 (0.6%)
Generally unwell, n(%)			
No problem	383 (4.2%)	381 (4.2%)	764 (4.2%)
Minor problem	3449 (37.8%)	3521 (38.5%)	6970 (38.1%)
Moderate problem	4160 (45.6%)	4138 (45.2%)	8298 (45.4%)
Major problem	1128 (12.4%)	1114 (12.2%)	2242 (12.3%)
Fever, n(%)			
No problem	3990 (43.8%)	4052 (44.3%)	8042 (44.0%)
Minor problem	3428 (37.6%)	3481 (38.0%)	6909 (37.8%)
Moderate problem	1541 (16.9%)	1464 (16.0%)	3005 (16.4%)
Major problem	161 (1.8%)	157 (1.7%)	318 (1.7%)
Cough, n(%)			
No problem	1004 (11.0%)	937 (10.2%)	1941 (10.6%)
Minor problem	4242 (46.5%)	4352 (47.5%)	8594 (47.0%)
Moderate problem	3277 (35.9%)	3291 (36.0%)	6568 (35.9%)
Major problem	597 (6.5%)	574 (6.3%)	1171 (6.4%)
Wellness score, mean(SD) [min,max]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]	5.1 (1.7) [0.0 to 10.0]
People in household, n(%)			
0	1245 (13.7%)	1236 (13.5%)	2481 (13.6%)
1	4489 (49.2%)	4368 (47.7%)	8857 (48.5%)
2	1376 (15.1%)	1409 (15.4%)	2785 (15.2%)
3	1156 (12.7%)	1309 (14.3%)	2465 (13.5%)
4	580 (6.4%)	547 (6.0%)	1127 (6.2%)
5	274 (3.0%)	285 (3.1%)	559 (3.1%)
Taking inhaled corticosteroids, n(%)	2848 (31.2%)	3010 (32.9%)	5858 (32.1%)

	Molnupiravir plus usual care (N=9120)	Usual Care (N=9154)	Overall (N=18274)
Taking inhaled corticosteroids for COVID, n(%)	159 (1.7%)	143 (1.6%)	302 (1.7%)
Monoclonal antibodies for COVID, n(%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Comorbidities			
Lung disease	2989 (32.8%)	3161 (34.5%)	6150 (33.7%)
Heart disease	993 (10.9%)	952 (10.4%)	1945 (10.6%)
Kidney disease	222 (2.4%)	253 (2.8%)	475 (2.6%)
Liver disease	158 (1.7%)	143 (1.6%)	301 (1.6%)
Neurological disease	423 (4.6%)	432 (4.7%)	855 (4.7%)
Learning disability	33 (0.4%)	27 (0.3%)	60 (0.3%)
Down's syndrome'	24 (0.3%)	29 (0.3%)	53 (0.3%)
Diabetes	1473 (16.2%)	1507 (16.5%)	2980 (16.3%)
Weakened immune system	1110 (12.2%)	1055 (11.5%)	2165 (11.8%)
Transplant recipient	50 (0.5%)	60 (0.7%)	110 (0.6%)
Obesity	1957 (21.5%)	1932 (21.1%)	3889 (21.3%)
Mental illness	196 (2.1%)	220 (2.4%)	416 (2.3%)
Hypertension	2285 (25.1%)	2303 (25.2%)	4588 (25.1%)
Other vulnerability	1886 (20.7%)	1883 (20.6%)	3769 (20.6%)

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

TABLE 7 PREVALENCE OF RISK FACTORS FOR SEVERE COVID-19 (MODIFIED DEFINITION) AMONG ELIGIBLE PARTICIPANTS

	Molnupiravir plus usual care (n=9120)	Usual care (n=9154)
Risk factors		
Older adults aged ≥ 65 years	3396 (37.2%)	3415 (37.3%)
Asthma	233 (2.6%)	290 (3.2%)
Cancer (Hematologic malignancies)	1 (0.0%)	1 (0.0%)
Stroke	16 (0.2%)	24 (0.3%)
Aneurysm	1 (0.0%)	0 (0.0%)
Kidney disease	222 (2.4%)	253 (2.8%)
Lung disease	2989 (32.8%)	3161 (34.5%)
Liver disease	158 (1.7%)	143 (1.6%)
Diabetes	1473 (16.2%)	1507 (16.5%)
Down syndrome	24 (0.3%)	29 (0.3%)
Heart disease	993 (10.9%)	952 (10.4%)
Immune disease	1110 (12.2%)	1055 (11.5%)
Mental illness	196 (2.1%)	220 (2.4%)
Neurologic conditions	423 (4.6%)	432 (4.7%)
Obesity (BMI ≥ 35 kg/m^2)	1957 (21.5%)	1932 (21.1%)
Current smoker	787 (8.6%)	799 (8.7%)
Transplant	50 (0.5%)	60 (0.7%)
Use of corticosteroids or other immunosuppressive medications	28 (0.3%)	37 (0.4%)

4.3 NUMBER ANALYSED

Of the 18274 participants included in the subgroup analysis 17754 (97.2%) had data collected on hospitalisation/death and so could be included in the primary analysis. 17334 (94.9%) completed any diaries or calls and so could be included in the secondary analysis.

4.4 PRIMARY ANALYSES

4.4.1 PRIMARY OUTCOME

The primary outcome is defined as all cause unplanned hospitalisation or death from randomisation to 28 days follow-up. Data is derived from participant daily diaries, phone calls, and routine electronic data. If a primary endpoint is reported from any data source then this outcome is counted as "yes". If the participant has completed 28 days follow-up and is not hospitalised or is lost to follow-up but has been checked against routine electronic data and no hospitalisation or death is found then this outcome is coded "no". An odds ratio<1 suggests fewer hospitalisations/deaths in the Molnupiravir arm. The results show probability of superiority below 0.5, indicating no benefit of Molnupiravir compared to Usual Care.

TABLE 8 PRIMARY OUTCOME

	Molnupiravir plus usual care (N=9120)	Usual care (N=9154)	Estimated treatment effect (95% BCI)	Probability of superiority
Hospitalization or death	92/8932 (1.0%)	87/8822 (1.0%)	1.053 (0.775 to 1.396)	0.3919
Deaths	3/8932	5/8822	Not estimable	
Hospitalizations	90/8932 (1.0%)	85/8822 (1.0%)	1.055 (0.773 to 1.413)	0.3963

*OR < 1 favours molnupiravir

4.4.2 SECONDARY OUTCOMES

Definition of outcomes:

1. Time to recovery: time to first reporting of feeling recovered in diary or call. A hazard ratio>1 suggests faster recovery in the Molnupiravir arm.
2. Time to sustained recovery: time to reporting recovery in diary or call followed by no subsequent relapse. A hazard ratio>1 favours Monupiravir.
3. Early sustained recovery: reported recovered within the first 14 days with no subsequent relapse. An odds ratio >1 favours Molnupiravir.
4. Alleviation of symptoms: Time to first rating of symptoms as mild/none. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
5. Sustained alleviation of symptoms: Time to rating of symptoms as mild/none followed by no subsequent relapse. If all symptoms are rated mild/none at baseline then the participant is censored at day 0. A hazard ratio>1 favours Molnupiravir.
6. Reduction of symptoms: Time to reduction of all symptoms by at least one grade. A hazard ratio>1 favours Molnupiravir.
7. Rating of how well participant feels (1 worst, 10 best): Participant rating of wellness at each day. Estimates represent the mean differences and a values >0 favours Molnupiravir.
8. Household infections: Participant reported another member of their household becoming unwell with COVID-19. Participants who live alone at baseline are excluded. An odds ratio <1 favours Molnupiravir (fewer household infections). For number of infections a rate ratio <1 favours Molnupiravir.

The following assumptions have been made in the following analysis:

1. For time to event outcomes participants are censored at the last point of contact or 28 days, whichever is sooner. For time to sustained recovery if a participant reported feeling recovered and is subsequently lost to follow-up it is assumed they remained recovered (last

observation carried forward). A similar principle is used for time to sustained alleviation of symptoms. Therefore the only missing data for time to event outcomes is participants who completed no diary data

2. For early sustained recovery if a participant is lost to follow-up, such that it is not possible to establish if they remained recovered, then this outcome is treated as missing.
3. For time to alleviation and time to reduction of symptoms if a symptom is missing but the participant reported feeling recovered, that symptom is assumed to be rated “none”.
4. For household infections if a participant has incomplete diaries but has not stated that they have an infection within the household this outcome is assumed to be zero. Participants who live alone at baseline are excluded from the analysis.
5. Analysis of daily symptom scores uses a frequentist mixed model, due to the computational difficultly running the Bayesian model with the number of parameters.

Results in Table 9 have showed estimated median (95% BCI) time to first reported recovery from the Bayesian model were 10.381 (10.137 to 10.640) days and 14.853 (14.383 to 15.345) days, respectively, which suggested that Molnupiravir has a 4.5 days benefit in TTR compared with Usual Care.

There was a significant benefit in early sustained recovery by 9.7%, i.e. recovered within the first 14 days and remained well until day 28 from randomisation, in Molnupiravir group (31.4%) compared to Usual Care (21.7%) (OR = 1.7; 95% BCI (1.56 to 1.81)).

TABLE 9 SECONDARY OUTCOMES

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% BCI)	Estimated benefit (95% BCI)	Probability of superiority
First reported recovery	6860/8837 (77.6%)	5722/8497 (67.3%)			
Days to first reported recovery	10.381 (10.137 to 10.640)	14.853 (14.383 to 15.345)	1.374 (1.326 to 1.423) *	-4.472 (-5.001 to -3.953) †	>0.99
Early sustained recovery	2530/8062 (31.4%)	1625/7495 (21.7%)	1.679 (1.558 to 1.807) **		>0.99
Sustained recovery	5995/8837 (67.8%)	4950/8497 (58.3%)			
Days to sustained recovery	20.215 (19.771 to 20.686)	23.746 (23.430 to 24.066)	1.262 (1.213 to 1.310) *	-3.533 (-4.055 to -2.978) †	>0.99
Alleviation of all symptoms	6447/6997 (92.1%)	5839/6720 (86.9%)			
Days to alleviations of all symptoms	3.794 (3.691 to 3.896)	4.625 (4.493 to 4.770)	1.220 (1.177 to 1.263) *	-0.833 (-0.993 to -0.676) †	>0.99
Sustained alleviation of all symptoms	5799/6997 (82.9%)	5187/6720 (77.2%)			
Days to sustained alleviation of all symptoms	9.912 (9.533 to 10.304)	11.956 (11.489 to 12.442)	1.158 (1.117 to 1.202) *	-2.040 (-2.592 to -1.505) †	>0.99
Initial reduction of symptom severity	7634/8820 (86.6%)	6732/8487 (79.3%)			
Days to initial reduction of symptom severity	7.500 (7.333 to 7.673)	9.435 (9.202 to 9.672)	1.292 (1.248 to 1.336) *	-1.934 (-2.204 to -1.666) †	>0.99
Participant rating of wellness					
Day 7	7.3 (1.8) [8396]	6.7 (1.8) [7800]	0.5 (0.5 to 0.6) ¶		P<0.001 ‖
Day 14	7.8 (1.7) [8142]	7.5 (1.8) [7422]	0.3 (0.2 to 0.3) ¶		P<0.001 ‖
Day 21	8.1 (1.7) [7535]	7.9 (1.7) [6602]	0.2 (0.1 to 0.2) ¶		P<0.001 ‖
Day 28	8.3 (1.6) [7515]	8.2 (1.6) [6731]	0.2 (0.1 to 0.2) ¶		P<0.001 ‖
New infections in household	2852/7630 (37.4%)	2803/7307 (38.4%)	0.960 (0.898 to 1.025) **		0.8879
Contact with health and social care services					
NHS 111	487/8835 (5.5%)	614/8492 (7.2%)	0.746 (0.660 to 0.843) **		>0.99
General practitioner	2009/8835 (22.7%)	2332/8493 (27.5%)	0.774 (0.721 to 0.830) **		>0.99
Ambulance service (not hospitalised)	256/8831 (2.9%)	233/8479 (2.7%)	1.060 (0.881 to 1.267) **		0.2847

Community nurse	226/8835 (2.6%)	243/8489 (2.9%)	0.894 (0.736 to 1.073) **		0.8927
Physiotherapist	115/8835 (1.3%)	66/8489 (0.8%)	1.696 (1.239 to 2.277) **		0.0006
Counsellor	72/8835 (0.8%)	89/8489 (1.0%)	0.784 (0.565 to 1.063) **		0.9464
Social worker	21/8835 (0.2%)	27/8489 (0.3%)	0.774 (0.420 to 1.296) **		0.8498
Home carer	82/8834 (0.9%)	77/8487 (0.9%)	1.027 (0.747 to 1.397) **		0.4688
Occupational therapist	191/8834 (2.2%)	169/8489 (2.0%)	1.095 (0.884 to 1.338) **		0.2049
Hospital emergency department	512/8835 (5.8%)	489/8490 (5.8%)	1.009 (0.886 to 1.144) **		0.4584
Outpatient respiratory clinic	208/8835 (2.4%)	218/8489 (2.6%)	0.914 (0.751 to 1.101) **	0.8319	
Hospital at home for COVID-19	298/8835 (3.4%)	356/8489 (4.2%)	0.798 (0.679 to 0.930) **	0.9980	
Other services	485/8835 (5.5%)	539/8488 (6.4%)	0.856 (0.751 to 0.970) **	0.9926	

*Estimated HR derived from a piecewise exponential model adjusted for age, comorbidity and vaccination status. HR > 1 favours Molnupiravir.

†Model based estimated benefit median time to event <0 favours Molnupiravir.

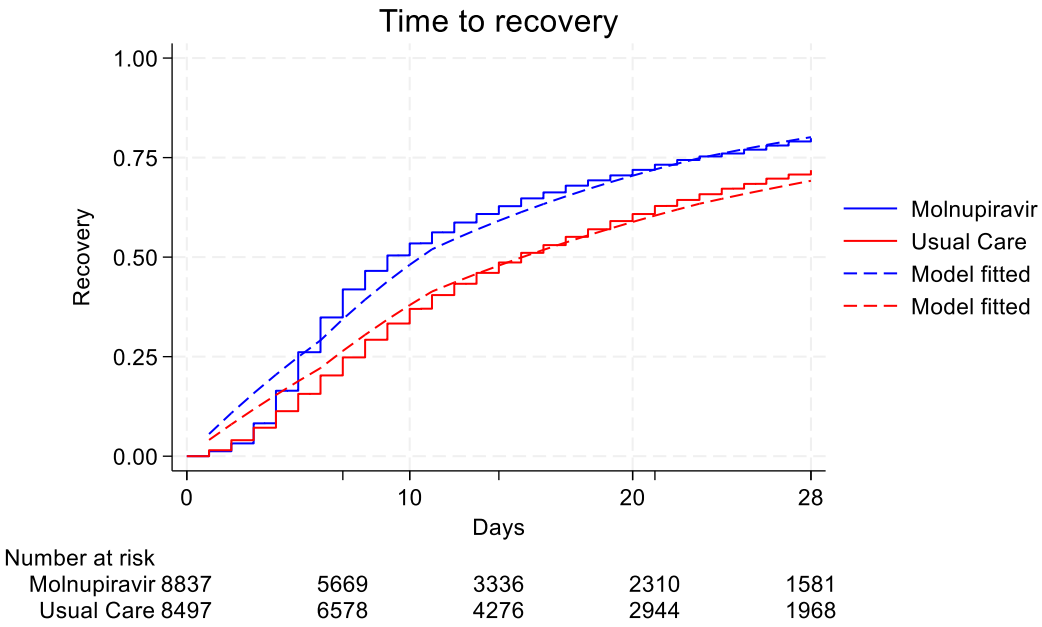
‖ Frequentist model estimates display p-value rather than a probability

¶Linear mixed effect model adjusted for age, comorbidity and vaccination status. Participant fitted as a random effect. Estimated mean difference > 0 favours Molnupiravir.

**Bayesian logistic regression, adjusted for, age, comorbidity and vaccination status

The following plot shows the actual data for time to recovery (solid lines) and the model based estimates (dashed lines). The model based estimates are derived from the piecewise exponential where all the standardised covariates are set to zero (corresponding to the sample average).

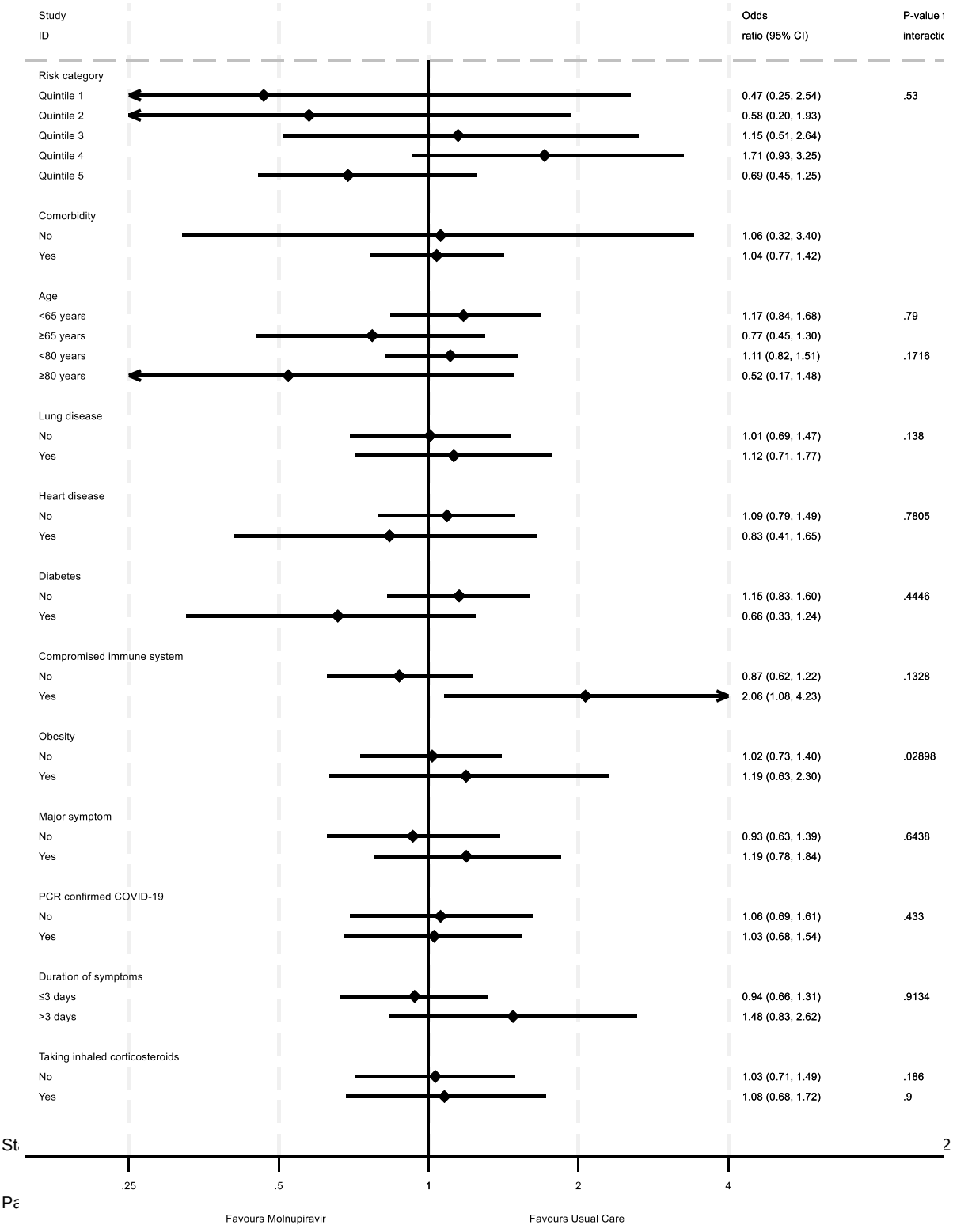
FIGURE 2 KAPLAN-MEIER CURVE AND MODEL ESTIMATES FOR TIME TO RECOVERY



4.5 SUBGROUP ANALYSES

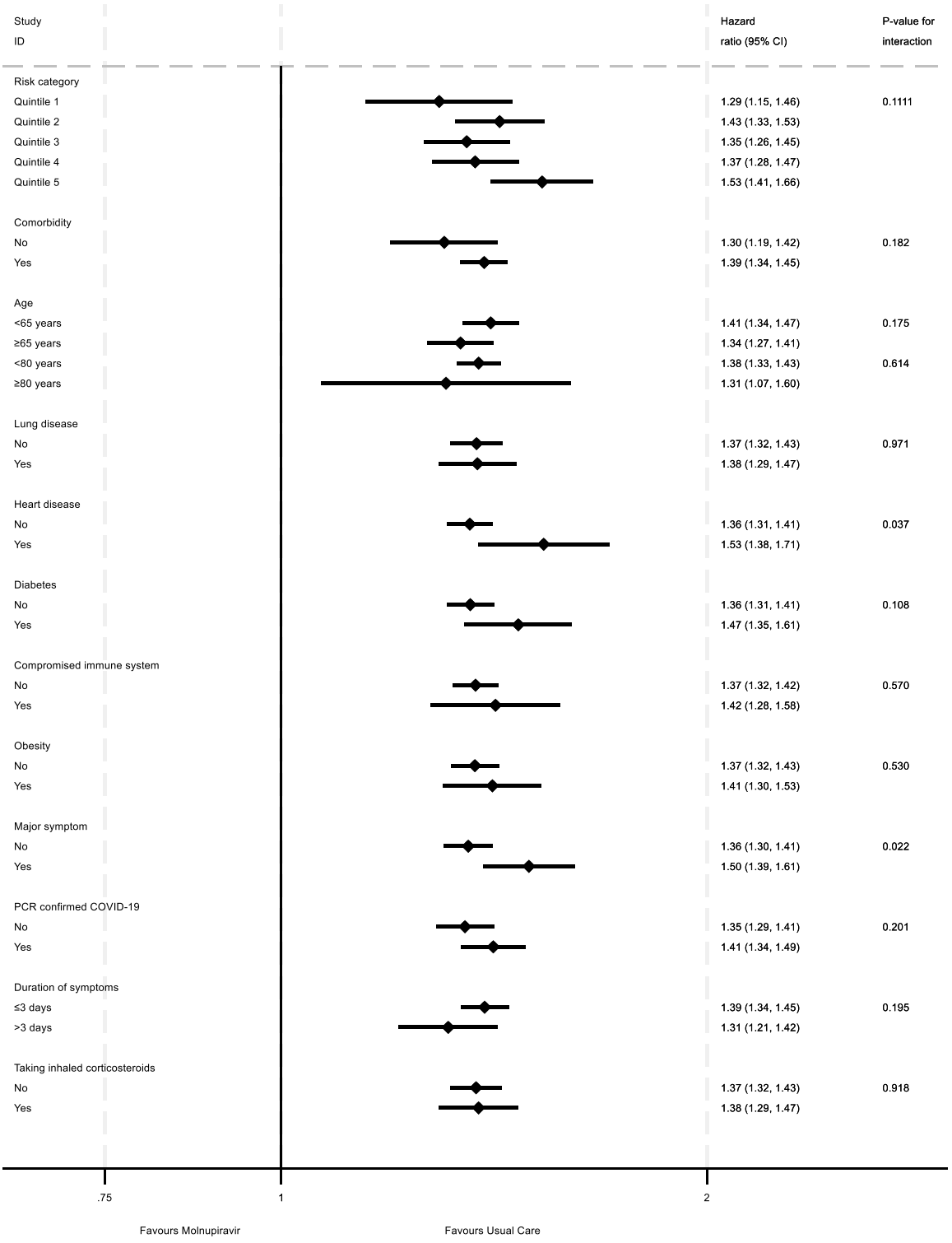
Frequentist model estimates are presented for the moderation analysis of the primary outcome. An odds ratio<1 favours Molnupiravir. P-values indicate the test for the interaction and statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 3 FOREST PLOT OF SUBGROUP ANALYSIS OF PRIMARY OUTCOME



Frequentist model estimates are presented for the moderation analysis of time to recovery. A hazard ratio>1 favours Molnupiravir. P-values indicate the test for the interaction and a statistically significant p-value suggests a differential effect size between subgroups.

FIGURE 4 FOREST PLOT OF SUBGROUP ANALYSIS OF TIME TO RECOVERY



4.6 VIROLOGY SUB-STUDY ANALYSIS

TABLE 10 SUMMARY OF VIROLOGY SUB-STUDY

	Molnupiravir	Usual Care	Total
Number of participants, n			
Intensive samples cohort	22	28	50
Less intensive samples cohort	142	163	305
At least 7 samples received from intensive samples cohort, n/N (%)	22/22 (100.0%)	27/28 (96.4%)	49/50 (98.0%)
At least 2 samples received from less intensive sample cohort, n/N (%)	142/142 (100.0%)	163/163 (100.0%)	305/305 (100.0%)
Female, n/N (%)			
Intensive samples cohort	12/22 (54.5%)	14/28 (50.0%)	26/50 (52.0%)
Less intensive samples cohort	80/142 (56.3%)	102/163 (62.6%)	182/305 (59.7%)
Overall	92/164 (56.1%)	116/191 (60.7%)	208/355 (58.6%)
Age, mean (SD)			
Intensive samples cohort	58.1 (12.0) [27.0 to 79.0]	64.1 (9.6) [34.0 to 74.0]	61.4 (11.0) [27.0 to 79.0]
Less intensive samples cohort	59.2 (11.9) [29.0 to 82.0]	59.5 (13.0) [22.0 to 86.0]	59.4 (12.5) [22.0 to 86.0]
Overall	59.1 (11.9) [27.0 to 82.0]	60.2 (12.7) [22.0 to 86.0]	59.7 (12.3) [22.0 to 86.0]

TABLE 11 VIROLOGY SUBSTUDY

	Molnupiravir plus usual care	Usual care	Estimated treatment effect (95% CI)	P value
Intensive samples				
Undetectable viral load				
Day 2	0/22	0/27		
Day 3	0/22	0/27		
Day 4	1/22 (4.5%)	0/28		
Day 5	3/22 (13.6%)	0/27		
Day 6	4/22 (18.2%)	1/28 (3.6%)	4.605 (0.579 to 36.623) †	0.1489
Day 7*	5/22 (22.7%)	1/28 (3.6%)	5.769 (0.797 to 41.752) †	0.0827
Viral load, mean(SD)				
Day 1	7.268 (1.252)	7.303 (1.309)		
Day 2	6.764 (1.422)	7.083 (1.187)	-0.352 (-0.952 to 0.247) ‡	0.2498
Day 3	6.258 (1.353)	6.474 (1.149)	-0.250 (-0.849 to 0.350) ‡	0.4145
Day 4	5.350 (1.437)	5.919 (1.299)	-0.586 (-1.182 to 0.009) ‡	0.0537
Day 5	4.435 (1.518)	5.786 (1.113)	-1.385 (-1.984 to -0.785) ‡	<0.0001
Day 6	4.020 (1.552)	5.457 (1.380)	-1.454 (-2.049 to -0.858) ‡	<0.0001
Day 7	3.633 (1.392)	5.048 (1.379)	-1.432 (-2.027 to -0.836) ‡	<0.0001
All samples				
Undetectable viral load				
Day 5	14/160 (8.8%)	4/185 (2.2%)	6.038 (1.513 to 24.094) **	0.0109
Day 14	64/138 (46.4%)	75/154 (48.7%)	0.867 (0.436 to 1.721) **	0.6826
Viral load, mean(SD)				
Day 5	4.409 (1.527)	5.607 (1.323)	-1.201 (-1.609 to -0.794) ‡	<0.0001
Day 14	2.828 (1.335)	2.530 (1.113)	0.277 (-0.035 to 0.589) ‡	0.0821

* Primary outcome

† Firth logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours molnupiravir

‡Mixed effect model adjusting for sex, age, and baseline $\log_{10}$(viral load); adjusted difference < 0 favours molnupiravir

** Mixed effects logistic regression adjusting for sex, age, and baseline $\log_{10}$(viral load). Adjusted OR > 1 favours molnupiravir

~~~ END OF REPORT ~~~