National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[Q] Evidence review for molnupiravir

NICE guideline NG191

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Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Contents

Objective

This evidence review aims to review and evaluate the evidence on the effectiveness and safety of molnupiravir (7 days or less since symptom onset) for the treatment of adults, young people and children with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of molnupiravir for adults, young people and children with COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

NICE's information services team identified relevant evidence through focused evidence searches up to January 5, 2022 (see appendix B for full details). The search identified 37 references. These references were screened using their titles and abstracts and 10 full text references were obtained and assessed for relevance against the criteria in the PICO.

8 studies were excluded. Details of excluded studies are in appendix E.

2 studies are included in this evidence review. A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Jayk Bernal 2021 ["MOVe-OUT"] Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalised Patients Country: 20 countries across Europe (incl. UK), Latin America, North America and Asia Pacific	RCT (Ph. III)	Non-hospitalised Mild to moderate COVID-19	1433 non-hospitalised adults with SARS-CoV-2 infection confirmed within 5 days before randomisation, who did not require hospitalisation. Median age 43 51.3% females At least one sign or symptom of COVID-19 within 5 days before randomisation Patients had at least one sign or symptom for COVID-19 and at least one risk factor for severe COVID-19 illness: age >60; active cancer; chronic kidney disease; COPD; obesity, serious heart conditions, or diabetes mellitus. Key exclusions: people vaccinated against COVID-19, pregnant women	Molnupiravir 800mg (four 200 mg capsules) orally twice daily for 5 days	Placebo Standard-of-care treatment with antipyretic agents, antiinflammatory agents, glucocorticoids, or a combination was permitted. Use of therapies for COVID-19, such as monoclonal antibodies and remdesivir, was prohibited until day 29	All cause hospitalisation or death at day 29 COVID-19 related hospitalisation or death day at 29 Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Fischer 2021 Molnupiravir, an Oral Antiviral Treatment for COVID-19 Country: USA	RCT (Ph. IIa)	Non-hospitalised Mild to moderate COVID-19	204 adults with confirmed SARS-CoV-2 infection within 96 hours and onset of COVID-19 symptoms within 7 days of treatment initiation who did not require hospitalisation. Key exclusions: People who have been treated with anti-SARS-CoV-2 therapeutics in the last 30 days, people who have been vaccinated against COVID-19	Molnupiravir 800mg (four 200 mg capsules) orally twice daily for 5 days n=55 Median age 42 49.1% female Findings are presented for licensed dose only (800 mg) Other intervention groups included: 200 mg molnupiravir (n=23) 400 mg molnupiravir (n=62)	Placebo n=62 Median age 39 54.8% female	Time to viral clearance / change in viral load Adverse events Outcomes were assessed for up to 28 days following study treatment initiation

See appendix F for full evidence tables.

Results

What is the effectiveness and safety of molnupiravir for adults, young people and children with COVID-19?

Key results

The evidence suggests that molnupiravir reduces the risk of hospitalisation or death and COVID-19-related death in unvaccinated, non-hospitalised people with mild or moderate COVID-19 who are at increased risk of developing severe COVID-19 disease, and may also reduce time to viral RNA clearance, compared to placebo.

What is the evidence informing this conclusion?

The evidence comes from two randomised controlled trials comparing 800 mg molnupiravir twice a day for five days with placebo in non-hospitalised adults with mild or moderate COVID-19 (Jayk Bernal 2021; Fischer 2021). Jayk Bernal 2021 is a phase III trial (known as MOVe-OUT) that included 1433 patients to either molnupiravir or placebo. Recruitment of participants was carried out in 20 countries.

Fischer 2021 is a phase IIa trial in which 55 patients received 800mg molnupiravir and 62 received placebo. This trial was conducted in the USA.

The published results were for people who had treatment within 5 days of symptom onset in MOVe-OUT and within 7 days in the Fischer 2021 study. In MOVe-OUT, standard-of-care treatment was allowed with antipyretic agents, anti-inflammatory agents, glucocorticoids, or a combination.Use of therapies for COVID-19 treatments, such as monoclonal antibodies and remdesivir, was prohibited until day 29. The study by Fischer 2021 did not report details about standard of care, however use of therapeutic interventions for COVID-19 prior to study entry was one of the exclusion criteria.

Publication status

Both studies are full publications.

Study characteristics

The MOVe-OUT study enrolled participants who were at increased risk of disease progression due to at least one of the following factors: age over 60, obesity, or another comorbidity including active cancer; chronic kidney disease; COPD; serious heart conditions, or diabetes mellitus. In the Fisher 2021 study, 60% of participants had at least one risk factor for developing severe COVID-19 disease (risk factors not reported). The MOVe-OUT trial followed up participants through to 29 days after randomisation while Fischer 2021 assessed outcomes for up to 28 days following treatment initiation. Pregnant women were excluded from both studies. Both studies excluded SARS-CoV-2 vaccinated participants. Both studies excluded patients who need supplemental oxygen or have an anticipated need for hospitalisation.

In the MOVe-OUT study, the median age of the participants was 43 (range 18-90). In Fischer 2021, the age range was 18 to 71 years. In MOVe-OUT, the proportion of females was 51.3% overall, and was higher in the molnupiravir group (53.6%) than the placebo group (49.0%). In Fischer 2021, 54.8% of the study population in placebo and 49.1% in molnupiravir were female.

What are the main results?

Hospitalisation or death

The MOVe-OUT study reported a statistically significant reduction in the composite outcome of all-cause hospitalisation or death, and in COVID-19-related death to day 29 in people treated with molnupiravir compared to placebo.

The composite outcome of hospitalisation or death did not differ by subgroups for people treated within 3 days of symptom onset, or within 3-5 days of symptom onset. There was a potential subgroup effect of serostatus at baseline (subgroup effect I2 was 68.8%, P-value was 0.07)

Viral load

There was a statistically larger reduction in viral load from baseline to day 3 and day 5 in molnupiravir compared to placebo. Results for day 7-10, day 14-15 and day 29 showed no difference in change in viral RNA load from baseline between the groups.

Adverse Events

The frequency of adverse events and discontinuation of treatment due to adverse events was not significantly different between the molnupiravir and placebo groups in either study.

See appendix H for forest plots and appendix I for full GRADE profiles.

Our confidence in the results

Outcomes from both studies were rated as having a low risk of bias due to there being very few concerns around study design and results. In the MOVe-OUT trial, there was a greater proportion of females in the molnupiravir group (53.6%) compared with the placebo group (49%), however an analysis for the primary outcome of hospitalisation or death was adjusted for participant sex, and the results were consistent with the primary analysis.

In Fischer 2021, sample collection was carried out for antiviral efficacy and safety at day 1, 3, 5, 7, 14 and 28. However, no outcomes were reported at 28 days and only data at day 14 was available as an endpoint. Time to viral clearance was not reported in sufficient detail to be extracted and included in this review. Fischer 2021 did not report outcomes on hospitalisation or death.

Since both studies cited in this review took place before the emergence of the Omicron variant, and before the availability of vaccination against COVID-19, the populations measured in the study may not be directly relevant or comparable to current populations in the UK, where the Delta and Omicron variants are dominant and many people have been vaccinated against COVID-19. As a result, the certainty in all outcomes presented was downgraded due to indirectness.

Evidence to decision

Benefits and harms

The panel considered evidence presented in two randomised controlled trials: the MOVe-OUT trial and Fischer 2021. Both trials included people aged 18 and above, with at least one risk factor for progressing to severe disease and administered 800mg of molnupiravir for 5 days. Participants recruited to the MOVe-OUT trial had at least one risk factor for developing severe disease (including age over 60, obesity [BMI ≥30], diabetes, active cancer, chronic kidney disease, chronic obstructive pulmonary disease and serious heart conditions). In Fischer 2021, around 60% of the participants had at least one risk factor for developing severe disease. Both studies recruited people who did not require supplementary oxygen.

The panel noted that molnupiravir should not be offered in people below 18 years of age. There is no evidence for safety and efficacy in this age group in both trials. Both studies excluded people under 18 and pregnant women.

The panel noted that safety data in the summary of product characteristics raised concerns about the long-term safety of molnupiravir in children and young people, and that studies in animals have shown reproductive toxicity. They also acknowledged that there is no evidence on efficacy and safety of molnupiravir in people under 18 or pregnant women in either trial. Based on this information, the panel agreed that molnupiravir should not be offered to children and young people under 18, or pregnant women. For further information, see the summary of product characteristics.

The MOVe-OUT study suggested that molnupiravir statistically significantly reduced the risk of hospitalisation or death (all-cause) compared to placebo. Evidence from both studies suggested a larger reduction in viral load at day 3 and day 5 since baseline in people who received molnupiravir than those who received placebo. The panel noted that although reduction in viral load may not mean a reduction in time to recovery, it may shorten the time that the person is infectious. This may be an important factor for people living with vulnerable or at risk people. Overall, the panel noted that molnupiravir may have benefits in people at risk of progression to severe disease. In the MOVe-OUT study, the published results were for people who had

treatment within 5 days of symptom onset, and the panel agreed that this was when treatment was likely to be most effective.

Evidence on adverse events was pooled from both studies. There was no significant difference in adverse events or serious adverse events between the molnupiravir and placebo groups. In the MOVe-OUT trial, the risk of COVID-19 related death was statistically lower in the molnupiravir group compared with placebo (1 COVID-19 related death was reported in the molnupiravir group compared with 9 in the placebo group). In the 14 days beyond the treatment period, there were 2 additional deaths in the placebo group and 1 in the molnupiravir group. The panel agreed that molnupiravir could potentially benefit people with high risk of developing severe disease compared with placebo. The panel considered that the absolute benefit would potentially be smaller among vaccinated people.

The panel also discussed the potential benefits and harms of combination treatment with an antiviral drug and a neutralising monoclonal antibody or another antiviral drug in people who do not need supplemental oxygen for COVID-19 and who are at high risk of progression to severe disease. The panel were not aware of any clinical trial evidence on combination treatment in this population.

Certainty of the evidence

The certainty of all outcomes from the included studies was downgraded due to indirectness, as the studies took place before the emergence of the Omicron variant of COVID-19 and because no patients in the studies had been vaccinated for COVID-19. The panel agreed that these factors meant evidence from the included studies was not directly relevant to the current situation of COVID-19 in the UK, where the Omicron variant is dominant and many people are vaccinated for COVID-19. The panel were aware that the ongoing UK-wide PANORAMIC study would provide more direct evidence on the effectiveness of molnupiravir in people with COVID-19 in the UK.

In the MOVe-OUT trial, the incidence of all-cause hospitalisation or death and COVID-19 related hospitalisation or death were graded as ‘moderate’ certainty due to indirectness of the study population. Change in viral load at days 3 and 5 were of ‘moderate’ certainty due to the same concern. Other outcomes such as adverse

events and serious adverse events were of ‘low’ certainty, because the confidence intervals crossed the line of no effect in addition to indirectness. Imprecision resulted in downgrading of other outcomes to ‘low’ certainty such as risk of COVID-19 related hospitalisation and change in viral load at days 7-10 and days 14-15.

The panel noted that there were subgroup differences for the outcome of hospitalisation or death, according to serostatus. There was a statistically significant difference in all-cause hospitalisation or death in the seronegative subgroup, but not in the seropositive subgroup. The panel discussed this and agreed that as the result for the overall population showed a significant reduction, and the absolute numbers for the subgroup results were small, they would not differentiate between seronegative and seropositive groups in the recommendation. They also pointed out that it was unlikely to be possible to test for serostatus within the timeframes of these treatments, and that delaying for testing would reduce the benefit of treatment.

The panel noted that the evidence was from non-hospitalised people with COVID-19, however the results could also be generalised to people in hospital for reasons other than COVID-19 who meet the criteria set out in the recommendation.

There is no evidence on the safety and efficacy of molnupiravir in children and young people or pregnant women. The panel were not presented with risk of hospitalisation or risk of COVID-19 related death in these groups.

Values and preferences

The panel were not aware of any systematically collected data on peoples’ preferences and values. Molnupiravir can be administered orally and the current formulation is in 200mg capsules, meaning four capsules must be taken twice a day to achieve the dose recommended in the Summary of Product Characteristics (SmPC). The panel noted that the capsules are large and that some people might find them difficult to take. Therefore adherence and patient preferences might vary.

The panel noted that there is no evidence on the efficacy and safety of molnupiravir in children and young people, or pregnant women, and therefore it cannot be recommended in these groups. The panel believed that, if fully informed, most

pregnant women and people under 18 would not choose molnupiravir because of the lack of evidence and the potential harms.

Resources

The recommendations were not informed by a cost effectiveness analysis, however use of molnupiravir on a large scale is likely to incur costs to the healthcare system. These costs may be offset by a reduction in hospitalisation of people with COVID-19 who are at risk of progressing to severe disease.

Equity

The panel noted that the ability to access molnupiravir in the community may benefit people who have limited access to healthcare facilities as it can be delivered to their home. This may be especially relevant for those who find it difficult to travel, for example due to poor access to transport, disability or mobility issues, or childcare or caring responsibilities. In addition, having treatment whilst self-isolating at home may also minimise spread of the virus. However, there may be challenges for some patient groups if travel is needed to access treatment.

The panel noted that the use of molnupiravir to prevent progression to severe COVID-19 disease may not be safe for children and young people under 18, or for pregnant women. The panel noted the inequity of access that this presents however they agreed that this was justified based on safety concerns..

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. However, they noted that receiving a treatment outside of hospital may be more acceptable for many people. The panel noted that although the risks of long-term effects of molnupiravir were assessed as low in the Summary of Product Characteristics (SmPC), these concerns may cause some people to choose not to take molnupiravir. The panel discussed the potential harms of molnupiravir and concluded that there is not enough evidence in children and young people or pregnant women to recommend it. They agreed that its use in these groups is not likely to be acceptable.

Feasibility

The dosage administration of molnupiravir might cause adherence issues for some patients. The panel noted that four capsules of 200mg twice a day may be difficult for patients to adhere to for five days.

Appendices

Appendix A: PICO table

Question 1:

What is the effectiveness and safety of molnupiravir for adults, young people and children with COVID-19?

Criteria	**Notes**
Population	Adults, young people and children with COVID-19 with symptom onset within the previous 7 days who do not need supplementary oxygen.
Interventions	Molnupiravir
Comparators	• Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as corticosteroids, antivirals, and neutralising monoclonal antibodies).
Outcomes	Effectiveness outcomes • Mortality • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) • Hospitalisation (requirement and duration) • Supplemental oxygen (requirement and duration) • High-flow oxygen, continuous positive airway pressure or non-invasive respiratory support (requirement and duration) • Symptom resolution or clinical recovery (number and time until) • Clinical worsening / deterioration (number and time until) • Sustained recovery (absence of long-term effects of COVID measured at least 4 weeks from onset of acute COVID-19) • Virological clearance (negative PCR) / viral load Safety outcomes • Adverse events

	• Discontinuation due to adverse events The definitions of mechanical ventilation, non-invasive respiratory support and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive respiratory support:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. **Supplemental oxygen**: includes oxygen via (low flow) nasal cannulae or face mask.
Settings	All settings
Subgroups	• Community vs enhanced medical supervision outside a hospital setting (e.g. oximetry at home or virtual ward) vs hospital • Vaccination status • PCR confirmed COVID vs. not confirmed • COVID variants • Time from symptom onset • Adults > 50 years • Children <12 years of age • Disease severity (mild / moderate) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • People who are Immunocompromised
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs

	If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, and migrant workers.

Appendix B: Search strategies

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 06/01/2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

The search was limited from 2020 to date as defined in the review protocol.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- Systematic reviews filters

The MEDLINE SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

The Embase SR filter was "Health-evidence.ca Systematic review search filter" from Lee et al. (2012). The standard NICE modifications were used: pubmed.tw added to line medline.tw.

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

- RCT filters

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomised.mp changed to randomi?ed.mp.

Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.
The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results

				downloaded
MEDLINE ALL	06/01/22	Ovid	Ovid MEDLINE(R) ALL 1946 to January 05, 2022	11
Embase	06/01/22	Ovid	Embase 1974 to 2022 January 05	11
Cochrane - Cochrane Database of Systematic Reviews	06/01/22	Wiley	Cochrane Database of Systematic Reviews Issue 12 of 12, December 2021	0
Cochrane - CENTRAL	06/01/22	Wiley	*Cochrane* Central Register of Controlled Trials Issue 12 of 12, December 2021	7
MedRxiv/BioRxiv/Europe PMC/NIH Portfolio Preprints [EPPI review]	06/01/22	Wiley	pre-prints v3 14.50	24
WHO Covid-19 Database	06/01/22	N/A	N/A	0 (Searched but nothing unique found)
NICE Evidence Search	06/01/22	N/A	N/A	0 (Searched but nothing unique found)

Records	
Total number of records	53
Total number after deduplication	37
Records excluded by the classifier [Medline/Embase only]	N/A

Search strategy history

Database name: MEDLINE ALL

1 SARS-CoV-2/ or COVID-19/ (131175)
2 (corona* adj1 (virus* or viral*)).ti,ab. (2723)
3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. (63611)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (220542)
5 or/1-4 (227440)
6 limit 5 to yr="2020-Current" (214298)
7 (6 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (159501)
8 (molnupiravir or lagevrio or "mk-4482" or mk4482 or "EIDD-2801" or EIDD2801).ti,ab. (86)
9 (NCT04575584 or "2020/003367/26" or NCT04575597 or "2020/003368/24" or NCT04392219 or "2020/001407/17" or NCT04405570 or NCT04405739 or NCT04746183 or "2020/001860/27" or ISRCTN27106947 or "CTRI/2021/05/033736" or "CTRI/2021/05/033739" or "CTRI/2021/05/033864" or "CTRI/2021/05/033904" or "CTRI/2021/06/033938" or "CTRI/2021/06/033992" or "CTRI/2021/06/034015" or "CTRI/2021/06/034130" or "CTRI/2021/06/034220" or "CTRI/2021/07/034588" or "CTRI/2021/08/035424" or NCT04939428 or "2021/000904/39" or "CTRI/2021/05/033693" or "JPRN/jRCT2031210010").af. (10)
10 (7 and 8) or 9 (70)
11 (MEDLINE or pubmed).tw. (261337)
12 systematic review.tw. (208981)
13 systematic review.pt. (181023)
14 meta-analysis.pt. (149964)
15 intervention$.ti. (173348)
16 or/11-15 (566194)
17 10 and 16 (5)
18 randomised controlled trial.pt. (554956)
19 randomi?ed.mp. (977891)
20 placebo.mp. (231814)
21 or/18-20 (1039816)
22 10 and 21 (8)
23 17 or 22 (11)

Database name: Embase

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (186266)
2 (corona* adj1 (virus* or viral*)).ti,ab. (3204)
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab. (65052)

4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. (225475)
5 or/1-4 (242227)
6 limit 5 to yr="2020-Current" (227372)
7 (6 and english.lg.) not (letter or editorial or conference).pt. not (nonhuman/ not human/) not "case report".sh. not medline*.db. (103598)
8 (molnupiravir or lagevrio or "mk-4482" or mk4482 or "EIDD-2801" or EIDD2801).ti,ab. (70)
9 (NCT04575584 or "2020/003367/26" or NCT04575597 or "2020/003368/24" or NCT04392219 or "2020/001407/17" or NCT04405570 or NCT04405739 or NCT04746183 or "2020/001860/27" or ISRCTN27106947 or "CTRI/2021/05/033736" or "CTRI/2021/05/033739" or "CTRI/2021/05/033864" or "CTRI/2021/05/033904" or "CTRI/2021/06/033938" or "CTRI/2021/06/033992" or "CTRI/2021/06/034015" or "CTRI/2021/06/034130" or "CTRI/2021/06/034220" or "CTRI/2021/07/034588" or "CTRI/2021/08/035424" or NCT04939428 or "2021/000904/39" or "CTRI/2021/05/033693" or "JPRN/jRCT2031210010").af. (23)
10 (7 and 8) or 9 (57)
11 (MEDLINE or pubmed).tw. (325502)
12 exp systematic review/ or systematic review.tw. (391345)
13 meta-analysis/ (233623)
14 intervention$.ti. (229047)
15 or/11-14 (794248)
16 10 and 15 (6)
17 random:.tw. (1739103)
18 placebo:.mp. (486848)
19 double-blind:.tw. (226317)
20 or/17-19 (2004171)
21 10 and 20 (7)
22 16 or 21 (11)

Database name: Cochrane Database of Systematic Reviews / Central Register of Controlled Trials

#1 MeSH descriptor: [SARS-CoV-2] this term only 627
#2 MeSH descriptor: [COVID-19] this term only 1042
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 292
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 614
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe

acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw 9401
#6 {or #1-#5} 9453
#7 (molnupiravir or lagevrio or "mk-4482" or mk4482 or "EIDD-2801" or EIDD2801):ti,ab 32
#8 (NCT04575584 or "2020/003367/26" or NCT04575597 or "2020/003368/24" or NCT04392219 or "2020/001407/17" or NCT04405570 or NCT04405739 or NCT04746183 or "2020/001860/27" or ISRCTN27106947 or "CTRI/2021/05/033736" or "CTRI/2021/05/033739" or "CTRI/2021/05/033864" or "CTRI/2021/05/033904" or "CTRI/2021/06/033938" or "CTRI/2021/06/033992" or "CTRI/2021/06/034015" or "CTRI/2021/06/034130" or "CTRI/2021/06/034220" or "CTRI/2021/07/034588" or "CTRI/2021/08/035424" or NCT04939428 or "2021/000904/39" or "CTRI/2021/05/033693" or "JPRN/jRCT2031210010"):ti,ab 4
#9 (#6 and #7) or #8 34
#10 #9 with Cochrane Library publication date Between Jan 2020 and Jan 2022, in Cochrane Reviews, Cochrane Protocols 0
#11 #9 with Publication Year from 2020 to 2022, in Trials 34
#12 "conference":pt or (clinicaltrials or trialsearch):so 582582
#13 #11 not #12 7

Database name: Pre-print - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ALL and AND Title and Abstract HAS ANY.Search terms molnupiravir, lagevrio, mk-4482, mk4482, EIDD-2801, EIDD2801

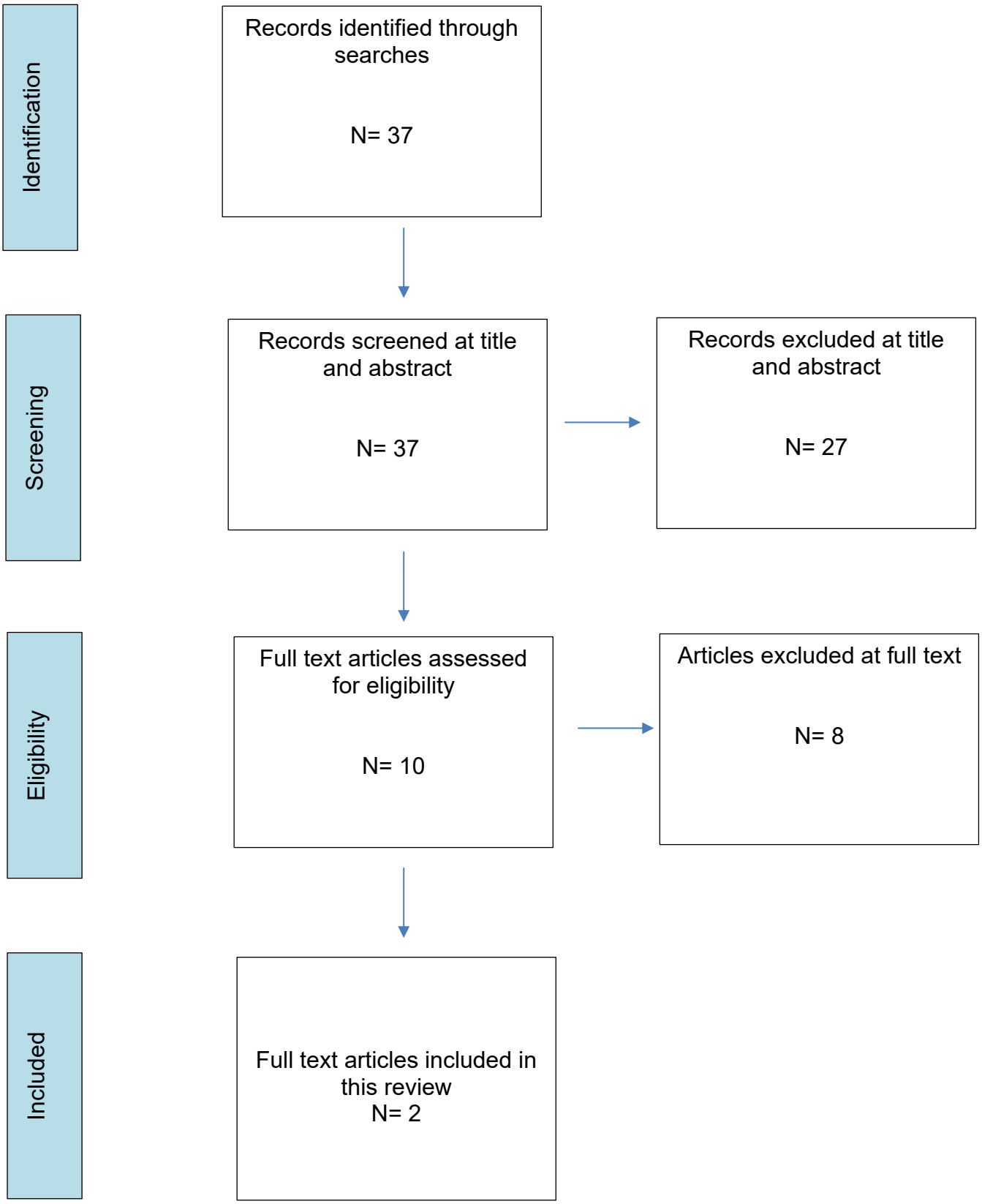
Database name: World Health Organisation Covid-19 database

This was searched by using search terms molnupiravir, lagevrio, mk-4482, mk4482, EIDD-2801, EIDD280

Database name: NICE Evidence Search

This was searched by using search terms molnupiravir, lagevrio, mk-4482, mk4482, EIDD-2801, EIDD2801

Appendix C: PRISMA diagram



Appendix D: Included studies

Fischer, William, Eron, Joseph J, Holman, Wayne et al. (2021) Molnupiravir, an Oral Antiviral Treatment for COVID-19. medRxiv : the preprint server for health sciences

Jayk Bernal, Angelica, Gomes da Silva, Monica M, Musungaie, Dany B et al. (2021) Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalised Patients. The New England Journal of Medicine

Appendix E: Excluded studies at full text screening

Study	Reason for Exclusion
FitzGerald, Richard, Dickinson, Laura, Else, Laura et al. Pharmacokinetics of ?-d-N4-hydroxycytidine, the active metabolite of prodrug molnupiravir, in non-plasma compartments of patients with SARS-CoV-2 infection. medrxiv preprint	- Outcomes reported in the study do not match with the outcomes of interest of this evidence review, ref PICO table
Holman, Wendy, Holman, Wayne, McIntosh, Stacy et al. (2021) Accelerated first-in-human clinical trial of EIDD-2801/MK-4482 (molnupiravir), a ribonucleoside analog with potent antiviral activity against SARS-CoV-2. Trials 22(1): 561	- This is not a publication of results of the trial. It briefly summarises the protocol
Khoo Saye, H, FitzGerald, Richard, Fletcher, Thomas et al. Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a phase 1, dose-escalating, randomised controlled study. medrxiv preprint	- Duplicate, preprint of another publication. Dose escalating study with very small sample size (n=4 in molnupiravir and n=6 in control group)
Khoo, Saye H, Fitzgerald, Richard, Fletcher, Thomas et al. (2021) Optimal dose and safety of molnupiravir in patients with early SARS-CoV-2: a Phase I, open-label, dose-escalating, randomised controlled study. The Journal of antimicrobial chemotherapy 76(12): 3286-3295	- Dose escalating study with very small sample size (n=4 in molnupiravir and n=6 in control group)
Painter Wendy, P, Holman, Wayne, Bush James, A et al. Human Safety, Tolerability, and Pharmacokinetics of a Novel Broad-Spectrum Oral Antiviral Compound, Molnupiravir, with Activity Against SARS-CoV-2. medrxiv preprint	- Population is healthy volunteers, as per the PICO of current review, only patients with confirmed SARS-CoV-2 infection to be included
Painter, Wendy P, Holman, Wayne, Bush, Jim A et al. (2021) Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. Antimicrobial agents and chemotherapy	- Population is healthy volunteers, as per the PICO of current review, only patients with confirmed SARS-CoV-2 infection to be included
Singh, Awadhesh Kumar, Singh, Akriti, Singh, Ritu et al. (2021) Molnupiravir in COVID-19: A systematic review of literature. Diabetes & metabolic syndrome 15(6): 102329	- Narrative review: It highlighted two additional phase III trials for molnupiravir, which were not captured from other sources. This is probably because those two trials have not been published yet.
Wagenmakers, Eric-Jan and Gronau, Quentin Frederik (2021) A Bayesian Analysis of the Molnupiravir Trial Data.	- Reanalysis of MOVe-OUT trial, which has been included in the analysis for this evidence

Appendix F: Evidence tables

Fischer, 2021

Bibliographic Reference	Fischer, William; Eron, Joseph J; Holman, Wayne; Cohen, Myron S; Fang, Lei; Szewczyk, Laura J; Sheahan, Timothy P; Baric, Ralph; Mollan, Katie R; Wolfe, Cameron R; Duke, Elizabeth R; Azizad, Masoud M; Borroto-Esoda, Katyna; Wohl, David A; Loftis, Amy James; Alabanza, Paul; Lipansky, Felicia; Painter, Wendy P; Molnupiravir, an Oral Antiviral Treatment for COVID-19.; medRxiv : the preprint server for health sciences; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04405570
Study start date	19-Jun-2020
Study end date	25-Jan-2021
Aim of the study	To evaluate the safety, tolerability and antiviral efficacy of molnupiravir in the treatment of COVID-19
Country/geographical location	United States
Study setting	Primary care/Community
Population description	Adults aged 18 years and over, who tested positive for SARS-CoV-2 infection within 96 hours and treatment was initiated within 7 days of symptom onset.
Inclusion criteria	1. Able to provide informed consent prior to initiation of any study procedures. 2. ≥18 years of age at Screening. 3. Study treatment is expected to begin within ≤168 hours from first symptom onset. 4. Ability to swallow pills. 5. Documentation of confirmed active SARS-CoV-2 infection, as determined by a molecular test conducted at any US clinic or laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent from an NP swab collected ≤96 hours prior to study entry. 6. Experiencing at least one of the following SARS-CoV-2 infection symptoms: fever (can be subjective including feeling feverish or having chills) OR signs/symptoms of respiratory illness (including but not limited to upper respiratory congestion, loss of sense of smell or taste, sore throat OR lower respiratory illness - cough, shortness of breath).

7. Agrees to not participate in another interventional clinical trial for the treatment of SARS-CoV-2 during the study period (28 days) unless hospitalised.
8. Agrees to not obtain investigational medications outside of the EIDD-2801 study.
9. Agrees to the sampling detailed in the schedule of evaluations (SOE) and to comply with study requirements including contraception requirements.

Female participants of childbearing potential must meet the following criteria to be enrolled:

i. Have a negative pregnancy test at Day 1, prior to randomisation.

ii. Must agree to undergo a follow-up pregnancy test on Study Day 28.

iii. Must agree to use at least 2 forms of contraception during the study and for at least 50 days after dosing of the study drug is complete, as discussed with and approved by the investigator.

OR Must have an azoospermic partner (vasectomized or due to a to medical cause). Note: azoospermic partner is acceptable provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed.

Note that female not of childbearing potential is defined as either:

1. Surgically sterile: females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening. OR
2. Postmenopausal: Females at least 60 years of age with amenorrhea for ≥12 months (by history) or 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle stimulating hormone levels of ≥40 mIU/mL. The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin releasing hormones, anti-estrogens, or selective estrogen receptor modulators.
3. Male participants must refrain from donating sperm during the study and for 100 days after dosing of the study drug is complete.

Male participants with female partners must have either

	1. Surgical sterilization (vasectomy ≥1 month before screening) OR 2. Female partner must be of not be of childbearing potential OR 3. Agree to use 2 forms of contraception during the study and for 100 days after dosing of the study drug is complete, as discussed with and approved by the investigator
Exclusion criteria	1. Need for hospitalisation or immediate medical attention in the clinical opinion of the study investigator. 2. Hemoglobin <10 g/dL in men and <9 g/dL in women. 3. Platelet count <125,000/L. 4. Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73m2 5. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≥3x upper limit normal (ULN). 6. History of or current hospitalisation for COVID-19. Note: Individuals hospitalised and then discharged, even if only hospitalised for 1 day, are excluded. 7. History of significant kidney disease in the opinion of the site investigator. Note: If the individual responds "yes" but can provide a creatinine clearance value ≥60 mL/min by Cockcroft Gault equation within 1 year prior to study entry, the individual may participate. 8. History of significant liver disease in the opinion of the site investigator or active Hepatitis B or active Hepatitis C. Human immunodeficiency virus (HIV) that is advanced (CD4<200/mm3) and/or on treatment with nucleoside analogues. 9. History of known blood dyscrasia 10. Use of therapeutic interventions with possible anti-SARS-CoV-2 activity within 30 days prior to study entry, e.g., remdesivir, lopinavir/ritonavir fixed dose combination, ribavirin, chloroquine, hydroxychloroquine, convalescent plasma, or participation in a clinical trial involving any of these drugs whether for treatment or prophylaxis. 11. Receipt of a SARS-CoV-2 vaccination prior to study entry. 12. Known allergy/sensitivity or any hypersensitivity to components of EIDD-2801, or its formulation. 13. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements. 14. History of recent hemorrhagic cerebrovascular accident (CVA) or major bleed. 15. Presence of a condition, that in the opinion of the investigator, would place the subject at increased risk from study participation.
Intervention dosage (loading)	200mg, 400mg or 800mg molnupiravir orally
Intervention dosage (maintenance)	Doses were administered twice daily and dose escalations occurred following review of safety and virology data

Intervention scheduled duration	5 days
Intervention actual duration	5 days
Intervention route of administration	Oral capsule
Comparator (where applicable)	Placebo
Methods for population selection/allocation	Participants were randomised 1:1 to 200 mg molnupiravir or matching placebo or 3:1 to molnupiravir (400 or 800 mg) or placebo. Doses were administered orally twice-daily for 5 days and dose escalations occurred following review of safety and virology data from this and other studies of molnupiravir.
Methods of data analysis	Time to response for viral RNA negativity was summarized using Kaplan-Meier methodology. Median time to response and cumulative probability of response by visit (with 95% confidence interval) was analyzed by treatment group. Comparisons of treatment effects were performed using log-rank tests. The number and percentage of subjects who were negative for infectious virus isolation were summarized and between-group comparisons were conducted using Fisher's exact test. Dose-response assessments were performed using the exact Cochran-Armitage trend test. Treatment comparisons between active drug and placebo groups for SARS-CoV-2 nasopharyngeal viral load change from baseline were analyzed using a mixed model for repeated measures, with restricted maximum likelihood estimation and an unstructured covariance matrix. The model included fixed effects of treatment, study visit, days since COVID-19 symptom onset, and baseline SARS-CoV-2 viral load (log10 copies/mL); and interaction terms of treatment by visit, days since COVID-19 symptom onset by visit, and baseline SARS-CoV-2 viral load by visit. The estimated mean treatment difference for active minus placebo at each visit is presented with the 95% confidence interval and corresponding p-value. Comparisons of next-generation sequencing data between treatments were performed using a two-sample t-test, based on the average number of treatment-emergent nucleotide changes. Analyses were conducted using SAS Version 9.4 (SAS Institute Inc., Cary NC) and two-sided tests were performed using an alpha of 0.05 for treatment comparisons. Adjustments for multiple testing were not performed.
Attrition/loss to follow-up	Not reported
Source of funding	Ridgeback Biotherapeutics, LP
Study limitations (Author)	Differences in antibody status were not accounted for in the trial and study design, despite this factor having an effect on overall results (confounding).
Study limitations (Reviewer)	The use of pooled placebo analysis for comparison.
Other details	This is a phase 2a trial, which is published as a pre-print in medXriv. It has not been peer-reviewed. Furthermore, the study

	was reported data for 200mg and 400mg participants, however only data for 800mg participants and placebo were extracted.

Study arms

Molnupiravir 800mg (N = 55)

Placebo (N = 62)

Characteristics

Arm-level characteristics

Characteristic	Molnupiravir 800mg (N = 55)	Placebo (N = 62)
Age Median (IQR)	42 (18 to 68)	39 (19 to 71)
Female No of events	n = 27 ; % = 49	n = 34 ; % = 54.8
Asian No of events	n = 3 ; % = 4.5	n = 2 ; % = 3.2
Black or African American No of events	n = 1 ; % = 1.6	n = 2 ; % = 3.2
White No of events	n = 49 ; % = 31	n = 54 ; % = 87.1
Other No of events	n = 2 ; % = 3.2	n = 1 ; % = 1.6
Multiple No of events	n = 0 ; % = 0	n = 3 ; % = 4.3
Hispanic or Latino No of events	n = 33 ; % = 60	n = 23 ; % = 37.1
BMI kg/m2 Median (IQR)	27.1 (0 to 0)	27 (0 to 0)

Outcomes

Molnupiravir vs Placebo

Outcome	Molnupiravir 800mg, , N = 53	Placebo, , N = 61
Day 3 Standardised Mean (SE)	-1.05 (0.12)	-0.85 (0.13)
Day 5 Standardised Mean (SE)	-1.87 (0.13)	-1.32 (0.15)
Day 7 Standardised Mean (SE)	-2.49 (0.11)	-1.95 (0.16)
Day 14 Standardised Mean (SE)	-3.04 (0.04)	-2.87 (0.11)
Any adverse event No of events	n = 11 ; % = 20	n = 18 ; % = 29
Adverse event grade 3 or higher No of events	n = 4 ; % = 7.3	n = 5 ; % = 8.1
Any adverse event leading to discontinuation No of events	n = 1 ; % = 1.8	n = 1 ; % = 1.6
Any serious adverse event No of events	n = 1 ; % = 1.8	n = 1 ; % = 1.6
Adverse event leading to death No of events	n = 0 ; % = 0	n = 1 ; % = 1.6

Jayk Bernal, 2021

Bibliographic Reference	Jayk Bernal, Angelica; Gomes da Silva, Monica M; Musungaie, Dany B; Kovalchuk, Evgeniy; Gonzalez, Antonio; Delos Reyes, Virginia; Martin-Quiros, Alejandro; Caraco, Yoseph; Williams-Diaz, Angela; Brown, Michelle L; Du, Jiejun; Pedley, Alison; Assaid, Christopher; Strizki, Julie; Grobler, Jay A; Shamsuddin, Hala H; Tipping, Robert; Wan, Hong; Paschke, Amanda; Butterton, Joan R; Johnson, Matthew G; De Anda, Carisa; MOVe-OUT Study, Group; Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalised Patients.; The New England journal of medicine; 2021

Study details

Trial registration (if reported)	Phase III Randomised Controlled Trial **NCT04575597**
Study start date	06-May-2021
Study end date	04-Nov-2021
Aim of the study	To evaluate the efficacy and safety of treatment with molnupiravir in unvaccinated, non-hospitalised patients with mild-to-moderate Covid-19, within 5 days since the start of symptoms and at least one risk factor for developing Covid-19 disease.
Country/geographical location	107 sites in 20 countries in North America, South America, Europe and Asia. Countries: Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico, Philippines, Russian Federation, South Africa, Spain, Taiwan, United Kingdom, Ukraine, United States of America
Population description	Non-hospitalised adults with mild or moderate Covid-19
Inclusion criteria	Patients who met following criteria were included: 1. SARS-CoV-2 infection <5 days earlier 2. Start of signs or symptoms <5 days earlier 3. Minimum of one sign or symptom of Covid-19 4. Minimum of one risk factor for developing severe Covid-19
Exclusion criteria	Patients were excluded if any of the following were met: • May require hospitalisation for Covid-19 in next 2 days • May require dialysis • If estimated glomerular filtration rate less than 30 ml per minute per 1.73 m2 • Pregnant • Unwillingness to use contraception during the study period • Severe neutropenia (absolute neutrophil count of <500 per milliliter) • Platelet count <100,000 per microliter • SARS-CoV-2 vaccination.
Intervention dosage (loading)	800 mg Molnupiravir (as four 200-mg capsules)
Intervention scheduled duration	Twice daily for 5 days
Intervention actual duration	
Intervention route of administration	Oral

Comparator (where applicable)	Placebo
Methods for population selection/allocation	Random allocation to either treatment arm or placebo group
Methods of data analysis	1. Adjusted risk difference by Cochran–Mantel–Haenszel weights. 2. Time to event analysis by stratified log-rank test and Cox proportional hazards model
Attrition/loss to follow-up	Missing mortality status was imputed as hospitalisation or death at end point of day 29
Source of funding	Merck Sharp and Dohme (MSD)
Study limitations (Author)	

Study arms

Molnupiravir (N = 716)

Intention-to-treat population (n=709)

Placebo (N = 717)

Intention-to-treat population (n=699)

Characteristics

Study-level characteristics

Characteristic	Study (N = 1433)
Gender Female No of events	n = 735 ; % = 51.3
Mild No of events	n = 785 ; % = 54.8
Moderate No of events	n = 638 ; % = 44.5
Severe or unknown Missing data or invalid samples No of events	n = 10 ; % = 0.7

Characteristic	Study (N = 1433)
at least one risk factor No of events	n = 1424 ; % = 99.4
Obesity body mass index of 30 or higher No of events	n = 1056 ; % = 73.7
Age>60 No of events	n = 246 ; % = 17.2
Diabetes mellitus No of events	n = 228 ; % = 15.9
Serious Heart Condition No of events	n = 167 ; % = 11.7
Chronic kidney disease No of events	n = 84 ; % = 5.9
Chronic obstructive pulmonary disease No of events	n = 57 ; % = 4
Chronic obstructive pulmonary disease No of events	n = 57 ; % = 4
Active cancer No of events	n = 29 ; % = 2
Time from onset of Covid-19 symptoms to randomisation of ≤3days (n (%)) signs or symptoms No of events	n = 684 ; % = 47.7

Arm-level characteristics

Characteristic	Molnupiravir (N = 716)	Placebo (N = 717)
Age Range	18 to 90	18 to 88
Age Median (IQR)	42 (*empty data* to *empty data*)	44 (*empty data* to *empty data*)
Female sex (n (%)) proportion	n = 384 ; % = 53.6	n = 351 ; % = 49

Characteristic	Molnupiravir (N = 716)	Placebo (N = 717)
No of events		
At least one risk factor No of events	n = 712 ; % = 99.4	n = 712 ; % = 99.3
Obesity BMI >30 No of events	n = 538 ; % = 75.1	n = 518 ; % = 72.2
Age>60 No of events	n = 119 ; % = 16.6	n = 127 ; % = 17.7
Diabetes mellitus No of events	n = 107 ; % = 14.9	n = 121 ; % = 16.9
Serious Heart Condition No of events	n = 86 ; % = 12	n = 81 ; % = 11.3
Chronic kidney disease No of events	n = 38 ; % = 5.3	n = 46 ; % = 6.4
Chronic obstructive pulmonary disease No of events	n = 22 ; % = 3.1	n = 35 ; % = 4.9
Active cancer No of events	n = 13 ; % = 1.8	n = 16 ; % = 2.2
Mild No of events	n = 395 ; % = 55.2	n = 390 ; % = 54.4
Moderate No of events	n = 315 ; % = 44	n = 323 ; % = 45
Severe or unknow missing data or invalid tests No of events	n = 6 ; % = 0.8	n = 4 ; % = 0.6

Outcomes

Study timepoints

- 0 day (0 day)
- 29 day (29 days since randomisation)

Incidence of adverse events in the population

Outcome	29 day, Molnupiravir, N = 710	29 day, Placebo, N = 701
≥1 Adverse event No of events	n = 216 ; % = 30.4	n = 231 ; % = 33
≥1 Adverse event related to assigned regimen determined by the investigators No of events	n = 57 ; % = 8	n = 59 ; % = 8.4
≥1 Serious adverse event No of events	n = 49 ; % = 6.9	n = 67 ; % = 9.6
≥1 Serious adverse event related to the assigned regimen determined by the investigators to be related to the assigned regimen No of events	n = 0 ; % = 0	n = 1 ; % = 0.1
Death No of events	n = 2 ; % = 0.3	n = 12 ; % = 1.7
Adverse event No of events	n = 10 ; % = 1.4	n = 20 ; % = 2.9
Adverse event related to the assigned regimen determined by the investigator No of events	n = 4 ; % = 0.6	n = 3 ; % = 0.4
Serious adverse event No of events	n = 5 ; % = 0.7	n = 13 ; % = 1.9
Serious adverse event related to the assigned regimen determined by the investigator No of events	n = 0 ; % = 0	n = 0 ; % = 0

COVID-19 related hospitalisation or death through day 29

Outcome	0 day, Molnupiravir, N = 709	0 day, Placebo, N = 699	29 day, Molnupiravir, N = 661	29 day, Placebo, N = 631
All cause hospitalisation or	n = 48 ; % = 6.8	n = 68 ; % = 9.7	n = 48 ; % = 6.8	n = 68 ; % = 9.7

Outcome	0 day, Molnupiravir, N = 709	0 day, Placebo, N = 699	29 day, Molnupiravir, N = 661	29 day, Placebo, N = 631
death no of events No of events				
COVID-19 related hospitalisation or death No of events	n = 45 ; % = 6.3	n = 64 ; % = 9.2	n = 45 ; % = 6.3	n = 64 ; % = 9.2
COVID-19 related death No of events	n = 1 ; % = 0.1	n = 9 ; % = 1.3	n = 1 ; % = 0.1	n = 9 ; % = 1.3
COVID-19 related hospitalisation No of events	n = 44 ; % = 6.2	n = 55 ; % = 7.9	n = 44 ; % = 6.2	n = 55 ; % = 7.9

All randomised MITT population

Incidence of Hospitalisation or Death by subgroups

Outcome	29 day, Molnupiravir, N =	29 day, Placebo, N =
Female No of events	n = 16	n = 27
Female Sample size	n = 379	n = 344
Male No of events	n = 32	n = 41
Male Sample size	n = 330 ; % = NR	n = 355 ; % = NR
≤3 days No of events	n = 25	n = 28
≤3 days Sample size	n = 339	n = 335
>3 days No of events	n = 23	n = 40

Outcome	29 day, Molnupiravir, N =	29 day, Placebo, N =
>3 days Sample size	n = 370	n = 364
Mild No of events	n = 19	n = 27
Mild Sample size	n = 395	n = 376
Moderate No of events	n = 29	n = 40
Moderate Sample size	n = 311	n = 321
Positive No of events	n = 5	n = 2
Positive Sample size	n = 136	n = 146
Negative No of events	n = 39	n = 64
Negative Sample size	n = 541	n = 520
>60 years of age No of events	n = 12	n = 16
>60 years of age Sample size	n = 118	n = 127
Obese No of events	n = 29	n = 46
Obese Sample size	n = 535	n = 507
Diabetes mellitus No of events	n = 17	n = 17
Diabetes mellitus	n = 107	n = 117

Outcome	29 day, Molnupiravir, N =	29 day, Placebo, N =
Sample size		
Serious Heart Condition No of events	n = 8	n = 9
Serious Heart Condition Sample size	n = 86	n = 78
American Indian or Native American No of events	n = 18	n = 21
American Indian or Native American Sample size	n = 207	n = 199
Asian No of events	n = 7	n = 7
Asian Sample size	n = 25	n = 23
Black No of events	n = 10	n = 15
Black Sample size	n = 157	n = 142
White No of events	n = 29	n = 54
White Sample size	n = 556	n = 573
>60 years No of events	n = 12	n = 16
>60 years Sample size	n = 118	n = 127
≤60 years No of events	n = 36	n = 52
≤60 years Sample size	n = 591	n = 572

Outcome	29 day, Molnupiravir, N =	29 day, Placebo, N =
High viral load defined as >10^6 copies/mL No of events	n = 32	n = 52
High viral load defined as >10^6 copies/mL Sample size	n = 389	n = 382
Low viral load defined as ≤10^6 copies/mL No of events	n = 10	n = 9
Low viral load defined as ≤10^6 copies/mL Sample size	n = 160	n = 162
Undetectable viral load defined as <500 copies/mL No of events	n = 0	n = 0
Undetectable viral load defined as <500 copies/mL Sample size	n = 64	n = 71
Unknown No of events	n = 6	n = 7
Unknown Sample size	n = 96	n = 84
SARS-CoV-2 nasopharyngeal RNA titer RNA Titer (log10 copies/ml) in all randomised population Sample size	n = 373	n = 362
SARS-CoV-2 nasopharyngeal RNA titer RNA Titer (log10 copies/ml) in all randomised population Mean (SD)	-3.91 (1.66)	-3.99 (1.71)
baseline RNA titer ≤10^6 copies/ml mean change from baseline over time Sample size	n = 108	n = 103

Outcome	29 day, Molnupiravir, N =	29 day, Placebo, N =
baseline RNA titer ≤10^6 copies/ml mean change from baseline over time Mean (SD)	-1.77 (0.96)	-1.76 (0.98)
baseline RNA titer >10^6 copies/ml Mean change from baseline over time Sample size	n = 265	n = 259
baseline RNA titer >10^6 copies/ml Mean change from baseline over time Mean (SD)	-4.78 (0.92)	-4.88 (0.96)

Change in RNA titre from baseline

Outcome	Molnupiravir, 29 day, N = 709	Placebo N=699
Day 3 Sample size	n = 499	n = 507
Day 3 Mean (SD)	-1.08 (1.29)	-0.84 (1.26)
Day 5 Sample size	n = 482	n = 482
Day 5 Mean (SD)	-2.09 (1.49)	-1.79 (1.51)
Day 10 Log10 copies/ml Sample size	n = 447	n = 438
Day 10 Log10 copies/ml Mean (SD)	-3.18 (1.62)	-2.99 (1.68)
Day 15 Log10 copies/ml Sample size	n = 424	n = 413
Day 15 Log10 copies/ml Mean (SD)	-3.61 (1.74)	-3.48 (1.84)
Day 29 Log10 copies/ml	n = 373	n = 362

Outcome	Molnupiravir, 29 day, N = 709	Placebo N=699
Sample size		
Day 29 Log10 copies/ml Mean (SD)	-3.91 (1.66)	-3.99 (1.71)

Appendix G: Risk of Bias

Fischer, 2021

Bibliographic Reference	Fischer, William; Eron, Joseph J; Holman, Wayne; Cohen, Myron S; Fang, Lei; Szewczyk, Laura J; Sheahan, Timothy P; Baric, Ralph; Mollan, Katie R; Wolfe, Cameron R; Duke, Elizabeth R; Azizad, Masoud M; Borroto-Esoda, Katyna; Wohl, David A; Loftis, Amy James; Alabanza, Paul; Lipansky, Felicia; Painter, Wendy P; Molnupiravir, an Oral Antiviral Treatment for COVID-19.; medRxiv : the preprint server for health sciences; 2021

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Change in viral load log10 copies/mL - Day 3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in viral load log10 copies/mL - Day 5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in viral load log10 copies/mL - Day 7

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions	Risk of bias judgement for deviations from the intended interventions	Low

Section	Question	Answer
(effect of adhering to intervention)	(effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in viral load log10 copies/mL - Day 14

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Any adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Adverse event grade 3 or higher

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Any adverse event leading to discontinuation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Any serious adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Adverse event leading to death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly

Section	Question	Answer
		applicable to the current situation of COVID-19 in the UK

Jayk Bernal, 2021

Bibliographic Reference	Jayk Bernal, Angelica; Gomes da Silva, Monica M; Musungaie, Dany B; Kovalchuk, Evgeniy; Gonzalez, Antonio; Delos Reyes, Virginia; Martin-Quiros, Alejandro; Caraco, Yoseph; Williams-Diaz, Angela; Brown, Michelle L; Du, Jiejun; Pedley, Alison; Assaid, Christopher; Strizki, Julie; Grobler, Jay A; Shamsuddin, Hala H; Tipping, Robert; Wan, Hong; Paschke, Amanda; Butterton, Joan R; Johnson, Matthew G; De Anda, Carisa; MOVe-OUT Study, Group; Molnupiravir for Oral Treatment of COVID-19 in Nonhospitalised Patients.; The New England journal of medicine; 2021

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All cause hospitalisation or death at day 29

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

COVID-19 related hospitalisation or death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

COVID-19 related death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

COVID-19 related hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Indirect, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – all participants day 3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – all participants day 5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – all participants day 10

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – all participants day 15

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – all participants day 29

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	Risk of bias for deviations from the intended interventions	Low

Section	Question	Answer
assignment to intervention)	(effect of assignment to intervention)	
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – higher viral load at baseline – day 3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – higher viral load at baseline – day 5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – lower viral load at baseline – day 3

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Change in RNA titre – lower viral load at baseline – day 5

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(blocks stratified randomisation based on time since symptoms of onset ≤3 days vs. >3 days)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable, since the study took place before the emergence of the Delta and Omicron variants and before the availability of vaccination for COVID-19, this outcome may not be directly applicable to the current situation of COVID-19 in the UK

Appendix H: Forest Plots

Change in Viral Load at Day 3, 5, 7 to 10, and 14 to 15

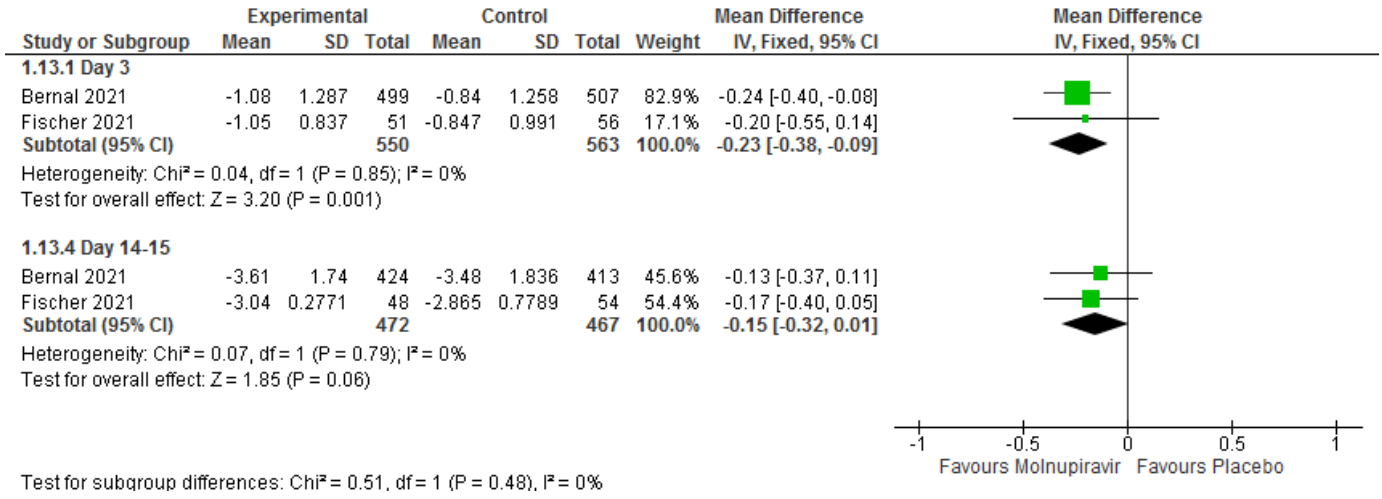


Figure 1: Forest plot indicating meta-analyses carried out at day 3, and day 14-15 using fixed-effects method. Day 5 and day 7-10 viral load has been pooled using random-effects method (shown in next figure)

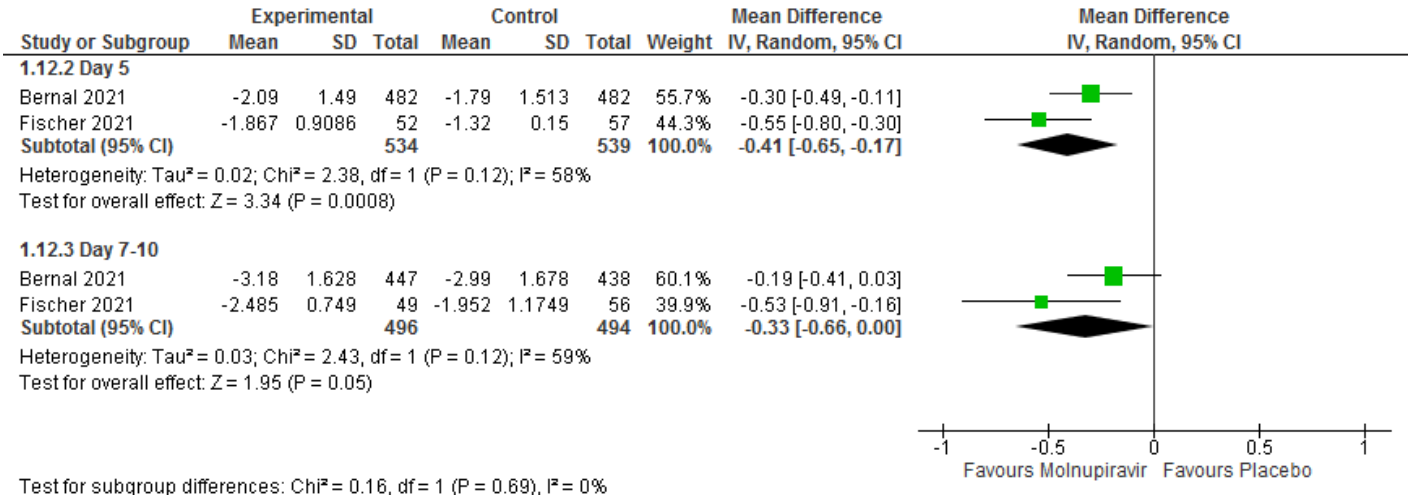


Figure 2: Forest plot indicating meta-analyses carried out at day 5, and day 7-10 using random-effects method due to greater heterogeneity

Participants with ≥1 adverse events and ≥1 serious adverse events

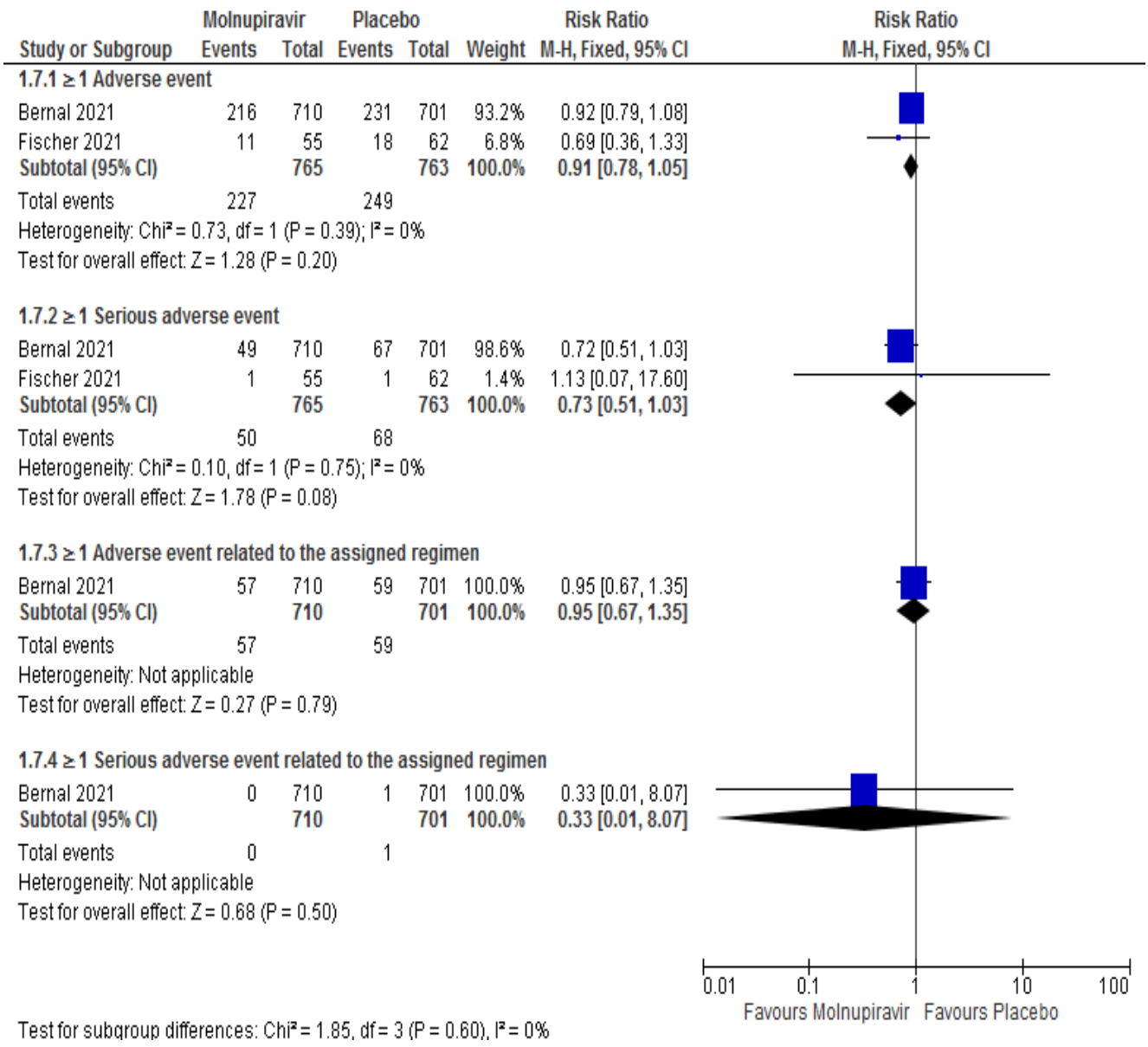


Figure 3: Forest plot indicating meta-analyses carried out for adverse events and serious adverse events using fixed-effect model. Adverse events related to the assigned regimen were also reported in by Jayk Bernal 2021.

Appendix I: GRADE profiles

Molnupiravir compared to placebo for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With molnupiravir		Risk with placebo	Risk difference with molnupiravir
All cause hospitalisation or death											
1408 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	68/699 (9.7%)	48/709 (6.8%)	**RR 0.70** (0.49 to 0.99)	97 per 1,000	**29 fewer per 1,000** (from 50 fewer to 1 fewer)
Hospitalisation or death - Seropositive nucleocapsid antibody status at baseline											
282 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	2/146 (1.4%)	5/136 (3.7%)	**RR 2.68** (0.53 to 13.60)	14 per 1,000	**23 more per 1,000** (from 6 fewer to 173 more)
Hospitalisation or death - Seronegative nucleocapsid antibody status at baseline											
1061 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	64/520 (12.3%)	39/541 (7.2%)	**RR 0.59** (0.40 to 0.86)	123 per 1,000	**50 fewer per 1,000** (from 74 fewer to 17 fewer)
COVID-19 related hospitalisation or death											
1408 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	64/699 (9.2%)	45/709 (6.3%)	**RR 0.69** (0.48 to 1.00)	92 per 1,000	**28 fewer per 1,000** (from 48 fewer to 0 fewer)
COVID-19 related death											

Certainty assessment							Summary of findings				
1408 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	9/699 (1.3%)	1/709 (0.1%)	**RR 0.11** (0.01 to 0.86)	13 per 1,000	**11 fewer per 1,000** (from 13 fewer to 2 fewer)
COVID-19 related hospitalisation											
1408 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	55/699 (7.9%)	44/709 (6.2%)	**RR 0.79** (0.54 to 1.16)	79 per 1,000	**17 fewer per 1,000** (from 36 fewer to 13 more)
Hospitalisation or death by subgroup - ≤ 3 days since symptom onset											
674 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	28/335 (8.4%)	25/339 (7.4%)	**RR 0.88** (0.53 to 1.48)	84 per 1,000	**10 fewer per 1,000** (from 39 fewer to 40 more)
Hospitalisation or death by subgroup - ≥ 3 days since symptom onset											
734 (1 RCT)	not serious	not serious	serious[a]	not serious	none	Moderate	40/364 (11.0%)	23/370 (6.2%)	**RR 0.57** (0.35 to 0.93)	110 per 1,000	**47 fewer per 1,000** (from 71 fewer to 8 fewer)
Participants who discontinued the assigned regimen because of adverse event											
1411 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	20/701 (2.9%)	10/710 (1.4%)	**RR 0.49** (0.23 to 1.05)	29 per 1,000	**15 fewer per 1,000** (from 22 fewer to 1 more)
Participants with adverse events - ≥1 Adverse event											
1528 (2 RCTs)	not serious	not serious	serious[a]	serious[b]	none	Low	249/763 (32.6%)	227/765 (29.7%)	**RR 0.91** (0.78 to 1.05)	326 per 1,000	**29 fewer per 1,000** (from 72 fewer to 16 more)
Participants with adverse events - ≥1 Serious adverse event											

Certainty assessment							Summary of findings				
1528 (2 RCTs)	not serious	not serious	serious[a]	serious[b]	none	Low	68/763 (8.9%)	50/765 (6.5%)	**RR 0.73** (0.51 to 1.03)	89 per 1,000	**24 fewer per 1,000** (from 44 fewer to 3 more)
Change in Viral Load - Day 3											
1113 (2 RCTs)	not serious	not serious	serious[a]	not serious	none	Moderate	563	550	-	**-**	MD **0.23 lower** (0.38 lower to 0.09 lower)
Change in Viral Load - Day 5											
1073 (2 RCTs)	not serious	not serious	serious[a]	not serious	none	Moderate	539	534	-	**-**	MD **0.41 lower** (0.65 lower to 0.17 lower)
Change in Viral Load - Day 7-10											
990 (2 RCTs)	not serious	not serious	serious[a]	serious[b]	none	Low	494	496	-	**-**	MD **0.33 lower** (0.66 lower to 0)
Change in Viral Load - Day 14-15											
939 (2 RCTs)	not serious	not serious	serious[a]	serious[b]	none	Low	467	472	-	**-**	MD **0.15 lower** (0.32 lower to 0.01 higher)
Change in RNA titre at day 29 - Overall											
735 (1 RCT)	not serious	not serious	serious[a]	serious[b]	none	Low	362	373	-	**-**	MD **0.08 higher** (0.16 lower to 0.32 higher)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Since the study took place before the emergence of the Delta and Omicron variants, and before the availability of vaccination against COVID-19, the population in the study may not be directly relevant to current populations.
b. CIs cross line of no effect