South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: Should molnupiravir be used to treat COVID-19?

Date: 20 December 2021

Key findings

- Evidence of the benefits and harms of molnupiravir (MOV) in treating patients aged 18 years and older with COVID-19 was obtained from a peer-reviewed publication of clinical trial data, as well as data submitted to the US Food and Drug Administration (FDA) and placed in the public domain as an Antimicrobial Drugs Advisory Committee (AMDAC) briefing document.
- The phase 2/3 MOVe-OUT trial was conducted in adults with mild-to-moderate COVID-19 who were at high risk for progression to severe COVID-19. Based on an interim analysis conducted after about 50% of planned participants had been enrolled, the trial was stopped because of the positive results obtained.
- Based on the interim analysis (n=775), a significant 6.8% (95% CI: -11.3, -2.4) reduction in the proportion of participants who were hospitalised or died by day 29 was shown between the MOV and placebo groups. In the full analysis, the absolute risk reduction was reduced from 6.8% to 3.0%, (48/709 (6.8%) vs 67/699 (9.6%) hospitalisations or deaths reported in the MOV vs placebo groups, risk difference -3.0%, 95% CI: -5.9, - 0.1). In the full analysis, there was 1 (0.1%) death in the MOV group and 9 (1.3%) deaths in the placebo group, so hospitalisations accounted for most of the events in the composite outcome.
- Those treated with MOV showed better outcomes on the WHO 11-point ordinal scale (used to assess clinical progression of COVID-19 illness) at day 5, compared with placebo, but the majority (66.3%) of both groups improved to a score of 0 (no viral RNA detected) or 1 (asymptomatic disease) by day 29.
- Given the mechanism of action of MOV, the potential for increasing the emergence of novel mutations was closely monitored. Higher mean error rate (number of mutations/10,000 bases, [SD]) was observed in the MOV group (7.4 [10.1]) compared with placebo (3.4 [6.4]) among participants with paired baseline and day 5 SARS-CoV-2 viral sequences. A higher percentage of participants in the MOV group had >3, >6, or >9 mutations/10,000 bases at day 5 compared with placebo.
- Overall, the trial was assessed as moderate quality.
- MOV reduced the risk of hospitalisation or death in adults with mild to moderate COVID-19 who are at high-risk for progression to severe COVID-19 and appeared generally safe. Generalisability of the available data is limited by the small size of the study and the wide definition of hospitalisation. In addition, the requirement that treatment be initiated within 5 days of the onset of symptoms limits the feasibility of this intervention. MOV is also contraindicated in pregnancy, so women of child-bearing potential need to take effective contraception. Lastly, as the study was conducted in unvaccinated patients, the efficacy and safety of MOV in a vaccinated population is unknown.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Although MOV modestly reduces the risk of hospitalisation or death in adults with mild to moderate COVID-19 who are at high-risk for progression to severe COVID-19, and is well tolerated, its use requires rapid access to definitive diagnosis and initiation within 5 days of the onset of symptoms. MOV is contraindicated in pregnancy, so women of child-bearing potential need to take effective contraception. The efficacy and safety of MOV has not been studied in patients previously vaccinated against COVID-19. MOV products have yet to be registered in South Africa and are not available in South Africa. Generic products will only be available to the public sector, and the prices of both generic and innovator brands in South Africa are unknown.
Level of Evidence: Moderate certainty evidence.
Review indicator: Registration of generic and/or innovator brands in South Africa, or access via section 21, with declared prices.

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC for COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

PROSPERO registration: CRD42021286710

BACKGROUND

Molnupiravir (MOV) is an oral prodrug of the antiviral ribonucleoside analog N-hydroxycytidine (NHC), with antiviral activity against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). MOV inhibits viral replication through an accumulation of errors in the viral genome leading to inhibition of replication.

The recommended adult oral dosage was the highest studied dose of 800 mg every 12 hours for 5 days; with treatment initiated within 5 days of symptom onset.

Following a positive press release (1 October 2021) by Merck & Co., Inc and Ridgeback Biotherapeutics, the World Health Organization (WHO) encouraged the release of company data for review and welcomed the signing of a voluntary licencing agreement between MSD and the Medicines Patent Pool (MPP) to facilitate affordable global access (https://medicinespatentpool.org/news-publications-post/mpp-msd-new-licence-announcement-molnupiravir).[1] Some regulatory authorities have assessed submissions from the manufacturer. The United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) were the first (4 November 2021) to authorise MOV for use in mild to moderate COVID-19 with at least one risk factor for developing severe COVID-19 (obesity, older age (>60 years), diabetes mellitus, or heart disease) (https://www.gov.uk/government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra).[2] The US Food and Drug Administration (FDA) have recently (30 November 2021) assessed the submission for the emergency use authorisation of MOV. The FDA Antimicrobial Drugs Advisory Committee (AMDAC) narrowly voted in favour of the US FDA granting an emergency authorisation for the use of MOV for COVID-19 (https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-30-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-11302021-11302021#event-materials).[3] Final FDA approval is still pending. The European Medicines Agency (EMA) is also reviewing data submitted by the manufacturer (https://www.ema.europa.eu/en/news/covid-19-ema-heads-medicines-agencies-update-molnupiravir).[4]

This rapid review summarises the data from the peer-reviewed publication,[5] as well as that submitted to US FDA by Merck & Co., Inc in support of the Emergency Use Authorization (EUA) of MOV.[3] The published data were from the phase 2/3 MOVe-OUT clinical trial (Trial MK-4482-002, also referred to as P002; NCT #04575597) of the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19. The data were placed in the public domain before the 30 November 2021 meeting of the FDA Antimicrobial Drugs Advisory Committee (AMDAC) (https://www.fda.gov/media/154418/download), prior to publication in the New England Journal of Medicine.

RESEARCH QUESTION: What is the efficacy and safety of molnupiravir for the treatment of confirmed COVID-19?

METHODS

This rapid review relied on the data from a single peer-reviewed publication[5] as well as data provided by the manufacturer (Merck & Co., Inc) to the FDA Antimicrobial Drugs Advisory Committee (AMDAC).[3] The published data reflected the full analysis of the phase 2/3 MOVe-OUT clinical trial. The FDA briefing document summarised relevant pre-clinical and earlier phase clinical trial data, as well as the interim and full analyses of MOVe-OUT.

Eligibility criteria for review

Population: Patients with confirmed SARS-CoV-2 infection; no restriction to age or co-morbidity

Intervention: Molnupiravir, either alone or in combination with other medicines

Comparators: Standard of care or placebo

Outcomes: Mortality; progression to hospitalisation; duration of hospitalisation; progression to requiring oxygen; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement; adverse reactions and adverse events

Study design: Systematic reviews of randomised controlled trials; individual randomised controlled trials

RESULTS

Results of the search

A peer reviewed publication[5] and the data submitted by Merck & Co., Inc (8 October 2021) to the US FDA to support the Emergency Use Authorization (EUA) of MOV, and included in the advisory committee briefing document,[3] were retrieved, reviewed and summarised. The main characteristics and outcomes from the phase 2/3 MOVe-OUT clinical trial (Trial MK-4482-002; P002; NCT #04575597) are shown in Table 2.

Description of the included study

The MOVe-OUT trial, a phase 2/ 3 multi-centre, randomised, placebo-controlled, double-blind clinical trial of MOV in non-hospitalised adult patients with mild-to-moderate COVID-19 disease, was conducted at sites in Africa, Asia, Europe, Latin America, and North America. The majority (55.5%) of participants were enrolled at sites in Latin America, while 15.2% were enrolled in Africa. The majority (70.3%) were aged 18-49 years.

Adult patients were eligible for inclusion if they were being treated for mild or moderate COVID-19 in ambulatory settings. Participants had to have laboratory-confirmed SARS-CoV-2 infection, with sample collection ≤5 days prior to randomisation. In addition, the initial onset of COVID-19 signs/symptoms had to be ≤5 days prior to randomisation. Participants had to be at increased risk of severe illness from COVID-19 (i.e., > 60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (BMI ≥ 30), serious heart conditions (coronary artery disease, heart failure, cardiomyopathies), diabetes mellitus). Participants were also required not to have received SARS-CoV-2 vaccines, either prior to the study or during the study, and in the case of female participants, to be non-pregnant or on effective contraception.

Participants were randomised 1:1 to receive 800 mg of MOV or placebo orally every 12 hours for 5 days. The primary efficacy endpoint was a composite of hospitalisation or mortality by day 29. Hospitalisation (all-cause) was defined as ≥24 hours of acute care in a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalisation needs during the COVID-19 pandemic. The primary safety endpoint was the incidence of adverse events. Secondary endpoints included time to sustained improvement or resolution, and time to progression of each targeted self-reported COVID-19 sign/symptom by day 29. The time to sustained improvement or resolution was defined as the number of days from randomisation to the first of 3 consecutive days when resolution or improvement was demonstrated for the targeted self-reported sign/symptom. Time to progression was defined as the number of days from randomisation to the first of 2 consecutive days when the targeted self-reported sign/symptom worsened. The WHO 11-point ordinal scale was used to assess clinical progression of COVID-19 illness where a score of 0 is uninfected (no viral RNA detected), 1 is asymptomatic disease, 2 is symptomatic ambulatory disease without assistance, 3 is ambulatory disease requiring assistance, and 4 and higher require increasing hospital intervention. A score of 10 was assigned at death.

A total of 1433 participants underwent randomisation (n=716 to MOV; n=717 to placebo). At the recommendation of an independent external Data Monitoring Committee and with input from the US FDA, recruitment into the study was stopped early. This decision was reached due to a planned interim analysis, with nearly 50% of participants enrolled (n=775 for efficacy and n=765 for safety), which showed that treatment with MOV potentially had a greater benefit if initiated earlier in the disease course. The interim population analysis (n= 775; 386 on MOV) covered participants enrolled from 7 May 2021 to 5 August 2021. A full population analysis (n= 1433; 710 on MOV) covered participants enrolled from the start of the study to 2 October 2021. Safety data were available for 917 participants who received the 800 mg MOV dose in all clinical trials of the agent. Just over 98% of randomised participants (n=709 in the MOV group and n=699 in the placebo group) were included in the modified intention to treat analysis population (all participants who received at least 1 dose of study intervention and were not hospitalised prior to their first dose). Overall, 94% of participants received 9 or 10 doses of study intervention every 12 hours and completed follow up through day 29 of the study.

Appraisal of the trial

Overall, using the information that was accessible and available for review, the trial was judged to be of moderate quality. A centralised, interactive-response technology system was used for randomisation in this placebo-controlled

study. This was a double blinded RCT and therefore at low risk of bias regarding concealment. The authors reported on primary and secondary outcomes as set out at the start of the study, thus limiting reporting bias. Baseline and disease characteristics were comparable for the MOV and placebo groups, thus limiting selection bias. However, the primary endpoint did rely on the thresholds for hospitalisation, which might have varied between settings. In addition, a wide definition of hospitalisation was used, which included admission for ≥24 hours in either a hospital or similar acute care facility, including emergency rooms or facilities created to address hospitalisation needs during the COVID-19 pandemic.

Effects of intervention(s)

1. Mortality (Primary endpoint; death by day 29)

Full analysis*: MOV vs placebo*

- Death by day 29: 1/709 (0.1%) vs 9/699 (1.3%)

2. Hospitalisation or death (all cause) by day 29: (Primary endpoint)

Full analysis*: MOV vs placebo*

- Hospitalisation or death (all cause) by day 29: 48/709 (6.8%) vs 68/699 (9.7%) (difference 3.0%, 95% CI: -5.9 to -0.1; p=0.0218)

Analysis of hospitalisations or deaths (all cause) by day 29, considered by the investigators to be COVID-19-related: 45/709 (6.3%) in the MOV group vs 64/699 (9.2%) in the placebo group (difference, 2.8%, 95% CI -5.7 to 0.0).

3. Progression to hospitalisation and duration of hospitalisation, progression to requiring oxygen; Progression to ICU admission; Progression to mechanical ventilation; Duration of ICU stay

Not reported**.**

4. Clinical improvement on an ordinal scale at chosen time points; and time to clinical improvement

By day 5, a greater proportion of participants who received MOV showed improved outcomes versus placebo. However, 66.3% of participants in both groups improved to a score of 0 (uninfected (no viral RNA detected) or 1 (asymptomatic disease) by day 29. At baseline, > 98% of participants in the MOV and placebo groups had score of 2 (symptomatic ambulatory disease without assistance).

A lower percentage of participants who received MOV showed worse outcomes on the WHO 11-point ordinal scale compared with those who received placebo. For a score >3 the following observed differences were noted at day 10 and 15:

- Day 10: 34/673 (5.1%) vs 61/673 (9.1%)
- Day 15: 19/699 (2.7%) vs 48/667 (7.2%)

5. Safety (Adverse reactions and adverse events)

The proportion of participants with adverse events considered by the investigators to be related to the trial regimen was not different in those receiving MOV (57/710; 8.0%) or placebo (59/701; 8.4%); difference of -2.5% (95% CI -7.4% to 2.3%). The difference in the proportion reporting ≥ 1 adverse event was also not significantly different between the MOV (216/709; 30.4%) and placebo (231/701; 33.0%) groups; difference of -2.5% (95% CI -7.4 to 2.3). The most frequently reported adverse events (≥2% of participants in MOV vs placebo group) were:

- COVID-19 pneumonia (6.3% of participants in the MOV group vs 9.6% in the placebo group);
- Diarrhea (2.3% vs. 3.0%); and
- Bacterial pneumonia (2.0% vs. 1.6%).

Table 1: Adverse Event Summary

Adverse Events and Discontinuation	Molnupiravir (N=710)	Placebo (N=701)	Estimated Difference (95% CI)*
	number (percent)		*percentage points*
Participants with adverse events			
≥1 Adverse event	216 (30.4)	231 (33.0)	−2.5 (−7.4 to 2.3)
≥1 Adverse event related to the assigned regimen†	57 (8.0)	59 (8.4)	−0.4 (−3.3 to 2.5)
≥1 Serious adverse event	49 (6.9)	67 (9.6)	−2.7 (−5.6 to 0.2)
≥1 Serious adverse event related to the assigned regimen†	0	1 (0.1)	−0.1 (−0.8 to 0.4)
Death	2 (0.3)	12 (1.7)	−1.4 (−2.7 to −0.5)
Participants who discontinued the assigned regimen because of an adverse event			
Adverse event	10 (1.4)	20 (2.9)	−1.4 (−3.1 to 0.1)
Adverse event related to the assigned regimen†	4 (0.6)	3 (0.4)	0.1 (−0.8 to 1.1)
Serious adverse event	5 (0.7)	13 (1.9)	−1.2 (−2.5 to 0.0)
Serious adverse event related to the assigned regimen†	0	0	0.0 (−0.5 to 0.5)

* Differences shown are for molnupiravir as compared with placebo. Difference estimates were based on the Miettinen and Nurminen method.

† Related events were those determined by the investigators to be related to the assigned regimen.

Source: Bernal et al. & MOVe-OUT Study Group. N Engl J Med. 2021 Dec 16.[5]

An additional safety concern with MOV is the potential to enhance SARS-CoV-2 spike protein evolution, by increasing the rate of changes in the genes coding for those proteins. MOV-associated mutagenesis can occur anywhere in the SARS-CoV-2 genome, potentially resulting in amino acid changes in proteins targeted by therapeutics or the immune response. It remains unclear if the potential for MOV-associated changes in the SARS-CoV-2 spike protein presents a public health risk. A higher mean error rate (number of mutations/10,000 bases, [SD]) was observed in the MOV group (7.4 [10.1]) compared with placebo (3.4 [6.4]) among participants with paired baseline and day 5 SARS-CoV-2 viral sequences. A higher percentage of participants in the MOV group had >3, >6, or >9 mutations per 10,000 bases at Day 5 compared with placebo.

More importantly, from a programmatic perspective, MOV is contraindicated in pregnancy and women of child-bearing potential must be on effective contraception if they are to be prescribed this agent. The use of MOV in treating breakthrough infections in patients previously vaccinated against COVID-19 is also unclear, as prior vaccination was an exclusion criterion in the MOVe-OUT trial.

CONCLUSION

Although there is evidence, from the analysis of a study stopped prematurely due to positive outcomes that MOV modestly reduces the risk of hospitalisation or death in patients with mild to moderate COVID-19 treated in ambulatory settings, treatment must be initiated within 5 days of symptom onset. This poses feasibility challenges. In addition, pregnancy must be ruled out and access to effective contraception ensured for women of child-bearing potential. MOV has also only been studied in an unvaccinated population, so efficacy and safety in patients who have previously received a COVID-19 vaccine are unknown.

Reviewers: Andy Gray, Tamara Kredo, Karen Cohen, Jeremy Nel, Milli Reddy, Trudy Leong

Declaration of interests: Although AG serves on a number of South African Health Products Regulatory Authority (SAHPRA) expert committees, no application has yet been submitted for MOV, so no confidential data have yet been accessed. TK (Cochrane South Africa, South African Medical Research Council (SAMRC); Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network and TK, is partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104)

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Table 2. Characteristics of included trials

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
Bernal *et al.* & MOVe-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2021 Dec 16.[5] U.S. Food and Drug Administration Center for Drug Evaluation and Research. Briefing Document for the Antimicrobial Drugs Advisory Committee Meeting (30 November 2021). Available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-30-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-11302021-11302021#event-materials	Phase 2/3 randomised, placebo-controlled, double-blind trial (MK-4482-002; P002 /MOVe-OUT; NCT #04575597) Setting: Multicentre, ambulatory care settings in Latin America, Europe, Africa, North America and Asia Follow up: 29 days Trial stopped after part 1 (Phase 2) as MOV was likely to have a greater benefit if started earlier in the disease	Two populations were analysed: 1. Interim analysis: n = 775 (386 on MOV) 2. Full analysis: n = 1433 (710 on MOV) • Mean (range) age: 43 years (18-90); • Gender: 52.1% male (404/775) • >99% of those randomized had ≥ 1 risk factor for progressing to severe illness. • Common risk factors: obesity (BMI ≥30, 76.5%), age >60 years (13.7%), & diabetes mellitus (13.5%). • Severity: Moderate=43.4%; Mild=56.0% (standard protocol-definitions using clinical data [e.g., heart rate, respiratory rate, O_2 saturation]). • 85.5% had detectable SARS-CoV-2 RNA • 18.2% had positive SARS-CoV-2 antibody results. • Most common (self-reported by >60% of participants) signs and symptoms of COVID-19: cough, fatigue, muscle or body aches, headache, & nasal congestion.	**Efficacy** **Interim analysis:** *MOV vs placebo* •Hospitalisation or death by day 29: 28/385 (7.3%) vs 52/377 (14.1%) (risk difference: -6.8%, 95% CI: -11.3% to -2.4%) • Death by day 29: 0 (0%) vs 8/377 (2.1%) **Full analysis:** MOV vs placebo •Hospitalisation or death by day 29: 48/709 (6.8%) vs 68/699 (9.7%) (risk difference: -3.0%, 95% CI -5.9% to -0.1%) •Death by day 29: 1/709 (0.1%) vs 9/699 (1.3%) COVID-19: related hospitalisations or deaths: 45/709 (6.3%) in the MOV group vs 64/699 (9.2%) in the placebo group had hospitalisations or deaths considered by the investigators to be COVID-19–related (risk difference, 2.8%, 95% CI, −5.7% to 0.0%). **Adverse Events**: *MOV vs placebo* • ≥ 1 adverse event: 21/709 (30.4%) vs 231/701 (33.0%) • Higher mean error rate (number of mutations/10,000 bases, [SD]) was observed in the MOV group (7.4 [10.1]) vs placebo (3.4 [6.4]) among participants with paired baseline and Day 5 SARS-CoV-2 viral sequences. • Higher percentage of participants in the MOV group had >3, >6, or >9 mutations/10,000 bases at Day 5 vs placebo.	MOV reduced the risk of hospitalisation or death among adults with mild to moderate COVID-19 and who are at high-risk for progression to severe COVID-19 and appeared generally safe. Comparable drug-related adverse events in both groups.	**Overall judgement with regards to risk of bias: LOW to MODERATE RISK** *Randomisation:* Conducted by a centralised, interactive-response technology system, and stratified for time since onset of signs or symptoms (≤3 days vs. >3 days): **LOW RISK** *Allocation:* Double blinded study: **LOW RISK** *Selection Bias:* Small size of seropositive baseline subgroup with small number of events. Multi-centre trial involving several parts of the world. Study population does not include pregnant women and those who received any COVID-19 vaccine: **MODERATE RISK** *Testing bias:* Study criteria were explicit and easily followed in a clinical trial setting (noting that in routine clinical practice, assessing serostatus prior to the initiation of treatment may not always be feasible): **LOW RISK** *Measurement of the outcome:* Hospitalisation included a definition of 24 hours of acute care in a wide range of environments used to manage non ambulant patients. The outcome was sensitive to dose of intervention and duration of treatment: **MODERATE RISK**

Table 3. Characteristics of planned and ongoing studies (source: www.covid-nma.com: June 2021)

	Treatment (per arm)	Sample size	Severity at enrollment	Sponsor/Funder	Reg. number
1	Molnupiravir 400mg, 800mg & 200mg vs placebo (NCT04405570) - by Fischer W, 2021.[6] (This was an earlier phase study, including a dose-ranging effort, which has only been issued as a preprint)	202	Not listed	• US Government • Pharmaceutical Industry: Licensed by Ridgeback Biotherapeutics, all funds used for the development of MOV by Ridgeback Biotherapeutics have been provided by Wayne and Wendy Holman and Merck.	NCT04405570

Appendix 1: Summary of Findings

Author(s): Data extracted from Bernal et al. & MOVe-OUT Study Group. N Engl J Med. 2021 Dec 16.[5]

Question: Molnupiravir compared to placebo for mild to moderate COVID-19

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Molnupiravir	placebo / SoC	Relative (95% CI)	Absolute (95% CI)	
Hospitalisation or death (all cause) by day 29											
1	RCT	not serious	not serious	not serious[a]	serious[b]	none	48/709 (6.8%)	67/699 (9.6%)	**RR 0.71** (0.49 to 1.01)	**28 fewer per 1,000** (from 49 fewer to 1 more)	⊕⊕⊕◯ Moderate
Death											
1	RCT	not serious	not serious	not serious[a]	serious[b]	none	1/709 (0.1%)	9/699 (1.3%)	**RR 0.11** (0.01 to 0.86)	**11 fewer per 1,000** (from 13 fewer to 2 fewer)	⊕⊕⊕◯ Moderate
Clinical improvement (WHO ordinal scale)											
1	RCT	not serious	not serious	not serious[a]	serious[b]	none	46/709 (6.5%)	67/699 (9.6%)	**RR 0.68** (0.47 to 0.97)	**31 fewer per 1,000** (from 51 fewer to 3 fewer)	⊕⊕⊕◯ Moderate
Adverse events											
1	RCT	not serious	not serious	not serious[a]	serious[b]	none	216/710 (30.4%)	231/701 (33.0%)	**RR 0.92** (0.79 to 1.08)	**26 fewer per 1,000** (from 69 fewer to 26 more)	⊕⊕⊕◯ Moderate
Serious Adverse events (SAEs)											
1	RCT	not serious	not serious	not serious[a]	serious[b]	none	49/710 (6.9%)	67/701 (9.6%)	**RR 0.72** (0.51 to 1.03)	**27 fewer per 1,000** (from 47 fewer to 3 more)	⊕⊕⊕◯ Moderate
Resistance											
1	RCT	not serious	not serious	serious[c]	not serious	none	A higher mean error rate (number of mutations/10,000 bases, [SD]) was observed in the MOV group (7.4 [10.1]) compared with placebo (3.4 [6.4]) among participants with paired baseline and day 5 SARS-CoV-2 viral sequences. A higher percentage of participants in the MOV group had >3, >6, or >9 mutations per 10,000 bases at Day 5 compared with placebo.				⊕⊕⊕◯ Moderate

CI: confidence interval; **OR:** odds ratio; RCT: randomised controlled trial; **RR:** risk ratio

Explanations

a. The population does not include pregnant women and those who received vaccination. The performance of the medicine in the context of vaccination and with the current variants of concern is not known.

b. Downgraded for imprecision as events are few and confidence interval very wide.

c. Downgraded by one level as clinical implications of identified mutations unclear.

Appendix 1: Evidence to decision framework

Desirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small **X Moderate** ○ Large ○ Varies ○ Don't know	*MOV vs placebo:* **Death by day 29:** 1/709 (<1%) vs 9/699 (1.3%) **Hospitalisation or death (all cause) by day 29:** 48/709 (6.8%) vs 67/699 (9.6%); risk difference -3.0% (95% CI -5.9 to -0.1)) Analysis evaluating only hospitalisations or deaths that were considered by the investigators to be COVID-19–related: 45/709 (6.3%) vs 64/699 (9.2%); risk difference – 2.8%(95% CI: −5.7 to 0.0).	The possibility of combination antiviral therapy with other products (such as ritonavir-boosted nirmatrelvir) which potentially have synergistic mechanisms of action and reduced risk of developing resistance has been proposed.[7]
Undesirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate **X Small** ○ Trivial ○ Varies ○ Don't know	*MOV vs placebo:* **% with ≥ 1 adverse event:** 21/709 (30.4%) vs 231/701 (33.0%) **% with adverse events considered by the investigators to be related to the trial regimen:** 57/710 (8.0%) vs. 59/701 (8.4%) Most frequently reported adverse events (≥2% of participants in MOV vs placebo group) were: COVID-19 pneumonia (6.3% vs 9.6%); Diarrhea (2.3% vs. 3.0%); Bacterial pneumonia (2.0% vs. 1.6%)	The clinical implications of MOV-induced mutations are as yet unclear. MOV is contraindicated in pregnant women and those of child-bearing potential, unless receiving effective contraception.
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very ○ Low **X Moderate** ○ High ○ No included studies	Overall there is **moderate** certainty evidence for the outcomes of interest. • Hospitalisations • Death • Clinical progression of COVID-19 illness (WHO 11-point Ordinal Scale) • Safety	No evidence of safety or efficacy in patients previously vaccinated against COVID-19 is available.
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability **X Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		There is a lack of research evidence from stakeholders. Although a survival benefit is likely to be valued, reduced hospitalisation is also likely to be highly desirable when health systems are under pressure. Concern has been expressed that prescribers would refuse to restrict use to those with increased risk, but would feel ethically compelled to treat all identified patients.[8]
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison **X Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		The need to initiate therapy within 5 days of first symptoms, having obtained a laboratory diagnosis, and excluded contraindications (or, in the case of women of child-bearing potential, ensuring effective contraception), and the modest impact on the primary endpoint (the composite of hospitalisation and death), makes this intervention challenging to justify. Given the need to treat breakthrough infections in those who have previously received a COVID-19 vaccine, the lack of data on that patient group is concerning.

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies **X Don't know**	It is unclear when a product will be registered in South Africa and at what price. The affordability of the product could impact equity. A voluntary licensing agreement is in place between MSD and the Medicines Patent Pool (MPP) to facilitate affordable global access (https://medicinespatentpool.org/news-publications-post/mpp-msd-new-licence-announcement-molnupiravir). However, the terms of the licence restrict sale of the generic version(s) to the public sector in South Africa. The eventual price offered to the public sector is expected to be considerably lower than the approximately $700 per course paid by the United States federal government. [9]	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies **X No included studies**	No included studies	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ **X Don't know**	It is unclear when a product will be registered in South Africa and at what price. The affordability of the product could impact equity.	As the generic version(s) will be restricted to the public sector, the price of the innovator product will be critical to access in the private sector.
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence is available	Considering the potential benefit, the medicine might be considered acceptable by relevant users and stakeholders. However, pregnancy must be ruled out and access to effective contraception ensured for women of child-bearing potential.
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	No MOV-containing products have yet been registered in South Africa. Generic products will only be available to the public sector, and the prices of both generic and innovator brands in South Africa are as yet unknown. Initiation of therapy within 5 days of first symptoms will be challenging, as a laboratory diagnosis is needed, and then prescription by an authorized prescriber who also needs to consider the contraindications and possible need for contraception. Whether use will be justified in vaccinated patients with breakthrough infections is unknown.	

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	20 December 2021	AG, KC, TK, JN, MR, TL	Molnupiravir is not recommended. Modestly reduces the risk of hospitalisation or death in adults with mild to moderate COVID-19 (at high-risk for progression to severe COVID-19), but feasibility issues includes non-availability of a product locally, not for use in pregnancy or the unvaccinated and to be initiated within 5 days of definitive diagnosis.

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