Medicines Adverse Reactions Committee

Meeting date	8/06/2023	Agenda item	3.2.1
Title	**Molnupiravir: review of efficacy information**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient Molnupiravir	**Product name** Lagevrio	**Sponsor** Merck Sharp & Dohme	
PHARMAC funding	Funded for patients that meet PHARMAC access criteria for oral antiviral COVID-19 treatments and has been endorsed accordingly by the prescriber		
Previous MARC meetings	Molnupiravir has not been discussed at a previous MARC meeting		
International action	The European Medicines Agency has recommended the refusal of the marketing authorisation for Lagevrio on 23 February 2023. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/lagevrio		
Prescriber Update	Adverse drug reactions reported following use of oral COVID-19 therapeutics in New Zealand: https://www.medsafe.govt.nz/profs/PUArticles/December2022/Adverse-drug-reactions-reported-oral-COVID-19-therapeutics.html		
Classification	Pharmacist-only medicine		
Usage data	Number of courses dispensed up to 4 May 2023: # Molnupiravir dispensed 44,731		
Advice sought	**The Committee is asked to advise:** • If the evidence for efficacy is strong enough to support the use of molnupiravir for its current approved indication? • If no, are further regulatory actions required? • Whether any communication on this issue in addition to MARC's Remarks is needed?		

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1 PURPOSE

In February 2023, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the refusal of the marketing authorisation for molnupiravir (Lagevrio).

The CHMP concluded that the clinical benefit of molnupiravir (MOV) in the treatment of adults with coronavirus disease (COVID-19) who are not receiving supplemental oxygen, and who are at increased risk of developing severe COVID-19, could not be demonstrated. The balance of benefits and risks of MOV in the treatment of COVID-19 could not be established [1].

The sponsor subsequently requested a re-examination of EMA's opinion. This will be performed by EMA and a final recommendation will be made.

The purpose of this paper is to review the evidence relating to MOV efficacy. The MARC is asked to advise whether the evidence for efficacy is strong enough to support the continued use of MOV for its current approved indication.

2 BACKGROUND

2.1 Molnupiravir

MOV has provisional consent for the following indication: treatment of mild to moderate COVID-19 in adults aged 18 years and older who are at increased risk of progressing to severe COVID-19, hospitalisation, or death [2].

Risk factors for progressing to severe COVID-19, hospitalisation, or death include people with [3]:

- Increasing age
- Compromised immunity due to a medical condition and/or medical treatment
- High-risk medical condition(s) including asthma, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, Downs syndrome, obesity, mental health condition and addiction
- Smokers
- Reside in an aged care facility

Mechanism of action: MOV is an antiviral drug and a prodrug. It is metabolised to the cytidine nucleoside analogue NHC and distributed into cells, where it is phosphorylated to the pharmacologically active ribonucleoside triphosphate (NHC-TP). NHC-TP causes viral error catastrophe via incorporation into viral RNA by viral RNA polymerase. This leads to an accumulation of errors in the viral genome and inhibition of viral replication [2].

2.1.1 Availability and usage

The Therapeutics Technical Advisory Group (Therapeutics TAG), established by the Ministry of Health, advises healthcare professionals on the use of COVID-19 therapeutics in New Zealand. The guidance on the use of therapeutics for COVID-19 was updated on 24 February 2023, to reflect that the Therapeutics TAG no longer recommends the use of MOV [4]. The position statement released by the Therapeutics TAG noted concerns of MOV's lack of clinical effectiveness particularly when used in a highly vaccinated population and against Omicron variants, and the risk of COVID-19 mutations following MOV treatment [4].

MOV remains available in New Zealand and is funded for those who meet PHARMAC access criteria. Eligible patients can obtain MOV via prescription or consultation with a pharmacist trained in COVID-19 antiviral supply. Additionally, MOV can be privately purchased with a valid prescription [5].

On 4 April 2023, PHARMAC opened a consultation to clarify the role of MOV in New Zealand's portfolio of funded COVID-19 treatments [6]. Two possible options for the future role of MOV were proposed:

- Stop funding MOV and delist it from the Pharmaceutical Schedule- it would no longer be publicly funded for any person for COVID-19 treatment

- Make changes to the eligibility criteria for MOV to limit funded access to a smaller group of people who may still be expected to benefit from treatment

The PHARMAC consultation closed on 2 May 2023. The outcomes of the consultation have not yet been published.

Dispensing data for COVID-19 antivirals is captured in the Ministry of Health Qlik application. From 14 April 2022 up to 4 May 2023, there have been 44,731 courses of MOV dispensed in New Zealand (Figure 1).

Table 1. Number of oral COVID-19 antiviral courses dispensed by pharmacies, up to 4 May 2023. Source: Qlik App, COVID-19 Therapeutics: courses dispensed

# Courses dispensed	# Paxlovid dispensed	# Molnupiravir dispensed	# Pharmacies dispensed
149,466	104,735	44,731	907

Comments:

MOV remains available internationally, but its use has declined. In the United States, the CDC COVID-19 treatment guidelines only recommend MOV when other treatments such as nirmatrelvir/ritonavir (Paxlovid) and Remdesivir (Veklury) are not accessible or clinically appropriate.

Similarly to New Zealand, the Australian guidelines created by the National Clinical Taskforce for COVID-19 (Caring for people with COVID-19) do not recommend MOV for the treatment of COVID-19. The guidelines were updated 27 March 2023 and reference the PANORAMIC study (discussed in section 2.2), the findings of which suggests a lack of MOV efficacy.

Paxlovid is more widely used and the oral COVID-19 therapeutic of choice in the community setting (as reflected in the dispensing data). Paxlovid is contraindicated in people with severe renal or hepatic impairment and has a significant number of drug interactions. Therefore, it is not suitable for some patients who are categorised as 'high risk of severe COVID-19 disease' and eligible for antiviral treatment. MOV does not list any of the same contraindications and interactions and can be used in these patients.

2.2 Lack of efficacy

Lack of efficacy is a concern identified from the findings of the PANORAMIC study (discussed in section 3). If patients do not clinically benefit from MOV treatment and experience harm from adverse drug reactions, the risk benefit profile for MOV is unfavourable.

It is not clear what information the CHMP reviewed during their assessment for the marketing authorisation of Lagevrio. However, based on the review of the data presented to them, the CHMP was unable to conclude whether MOV reduced the risk of hospitalisation or death, or shortened the duration of illness/time to recovery in adults at risk of severe disease [1].

Comments:

The Medicines Assessment Advisory Committee (MAAC), met on the 12 April 2022 to consider recommendations on the approval of Lagevrio for the treatment of mild to moderate COVID-19 [7].

The MAAC were provided with Medsafe's Clinical Evaluation Report for Lagevrio (annex 1). The Committee considered the limitations of the pivotal clinical trial and noted risks relating to non-clinical data, SARS-CoV-2 spike protein evolution, and efficacy against different variants of concern.

The Committee considered MOV would still be useful for reducing hospitalisation and death, particularly in in unvaccinated people and where alternative treatments are unsuitable. Overall, the Committee was satisfied by the clinical evaluation and agreed that the clinical report was sufficient to consider recommending provisional consent.

3 SCIENTIFIC INFORMATION

3.1 Published literature

A summary of published literature is provided in this section. There are eleven studies in total: eight are observational studies and three are systematic reviews with a meta-analysis. The literature search focused on MOV use in a real-world setting.

Of the eight observational studies, five were conducted during an omicron dominant wave, a sixth study reported omicron infection in 21% of the participants. Seven of the observational studies included participants that had received at least one dose of a COVID-19 vaccine.

The full text of the PANORAMIC study has been attached as an annex.

3.1.1 Butler et al, 2023, Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open label platform adaptive randomised controlled trial [8].

Purpose: To establish whether the addition of MOV to usual care reduces hospital admissions and deaths associated with COVID-19 in a population at risk of morbidity and mortality.

Design, setting, participants: PANORAMIC was a UK-based, national, multicentre, open-label, multigroup, prospective, platform adaptive randomised controlled trial. Eligible patients were aged 50 years or older or aged 18 years or older with relevant comorbidities in the community, with confirmed COVID-19 infection for 5 days or fewer. The study period was 8 December 2021 to 27 April 2022.

Participants were randomly assigned (1:1) to receive 800mg MOV twice daily for 5 days plus usual care (antipyretics) or usual care only.

Outcomes measured: The primary outcome was all-cause hospitalisation or death within 28 days of randomisation. Secondary outcomes included time to self-reported recovery (defined as the first instance that a participant reported feeling fully recovered from COVID-19), time to early sustained recovery (recovery by day 14 sustained until day 28), time to sustained recovery, self-reported wellness, time to initial alleviation of symptoms, time to sustained alleviation of symptoms, time to initial reduction of symptom severity, contact with health or social services, hospital assessment without admission, oxygen administration, household COVID-19 infections, and safety outcomes.

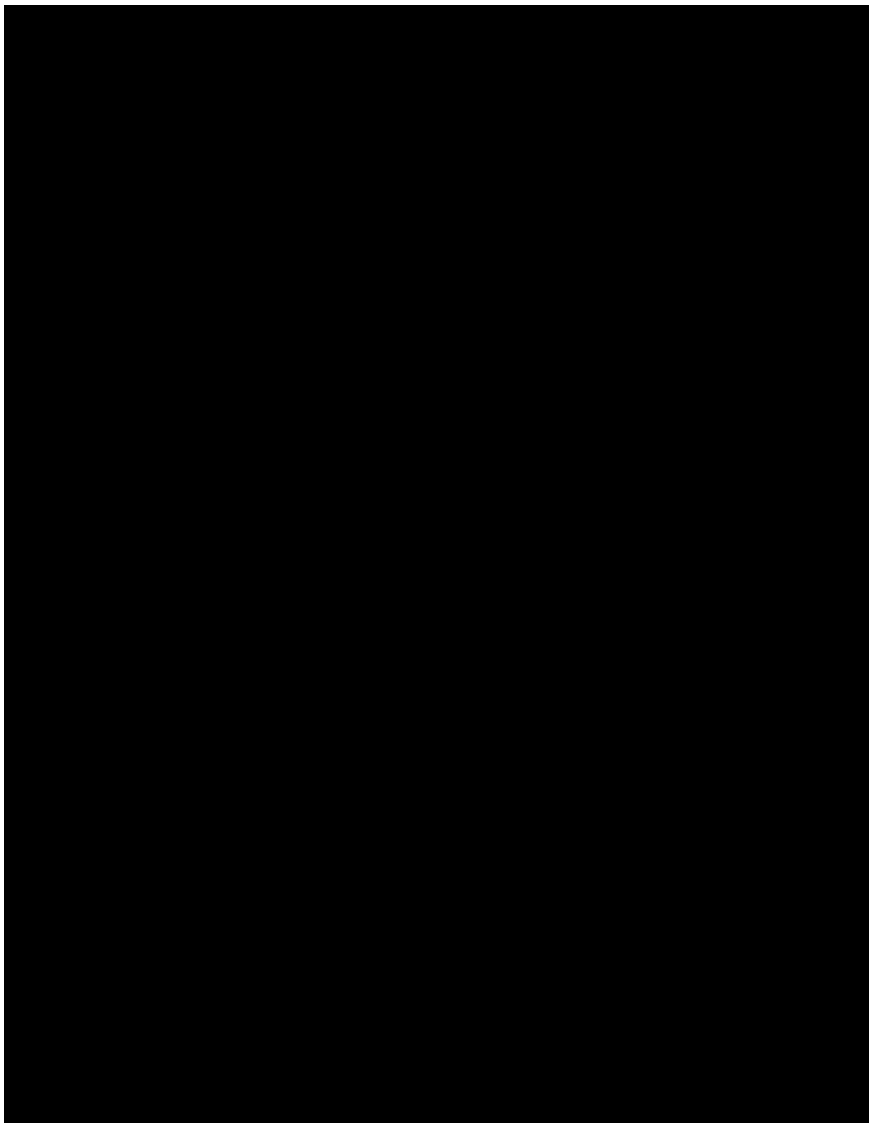
Methods: COVID-19 outcomes were tracked via a self-completed online daily diary for 28 days after randomisation. Bayesian logistic regression with Cauchy priors that regressed on treatment group, comorbidity, and stratification covariates (age and vaccination status) was performed to analyse the primary outcome. In the primary analysis, hospitalisation was lower than anticipated. Therefore, the authors revised the sample size calculation to 16,578 per group (90% power) and 12,4534 per group (80% power), assuming an event frequency of 1% in the control group and 0.67% in the MOV group. For secondary time-to-event outcomes, authors used a Bayesian piecewise exponential module to estimate hazard ratio, adjusting for age, vaccination status and any comorbidity.

Additionally, the authors included a virology sub-study where participants were offered the opportunity to participate in virology testing. These participants were asked to provide nasal and pharyngeal swabs and/or finger-prick dried blood spot samples on days 1 and 5 (or days 4 and 6), and day 14 (or day 13 or 15) counting from before the first molnupiravir dose in the MOV treatment group and the day after randomisation in the usual care group.

Results: There were 12,821 participants in the MOV plus usual care group and 12,962 participants in the usual care group. The mean age of the participants was 56.6 years and 17,703 (69%) of participants had at least one comorbidity. In terms of vaccination status 24,290 (94%) of participants had received at least three doses of a SARS-CoV-2 vaccine.

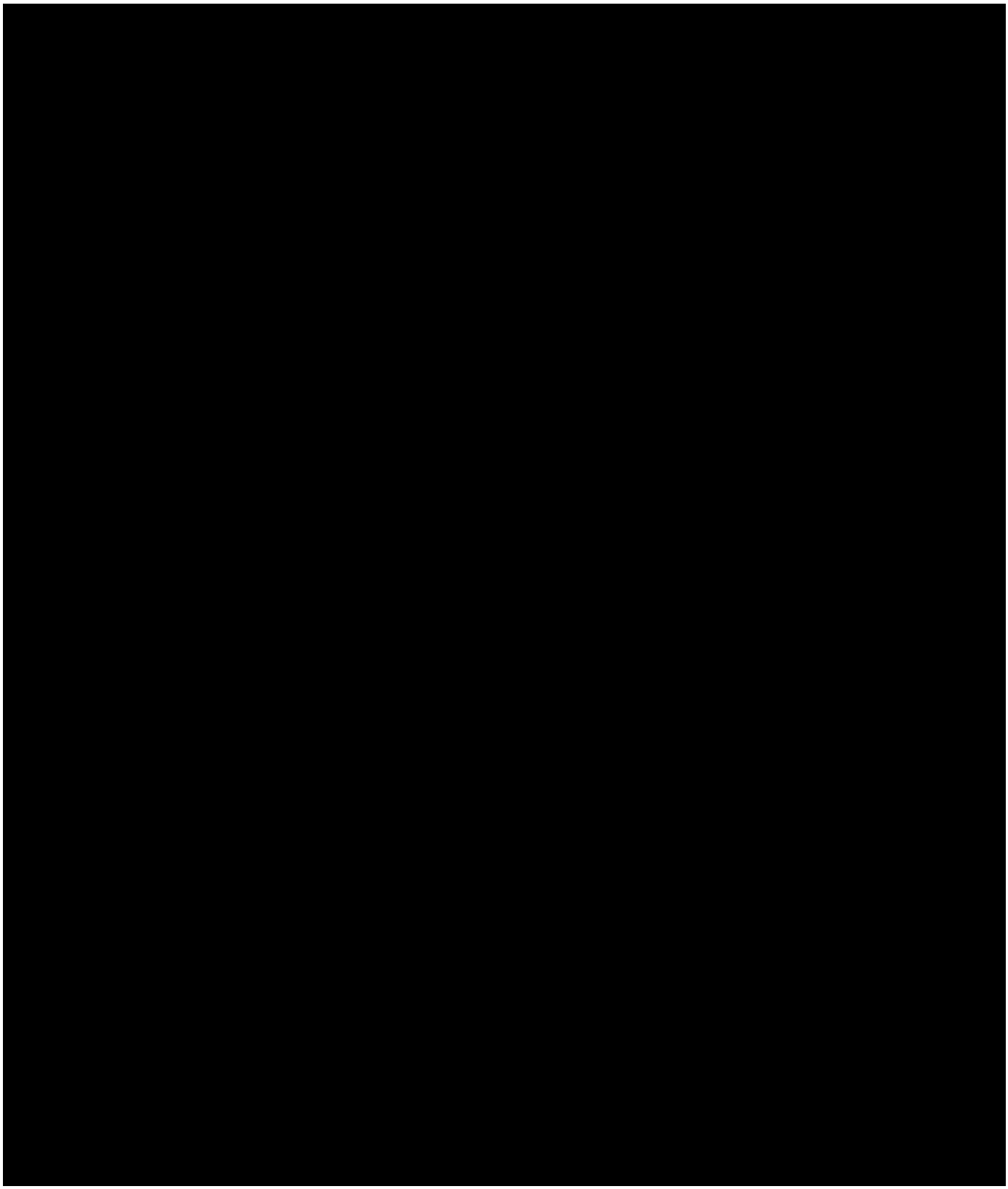
Participants in the MOV plus usual care group had a mean age of 56.7-years (SD 12.5) and the majority were female (58%) and of white ethnicity (94%). Only 9% of the MOV population were in the age group 18-74-years and considered clinically extremely vulnerable. In the MOV treatment group, 69% of patients had at least one comorbidity, the most prevalent comorbidity was lung disease (23%), followed by heart disease (8%), and kidney disease (2%). Baseline characteristics were very similar in the usual care group.

Figure 1. Forest plot group and subgroup analyses for hospitalisation, death, or both. Source: Butler et al.



Data for the primary analysis was available for 25,054 (97%) of participants. Hospitalisation or deaths were recorded in 105 (1%) of 12,529 participants in the MOV plus usual care group versus 98 (1%) in the usual care group (adjusted odds ratio 1.06 [95%CI 0.81-1.41]). Results in an analysis unadjusted for baseline covariables were identical. There was no evidence of a treatment interaction in any patient subgroup (Figure 1).

Table 2. Primary and secondary outcome results. Source: Butler et al



Median time from randomisation to first recovery was 9 days in the MOV plus usual care group and 15 days in the usual care group (estimated benefit 4.2 days [95%CI 3.8-4.6]). Estimated median time to first recovery was 10·4 days (95%CI 10.1–10.6) in the MOV plus usual care versus 14.6 days (14.2–15.0) in the usual care group

(hazard ratio 1.36 [95%CI 1.32–1.40]), which met the prespecified superiority threshold. Subgroup analyses showed that this benefit was consistent across all study groups (Table 2).

Compared with the usual care group, participants in the molnupiravir plus usual group more often reported early sustained recovery, higher self-rated wellness, reduced time to sustained recovery, reduced time to alleviation of all symptoms, reduced time to sustained alleviation of all symptoms, reduced time to reduction of symptom severity, fewer moderate or severe symptoms at days 7, 14, and 28, and less contact with general practitioners. Emergency department attendance and the number of new infections in participants' households were similar in both groups (Table 2).

In the intensively sampled virology cohort, SARS-CoV-2 viral load was undetectable on day 7 in seven (21%) of 34 participants in the MOV plus usual care group and one (3%) of 39 in the usual care group (p=0·039). In the less intensively sampled virology cohort, viral loads were lower in the MOV plus usual care group than in the usual care group at day 5. Viral load at day 14 was low overall but slightly higher in the MOV plus usual care group than in the usual care group (Table 2).

Serious adverse events were reported for 50 (0.4%) of 12,774 participants in the MOV plus usual care group and for 45 (0.3%) of 12,934 in the usual care group. No serious adverse events that were definitely related to the intervention were reported. 145 (1.1%) of 12,774 participants in the MOV plus usual care group withdrew because of adverse effects that were attributed to MOV. No adverse events of special interest were reported.

Discussion and conclusion: The results of this trial found that early addition of MOV to usual care did not reduce hospital admissions or death in people with COVID-19 at increased risk of adverse outcomes. Patients treated with MOV had a higher rate of self-reported sustained recovery and reduced contact with GP health services. Authors did not identify any patient subgroup in which MOV was associated with a reduced risk of hospital admission, and benefits in terms of time to first self-report of recovery were evenly distributed across subgroups. Few serious adverse events were recorded in the trial, and none definitely related to MOV.

The primary analysis estimated a 33% probability of superiority. The analysis can also be interpreted in terms of inferiority: the estimated probability of MOV use increasing hospitalisation or death by any non-zero amount is 67%. The primary analysis does not provide compelling evidence for either conclusion. The 95%CI for the primary outcome (0.81–1.41) indicates that plausible effects for MOV could range from a 19% reduction to a 41% increase in the risk of hospitalisation or death. Taken together, these estimates suggest that the effect of MOV is modest (in either direction). Under the best-case assumption of a 19% risk reduction, the number needed to treat in the population is 677.

Overall, the benefits of MOV in terms of faster time to recovery, reduced contact with health services, and reduced viral load need to be considered in the context of the prevailing disease, burden on healthcare services, social circumstances, and opportunity cost.

Comments:

There were several limitations when generalising the results of the PANORAMIC trial:

- MOV is indicated for individuals at high risk of developing severe infection. All patients included in the trial had at least one risk factor for severe disease or hospitalisation. However, people with multiple risk factors or who are severely immunocompromised (and could benefit from MOV treatment) were not included in the trial population. These patients were referred to specialised COVID-19 treatment clinics and received other therapeutic treatments.
- Trial participants in this study were relatively young (average age 56.7 years), highly vaccinated, and healthy (fewer comorbidities/risk factors per person) compared to other MOV studies (these studies are discussed in below). Most participants in the MOV group (99%) were vaccinated with at least one dose of a COVID-19 vaccine, and 92% of participants had three doses (time since last vaccination was not provided).
- The PANORAMIC study was conducted during an omicron predominant phase in a highly vaccinated population. The omicron strain is milder and less likely to cause severe disease, hospitalisations, and

death in those infected compared to other COVID-19 variants (delta). This was reflected by the low hospitalisation numbers in both the MOV group (n=105) and usual care group (n=98).
- Given this was an open label trial, participants were not blinded to treatment and were asked to self-report outcomes (symptoms, adverse events, recovery). Participant outcomes are often subjective, and bias will influence the results. It is interesting that self-reported outcomes (contact with health services, symptom severity) weren't significantly different between the two groups.

Overall, the incidence of serious adverse reactions was low in the MOV group. Although patients did not have a statistically significant reduced risk of hospitalisation or death, MOV treatment was associated with a faster time to recovery, reduced symptom severity, and less need for healthcare services. Additionally, participants treated with MOV had a faster time to a reduction in viral load, in those included in the virology sub-study.

3.1.2 Bernal et al, 2021, Molnupiravir for oral treatment of COVID-19 in non-hospitalised patients (MOVe-OUT) trial [9].

Purpose: To evaluate the efficacy and safety of MOV treatment when initiated within 5 days after the onset of signs and symptoms of mild-moderate COVID-19 infections in unvaccinated, non-hospitalised adults with at least one risk factor for severe disease.

Design, setting, participants: Phase III, double-blind, international, randomised, placebo-controlled trial. Initiated 6 May 2021 and completed 4 November 2021. Key inclusion criteria at randomisation were SARS-CoV-2 infection that had been laboratory-confirmed no more than 5 days earlier, onset of signs or symptoms no more than 5 days earlier, at least one sign or symptom of Covid-19, and at least one risk factor for development of severe illness from Covid-19.

Outcomes measured: Primary efficacy endpoint was the incidence of hospitalisation or death at day 29. The primary safety endpoint was the incidence of adverse events. A planned interim analysis was performed when 50% of participants had been followed through to day 29. Secondary efficacy end points were based on the WHO 11-point Clinical Progression Scale and on patients reported Covid-19 signs and symptoms through to day 29. Exploratory endpoints included mean changes in SARS-CoV-2 viral load from baseline.

Methods: Participants were randomised in a 1:1 ratio to receive either MOV (800mg twice daily) or placebo for five days. Randomisation was stratified in blocks of four according to the time since onset of signs or symptoms (≤ 3 days vs ≥ 3 days).

Miettinen and Nurminen method, was used to calculate the adjusted risk difference and associated 95%CI for analysis using Cochran–Mantel–Haenszel weights. The planned enrolment of 1550 participants was selected to ensure greater than 95% power to demonstrate superiority in the primary end point at a one-sided 2.5% alpha level if the underlying event rates were 6% with MOV and 12% with placebo.

Results: A total of 1433 participants underwent randomization; 716 were assigned to receive MOV and 717 to receive placebo. With the exception of an imbalance in sex, baseline characteristics were similar in the two groups.

The median age range of participants in the MOV group was 42-years (18-90), and 44-years (18-88) in the placebo group. The most common risk factor for severe COVID-19 disease was obesity, which was present in 73.7% of the participants. There were more females in the MOV group (53.6%) compared to men and most participants in the MOV group (55.2%) reported mild COVID-19 disease severity.

During the interim analysis, the risk of hospitalisation for any cause or death through to day 29 was significantly lower with MOV (28/385 participants [7.3%]), than with placebo (53/377 [14.1%]). The difference in hospitalisation/death at the interim analysis was -6.8% points (95%CI -11.3 to -2.4, P=0.001).

In the final analysis of all participants, the percentage of participants who were hospitalised or died through day 29 was lower in the MOV group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0% points; 95%CI −5.9 to −0.1), (Figure 2). Results of subgroup analyses were largely consistent with these overall results; in some subgroups, such as patients with evidence of previous SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes, the point estimate for the difference favoured placebo.

One death was reported in the MOV group and 9 were reported in the placebo group. Adverse events were reported in 216 of 710 participants (30.4%) in the MOV group and 231 of 701 (33.0%) in the placebo group. None of the serious adverse events experienced in the MOV group were assessed as being related to MOV (Table 3). Adverse events reported in the MOV and placebo groups were similar and included COVID-19 pneumonia, diarrhoea, bacterial pneumonia, worsening of COVID-19, nausea, and dizziness.

Discussion/conclusion: These data from the MOVe-OUT phase 3 trial in non-hospitalised at-risk adults with COVID-19 indicate that MOV, initiated within 5 days after the onset of symptoms, reduces the risk of hospitalisation for any cause or death through day 29. Secondary endpoints, including changes in the WHO Clinical Progression Scale and in patient-reported symptoms of Covid-19, also indicated clinical benefits with MOV over placebo.

Comments:

In the pivotal MOVe-OUT trial, MOV was associated with a lower risk of hospitalisation or death at day 29 compared with placebo. The reduction in risk was -6.8% in the interim analysis and -3% in the final analysis. The reasons for this difference are unknown, but potential contributing factors include imbalances between the analysis samples, shifts in the epidemiology of the pandemic, regional variation among the enrolled participants, and differences in hospital practice or capacity which may have affected hospitalisation rates.

Outcomes did not appear to be better with MOV than with placebo in several subgroups (some of relatively small sample size), including patients with evidence of previous SARS-CoV-2 infection, patients with low baseline viral load, and patients with diabetes mellitus; in all cases the 95% confidence intervals of the estimated risk differences included zero. No safety concerns with MOV were identified and there was no evidence of a pattern of clinically meaningful abnormalities in laboratory test results

In this trial all participants had at least two risk factors for severe disease (at least one comorbidity and were unvaccinated). This study was also conducted during different phases of SARS-CoV-2 variants (delta,

gamma, and mu). The benefits of MOV in vaccinated patients during the omicron phase were not studied in this trial.

3.1.3 Xie et al, 2023, Molnupiravir and risk of hospitalisation or death in adults with COVID-19: emulation of a randomised target trial using electronic health records [10].

Purpose: To emulate a randomised target trial to estimate the association between MOV and hospital admission or death in adults with SARS-CoV-2 infection in the community during the omicron predominant era who were at high risk of progression to severe COVID-19.

Design, setting, participants: Randomised target trial, using electronic health records from the US Department of Veterans Affairs (VA). The VA healthcare data captures information on preventative and maintenance health, outpatient care, inpatient hospital care, prescriptions, mental healthcare, home healthcare, primary, and specialist care. Participants were adults with SARS-CoV-2 infection between 5 January and 30 September 2022 with at least one risk factor for progression to severe COVID-19.

Outcomes measured: The primary outcome was a composite of all cause hospital admission based on information from the inpatient database, or death based on patient vital status data. Authors also examined the outcomes of hospital admission and death separately.

Methods: Participants who received MOV treatment were identified and matched in a 1:10 ratio to the control group who did not receive treatment. Participants were matched on personal characteristics, vital signs, health characteristics, and vaccination status.

Each participant was assigned (cloned) to both the treatment and the no treatment groups at the date of study enrolment. Populations were then defined with different baseline characteristics and several additional trials separately emulated to estimate effectiveness of MOV versus no treatment. Authors conducted three sensitivity analyses to test the robustness of results. This included conducting analyses only in participants with no events during the treatment initiation period (in the primary approach they included participants with events during this period). Second, they conducted a separate trial emulation process in which the treatment initiation period was three days from a positive SARS-CoV-2 test result (in the primary approach this period was five days after a positive result). Finally, they evaluated the effectiveness of molnupiravir in reducing the risk of COVID-19 related hospital admission or death (in the primary approach the outcome was all cause hospital admission or death). Findings were considered to be statistically significant when the 95%CI for risk on a relative scale did not cross 1 or when the 95%CI for risk difference on an absolute scale did not cross zero.

Results: Overall, 85,998 adults were enrolled: 7,818 were eligible and treated with MOV and 78,180 received no treatment. Before weighting, the study cohort had a mean age of 67.3-years, 75.7% were white, and 89.5% were men. In this trial 15-20% of participants were unvaccinated and 50-55% were reported to have had three COVID-19 vaccine doses.

Figure 3. Cumulative incidence of hospital admission or death in MOV (purple) and no treatment (orange) groups. Source: Xie et al.

Compared to no treatment, MOV was associated with a reduction of hospital admission or death at 30 days (RR 0.72 [95%CI 0.64-0.79]). The rate of hospital admission or death at 30 days was 2.7% (2.5%-3.7%) in the MOV group and 3.8% (3.7%-3.9%) in the no treatment group with an absolute risk reduction of 1.1% (95%CI 0.8%-1.4%) (Figure 3). Analysis of prespecified population groups in separately emulated trials suggest that MOV was effective in reducing hospitalisation or death at 30 days (Table 4). Following sensitivity analyses, the results were consistent with the primary approach suggesting that MOV was effective in reducing hospital admission or death at 30 days compared with no treatment.

Table 4. Relative risk, event rate, and absolute risk reduction for composite of hospital admission or death at 30 days in prespecified population groups eligible for treatment with MOV. Source: Xie et al.

Discussion/conclusion: The findings of this study emulating a randomised target trial suggest that MOV is effective in reducing hospital admission or death at 30 days and is effective in those who have not been vaccinated against COVID-19, have received one or two vaccine doses, and have received a booster dose; those infected during the omicron predominant era (BA.1 or BA.2 and BA.5); those with no history of SARS-CoV-2 infection and with a history of SARS-CoV-2 infection; in those 65 years and younger and older than 65 years; men and women; and those with and without cancer, cardiovascular disease, chronic kidney disease, and diabetes.

Comment:

In this large observational study using electronic records, MOV was shown to reduce the risk of hospital admission and death in participants with at least one risk factor for developing severe Covid-disease compared to no treatment.

In comparison to the PANORAMIC study, the participants included in this study had a higher baseline risk of hospitalisation, these participants were generally older (average age of 67.3-years compared to 56.7-years in PANORAMIC) and had higher rates of cardiovascular disease and diabetes (40.6% and 40.8% compared with 8% and 12% respectively in PANORAMIC). The authors of this study suggest a possibility of a graded erosion in MOV effectiveness as the baseline risk of the target population decreases- those at highest risk of progression to severe disease are most likely to benefit from MOV treatment.

Some study limitations included a lack of diversity in patient characteristics, most participants were white and men which limits the generalisability of the findings. There was potential for residual confounding and misclassification bias as those eligible for and treated with MOV had a higher baseline health burden that those who received no treatment. Residual confounding, if present, may have resulted in underestimation of the findings for MOV. Misclassification of drug use may have occurred if people obtained prescriptions for MOV outside of the Veterans Affairs system- although this is likely rare, and other types of misclassification may have occurred when recording previous SARS-CoV-2 infection, healthcare utilisation and health seeking behaviours. The authors did not evaluate the incidence of adverse events or risk of post-acute outcomes which is an area of interest.

3.1.4 Wong et al, 2023, Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study [11].

Purpose: Authors aimed to assess the clinical effectiveness of two oral antiviral drugs among community-dwelling COVID-19 outpatients in Hong Kong.

Design, setting, participants: Observational study using a retrospective cohort design (primary analysis) and case-control design (as a sensitivity analysis). Data was collected from the Hong Kong Hospital Authority. Non-hospitalised patients with SARS-CoV-2 infection were identified between 26 February and 26 June 2022. The omicron subvariant BA.2.2 was dominant during the study period.

Table 5. Baseline characteristics of non-hospitalised patients with COVID-19 after 1:10 propensity-score matching. Source: Wong et al.

Outcomes measured: Study outcomes were death, COVID-19-related hospitalisation, and in-hospital disease progression (in-hospital death, invasive mechanical ventilation, or intensive care admission).

Method: Electronic medical records were reviewed and patients with confirmed COVID-19 disease who received either MOV or nirmatrelvir plus ritonavir (NR) were identified. Patients were matched with controls using propensity score (1:10) according to age, sex, date of infection diagnosis, Charlson Comorbidity Index score, and vaccination status. Hazard ratios (HRs) were estimated by Cox regression for the primary analysis, and odds ratios in oral antiviral users compared with non-users by logistic regression for the sensitivity analysis. The study followed the STROBE guidelines and was approved by the University of Hong Kong and Hospital Authority Hong Kong West Cluster review boards.

Patients were followed up for a median of 103 days in the MOV group and 99 days in the NR group. In the case-control portion of the study, controls were followed up for 28 days after COVID-19 diagnosis.

Results: Among 1,074,856 non-hospitalised patients with COVID-19, there were 5,383 patients that received MOV and 6,464 patients who received NR in the community setting. Baseline characteristics of each group are presented on Table 5. A higher percentage of participants in the MOV group were aged >60-years compared with the NR group (88.7% and 85.9%). In terms of vaccination status 16.1% of MOV participants were fully vaccinated (at least two doses of Comirnaty or three doses of CoronaVac), whereas 33.4% of NR patients were reported to be fully vaccinated. The outcomes for outpatient MOV and NR use versus matched controls are shown on Tables 6 and 7.

Table 6. Outcomes for outpatient MOV users versus matched controls. Source: Wong et al.

Table 7. Outcomes for outpatient NR users versus matched controls. Source: Wong et al.

MOV use was associated with lower risks of death (HR 0.76 [95%CI 0.61–0.95]) and in-hospital disease progression (0.57 [0.43–0.76]) than non-use was, whereas risk of hospitalisation was similar in both groups (0.98 [0.89–1.06]).

NR use was associated with lower risks of death (0.34 [0.22–0.52]), hospitalisation (0.76 [0.67–0.86]), and in-hospital disease progression (0.57 [0.38–0.87]) than non-use was.

With respect to the sensitivity analysis using a case-control design, findings from sensitivity analyses were generally consistent with those of the primary analysis. In the subgroup analyses of study outcomes stratified by age and vaccination status, results comparing MOV use, and non-use were significant for reduced risks of all-cause mortality and in-hospital disease progression among patients older than 60 years, in addition to a significantly reduced risk of COVID-19-related hospitalisation (0.89 [0.81–0.97]; p=0·0067). Results comparing

NR with non-use were generally consistent across subgroups in reducing the risks of both mortality and hospitalisation.

Discussion/conclusion: In this retrospective cohort of community-dwelling patients with COVID-19 during a pandemic period dominated by the SARS-CoV-2 omicron variant, early initiation of oral antivirals was associated with a significant reduction of all-cause mortality risk, compared with no treatment.

Comments:
This study provided further real-world evidence that both oral antivirals are associated with a lower risk of hospitalisation and in-hospital disease progression. The authors mention several limitations including indication bias (difficulty matching participant groups with controls given patients exposed to antivirals are older and more likely to be unvaccinated), confounding by indication when choosing what antiviral to prescribe, and self-ascertainment bias (patients may have been missed from antiviral eligibility due to not reporting COVID-19 infection). Additionally the authors did not differentiate between all-cause mortality and deaths caused by COVID-19 which may have influenced the results.

3.1.5 Suzuki et al, 2022, Real-world clinical outcomes of treatment with Molnupiravir for patients with mild to moderate coronavirus disease 2019 during the Omicron variant pandemic [12].

Purpose: Authors aimed to evaluate the efficacy of MOV in highly vaccinated patients with mild-to-moderate COVID-19 during the Omicron variant surge in Fukushima Prefecture, Japan.

Design, setting, participants: This is a retrospective cohort study conducted by using an electronic database with data collected from 23 hospitals in Japan. Patients enrolled in the study were those hospitalised with mild-to-moderate COVID-19 between January and April 2022. The inclusion criteria for treatment with MOV were guided by those for the MOVe-OUT trial.

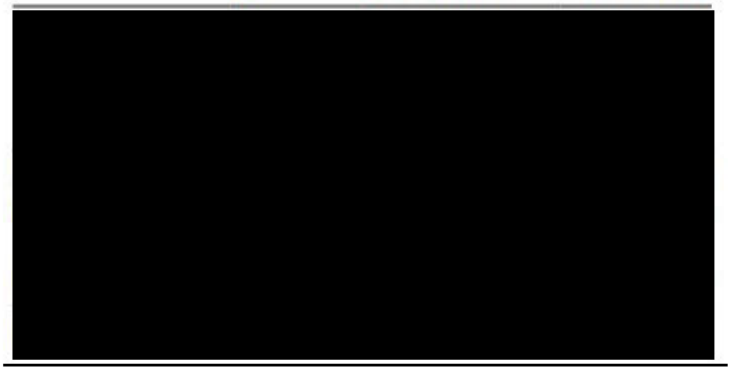
Outcomes measured: The primary outcomes of interest were any clinical deterioration, need for mechanical ventilation, and all-cause death after initiation of MOV. The secondary outcomes included the association between treatments and clinical deterioration after hospitalisation.

Method: Electronic health records were analysed for 1,929 eligible patients who were hospitalised with COVID-19. Clinical deterioration after admission was compared between MOV users and non-users after 1:3 propensity score matching. Additionally, authors performed forward stepwise multivariate logistic regression analysis to evaluate the association between clinical deterioration after admission and MOV treatment in the 1:3 propensity score-matched subjects.

Comparisons between groups for the continuous variables and categorical variables were performed using Mann–Whitney U test and Chi-square test, respectively. A two-tailed P value of <0.05 was considered statistically significant.

Results: Among the 1,929 COVID-19 patients enrolled in the study, 281 were administered MOV. Using the 1:3 propensity score matching method, 230 patients treated with MOV and 690 control patients were selected. Baseline characteristics were similar between the two groups. The median age of participants was 64.1-years, 53% were male, and 16.7% were current smokers. Most patients who received MOV were vaccinated (82.2%). Regarding comorbidities (active cancer, chronic kidney disease, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, and chronic liver disease), there was no imbalance between the two groups, except for the presence of hypertension, dyslipidaemia, diabetes mellitus, and cardiac disease. However, the differences in the presence of comorbidities was not statistically significant.

Table 8. Comparison of the clinical outcomes between the MOV users and non-users after adjustment with 1:3 propensity score. Source: Suzuki et al.



The clinical deterioration rate was significantly lower in the MOV users compared to the non-users (3.90% vs 8.40%; P=0.034). One of the non-users required mechanical ventilation however, there was no significant difference in mechanical ventilation need between the two groups. Three nonusers and two MOV users died. There was no significant difference regarding death rate between the two groups (Table 8).

Table 9. Multivariate logistic regression analysis of deterioration after hospitalisation among patients with COVID-19 matched using a 1:3 propensity scoring matching*. Source: Suzuki et al.

(DOATS score (1-5) is a tool established by the authors, used to evaluate the risk of deterioration after admission (5 represents highest risk)).

The results of multivariate logistic regression analysis of the association of COVID-19 deterioration during hospitalisation are shown in Table 9. According to this analysis, not receiving MOV was a risk factor related to the clinical deterioration of COVID-19 (OR 0.448; 95% CI0.206–0.973; P=0.042), independent of other covariates, including the use of sotrovimab.

Discussion/conclusion: This real-world retrospective study of high-risk mild-to-moderate COVID-19 patients, who had a high vaccination rate, during the Omicron variant pandemic demonstrated a low rate of clinical deterioration after treatment with molnupiravir. Treatment with MOV should be considered to prevent deterioration in high-risk patients with mild-to-moderate COVID-19.

Comment:

This Japanese study conducted during the omicron dominant period reports a reduction in clinical deterioration in MOV treated patients hospitalised for mild-moderate COVID-19.

The authors set the primary outcome in this study as clinical deterioration which is less objective that endpoints such as mechanical ventilation and death. The authors justify that clinical deterioration is an important outcome to measure individual disease burden, concerns about post COVID-19 conditions, and health economics. Missing information that could have influenced study results included data relating to the duration between COVID-19 symptom onset and MOV administration, and date of hospitalisation, data on whether MOV contributes to shortening the length of hospital stay, and data on the date between vaccination and infection.

3.1.6 Khoo et al, 2022, Molnupiravir verus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial [13].

Purpose: Authors aimed to evaluate the safety and virological efficacy of MOV in vaccinated and unvaccinated individuals with COVID-19.

Design, setting, participants: Randomised, placebo-controlled, double-blind, phase II trial conducted across five health and care research centres in the UK between November 18, 2020, and March 16, 2022. Eligible participants were adult outpatients with confirmed mild-to-moderate SARS-CoV-2 infection within five days of symptom onset, in generally good health, and free of uncontrolled chronic conditions.

Outcomes measured: The primary endpoint was the time from randomisation to a negative SARS-CoV-2 PCR test. Secondary endpoints were the 11-point WHO Clinical Progression Scale for COVID-19 at days 15 and 29, time to hospital admission and hospitalisation rates at days 15 and 29. Safety was evaluated using real-time serious adverse event reporting. Adverse events of grade 1–2 were categorised as mild and adverse events of a grade of 3 or more were defined as severe.

The primary outcome was analysed in the intention-to-treat population and safety was analysed in the safety population, comprising participants who had received at least one dose of allocated treatment.

Method: Using permuted blocks (block size 2 or 4) and stratifying by site, participants were randomly assigned (1:1) to receive either MOV plus standard of care or matching placebo plus standard of care. Results were analysed using Bayesian Cox proportional hazard models to estimate the probability of a superior virological response (hazard ratio [HR]>1) for MOV versus placebo. Authors defined a priori that if the probability of a HR of more than 1 was more than 80%, molnupiravir would be recommended.

Results: There were 1,723 patients were assessed for eligibility, of whom 180 were randomly assigned to receive either MOV (n=90) or placebo (n=90) and were included in the intention-to treat analysis. All 180 participants received at least one dose of treatment and four participants discontinued the study (one in the MOV group and three in the placebo group).

The median age of participants was 43 years (range 28-55), there were more female (57%) participants than males, and 90 (50%) of participants had received at least one dose of a COVID-19 vaccine. Participants were infected with the following variants of concern: delta (40%), alpha (21%), omicron (21%), and EU1 (16%).

Figure 4. Forest plot for time from randomisation to negative PCR by subgroup. Source: Khoo et al.

Participants in the MOV group had a faster median time from randomisation to negative PCR (8 days [95%CI 8–9]) than participants in the placebo group (11 days [10–11]; HR 1.30, 95% credible interval 0.92–1.71; log-rank p=0.074). The difference was not significant. The exploratory analysis of time to negative PCR by vaccination status, SARS-CoV-2 variant, sex, and ethnicity is shown in Figure 4. The probability of MOV being superior to placebo (HR>1) was 75·4%, which was less than the threshold of 80%.

No participants in the MOV group were hospitalised, there were three people in the placebo group hospitalised, none required mechanical ventilation. In terms of adverse events, 73 (81%) of 90 participants in the MOV group and 68 (76%) of 90 participants in the placebo group had at least one adverse event by day 29, most adverse events were non-serious (grade 1) and consistent with the known safety provide of MOV. One participant in the MOV group had a grade 3 adverse event of hypertension.

Authors evaluated changes in viral titre as an exploratory efficacy endpoint. Mean baseline titres were 7.1 $\log_{10}$ copies per reaction (SD 2.7) for the MOV group and 7.4 $\log_{10}$ copies per reaction (3.0) for the placebo group. Compared with baseline viral load decreased by a mean of 4.8 $\log_{10}$ copies per reaction (SD 2.6) in the MOV group and 3.9 $\log_{10}$ copies per reaction (3.2) in the placebo group at day 5 (p=0·042).

Discussion/conclusion: Patients in the MOV group had a faster median time from randomisation to PCR negativity than did patients in the placebo group. The subgroup analyses did not have sufficient power for statistical comparison, but there was no obvious loss of effect by vaccination status or with the omicron variant. Participants receiving MOV also had a significantly greater mean reduction in viral load from baseline to the end of treatment (5 days) compared with participants receiving placebo.

In conclusion, the authors state they have presented results showing that MOV has a moderate antiviral effect, but the evidence is not conclusive.

Comments:
This was a randomised control trial where the primary endpoint was time from randomisation to a negative PCR test. The study was not sufficiently powered to detect endpoints such as hospitalisation rates, in-hospital disease progression due to the limited number of study participants.

3.1.7 Ma et al, 2023, Clinical outcomes following treatment for COVID-19 with Nirmatrelvir/Ritonavir and Molnupiravir among patients living in nursing homes [14]

Purpose: To evaluate outcomes following oral antiviral treatment for COVID-19 among non-hospitalised older patients living in nursing homes.

Design, setting, participants: Territory-wide, retrospective cohort study conducted between 16 February and 31 March 2021 in patients living in nursing homes in Hong Kong.

The study analysed patients living in nursing homes across seven geographic clusters in Hong Kong who were diagnosed with PCR confirmed COVID-19.

Outcomes measured: The primary outcome was hospitalization for COVID-19, and the secondary outcome was risk of inpatient disease progression (ie, admission to intensive care unit, use of invasive mechanical ventilation, and/or death).

Method: This retrospective cohort study was conducted using the electronic database Clinical Data Analysis and Reporting System (CDARS) of the Hospital Authority, which manages all public hospitals in Hong Kong. Patients with COVID-19 who were treated with an oral antiviral were identified. Qualitative and quantitative differences between groups were compared by $\chi 2$ test or Fisher exact test for categorical parameters, and 1-way analysis of variance or Kruskal-Wallis test for continuous parameters. Propensity score of oral antiviral nonusers, MOV users, and NR users was estimated by multinomial logistic regression on 18 clinical characteristics.

Results: Of 14,617 patients; 8,939 (61.2%) did not use oral antivirals; 5,195 (35.5%) used molnupiravir; and 483 (3.3%) used nirmatrelvir/ ritonavir. At a median follow-up of 30 days, 6,223 of 14,167 patients (42.6%) were hospitalised. Of them, 5,332 (59.6%) did not use oral antivirals, 831 (16.0%) used MOV, and 60 (12.4%) used NR. Of 2,307 patients (15.8%) who experienced the secondary outcomes (ie,ICU admission, use of IMV, and/or death), 2102 (23.5%) did not use oral antivirals, 200 (3.8%) used MOV, and 5 (1.0%) used NR.

The mean age of participants was 84.8 years (SD 10.2). Compared with patients who did not use oral antivirals, patients taking MOV and NR were more likely to be female and less likely to have comorbid illnesses (cardiovascular diseases, respiratory diseases, digestive diseases, chronic kidney diseases, diabetes, neurological diseases, and malignant tumors) and hospitalisation in the past 1 year.

Table 10. Results of weighted Cox proportional hazard regression after propensity score weighting for nursing home patients with COVID-19 who recieved care in the community. Source: Ma et al.

The results after propensity scoring are summarised on Table 10. The use of MOV (weighted hazard ratio [wHR], 0.46; 95%CI, 0.37-0.57; P <.001) and NR (wHR, 0.46; 95%CI, 0.32-0.65; P <.001) were both associated with a reduced risk of hospitalisation. There was no significant difference between MOV and NR users in terms of the risk of hospitalisation. The use of both antivirals were associated with a reduced risk of the secondary outcomes (ICU admission, use of IMV, and/or death). There was no significant difference between the two oral antivirals and risk of the secondary outcomes (wHR, 0.49; 95%CI, 0.20-1.20; P =.12)

Discussion/conclusion: This territory-wide cohort study in Hong Kong reported the clinical effectiveness of 2 oral antivirals for treating COVID-19 among patients living in nursing homes during the omicron dominant period. Both antivirals were associated with reduced risks of hospitalisation and inpatient disease progression.

Comments:

This large observational study looked at the incidence of hospitalisation and in-hospital disease progression in nursing home patients with COVID-19. Compared to no antiviral use, this study found that MOV and NR use was associated with a statistically significant (P<0.001) reduced risk of both endpoints during an omicron dominant period.

Participants included in the trial were older and were more likely to have several comorbidities compared to those in PANORAMIC.

Of note though, participants taking antivirals were less likely to have comorbid illnesses compared to those not taking antivirals, which makes it less likely that the optimal patient population is studied.

The study suggests that MOV does have efficacy in reducing hospitalisation in a high-risk population and remains an option for the treatment of COVID-19.

3.1.8 Zheng et al, 2022, Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe covid-19 outcomes in patients in the community: observational cohort study with the OpenSAFELY platform [15].

Purpose: To compare the effectiveness of sotrovimab (a neutralising monoclonal antibody) with MOV in preventing severe outcomes of COVID-19 in adult patients infected with SARS-CoV-2 in the community and at high risk of severe outcomes from COVID-19.

Design, setting, participants: Real-world observational cohort study with the OpenSAFELY platform (software for analysis) using patient level electronic health record data in England. Participants were adult patients in the community at high risk of severe outcomes from COVID-19, treated with sotrovimab or MOV from 16 December 2021 to 10 February 2022.

According to eligibility criteria from the NHS, to receive sotrovimab or MOV in the community during this period, patients had to have PCR confirmed SARS-CoV-2 infection onset of within the past 5 days and belong to at least one of ten high risk cohorts: Down's syndrome, solid cancer, haematological disease or stem cell transplant, renal disease, liver disease, immune mediated inflammatory disorders, primary immune deficiencies, HIV/AIDS, solid organ transplant, or rare neurological conditions.

Outcomes measured: Admission to hospital with COVID-19 as the primary diagnosis or death from COVID-19 (with COVID-19 as the underlying or contributing cause of death) within 28 days of the start of treatment.

Method: Electronic health records for patients with COVID-19 who received sotrovimab or MOV were reviewed and identified from the OpenSAFELY platform. Covariates extracted at baseline include ethnicity, rural-urban classification, deprivation status, vaccination status, date of infection, BMI, age, sex, and presence of comorbidities. The risk of admission to hospital or death from COVID-19 within 28 days in the two treatment groups were compared with Cox proportional hazards models. Authors adopted the propensity score weighting method as an alternative approach to account for confounding bias.

Results: During the time period, 3331 and 2689 patients were treated with sotrovimab and MOV, respectively, with no substantial differences in baseline characteristics. Mean age of all patients was 52 (SD 16) years; 59% were women, 89% were white, and 88% had received three or more COVID-19 vaccinations.

Within 28 days of the start of treatment, 87 (1.4%) patients were admitted to hospital or died of infection from SARS-CoV-2 (32 treated with sotrovimab and 55 with MOV). Of these 87 patients, 25 (0.42%) died of COVID-19 during the 28 days of follow-up (seven in the sotrovimab group and 18 in the MOV group).

After Cox regression and adjustment of covariates, sotrovimab treatment was associated with a lower risk of admission to hospital or death from COVID-19 compared with MOV (HR 0.54, 95%CI 0.33-0.88, P=0.01). The results of the sensitivity analyses were consistent with the main findings.

Discussion/conclusion: The authors state our findings suggest that in routine care, sotrovimab was associated with a substantially lower risk of severe outcomes of covid-19 compared with MOV in adult patients in England with COVID-19 at high risk of severe outcomes from infection but who did not require admission to hospital, including those who were fully vaccinated.

Comments:

During the time period when this study was conducted (December 2021- February 2022), sotrovimab was shown to be more effective compared to MOV. The clinical relevance of this study is now outdated as new evidence has not proven sotrovimab efficacy against new variants of concern. This study did not investigate the clinical benefits of MOV.

3.1.9 Malin et al, 2023. Efficacy and safety of Molnupiravir for the treatment of SARS-CoV-2 infection: a systematic review and meta-analysis [16].

Purpose: To conduct a systematic review and meta-analysis of the most recent evidence evaluating the efficacy and safety of MOV in order to support guideline development and clinical decision making.

Design: Systematic review of full-text randomised control trials (published or preprint) comparing MOV with/without standard of care versus standard of care and/or placebo alone up until 1 November 2022.

Outcomes measured: Studies were included irrespective of reported outcomes; the following outcomes were analysed for:

1. Ambulatory managed patients with asymptomatic or mild COVID-19 (outpatients): all-cause mortality at day 28 and 60, time-to-event and up to the longest follow up, admission to hospital or death within 28 days, resolution of COVID-19 symptoms, duration of symptom resolution, quality of life at up to 7, and 28 days, or longest follow up available.

2. Hospitalised individuals with moderate to severe COVID-19 (inpatients): all-cause mortality at day 28 and 60, time-to-event, and at hospital discharge, clinical status at day 28 and 60 or up to longest follow up, improvement of clinical status, quality of life.

3. Safety of MOV: number of adverse events, number of serious adverse events, long term adverse events reported during the study period.

Method: Authors searched the Cochrane COVID-19 Study Register (comprising MEDLINE, Embase, clinicaltrials.gov, WHO International Clinical Trials Registry Platform, medRxiv and the Cochrane Central Register of Controlled Trials), Web of Science (Science Citation Index and Emerging Sources Citation Index) and the WHO COVID-19 Global literature on coronavirus disease until 1 November 2022.

Results: The original search yielded 519 records, after removal of duplicates and ineligible articles there were nine studies included in the review. In total there were 29,558 participants involved in the nine RCTs, six trials were multicentre trials conducted in the UK, USA, India, and internationally. The remaining single centre studies were conducted in China and the UK. Seven out of eight studies on outpatients included patients with mild COVID-19 defined according to the study protocols (WHO scale 2–3). In terms of the risk of bias per outcome measured, all-cause mortality at day 28 and any adverse events reported during the study period were given a low risk of bias. Outcomes with an unclear risk of bias were hospitalisation or death at day 28, symptom resolution by day 14 and day 28, and the incidence of serious adverse events.

Figure 5. Association between MOV and all-cause mortality by day 28 in outpatients. Source: Malin et al.

Table 11. Meta-analysis of efficacy and safety outcomes of MOV versus control in outpatients with COVID-19. Source: Malin et al.

Presented in Figure 5 is the efficacy of MOV treatment on all-cause mortality in outpatients from five studies. The results suggest that early treatment with MOV does not reduce all-cause mortality by day 28 in COVID-19 outpatients (eight deaths fewer per 10,000; RR 0.27, 95%CI 0.07–1.02, 28,161 participants). Table 11 presents the meta-analysis results relating to efficacy and safety outcomes of MOV versus control in outpatients with COVID-19.

Table 12. Meta-analysis of efficacy and safety outcomes of MOV versus control in inpatients with COVID-19. Source: Malin et al.

Safety data is presented in Table 11 for outpatients and Table 12 for inpatients. Authors describe that there was little or no difference between MOV and placebo/SoC groups in overall adverse events reported for in- and outpatients and for severe adverse events reported for inpatients. For severe adverse events in outpatients, they state probably little or no effect of MOV and during the study period. Certainty of evidence for serious adverse events was downgraded for serious risk of bias due to open-label study design. The largest trial (PANORAMIC) only reported on serious adverse events. The subgroup analysis on vaccination status showed no evidence for a difference for MOV on adverse events (P =0.48) or serious adverse events (P =0.08) between vaccinated and unvaccinated patients. Long-term adverse events were not reported in any study.

Discussion/conclusion: In a predominantly immunised population of COVID-19 outpatients, MOV has no effect on mortality, probably none on 'hospitalisation or death' and effects on symptom resolution are uncertain. MOV was safe during the study period in outpatients. Our analysis does not support routine use of MOV for COVID-19 treatment in immunocompetent individuals.

Comments:

This systematic review and meta-analysis of nine randomised control trials did not identify a benefit of MOV treatment on all-cause mortality. The authors report general limitations of the review which include the lack of severely immunosuppressed trial participants, this precludes any conclusions on effects in this vulnerable group. Additionally, given the rapidly changing pandemic situation, variant pathogenicity, drug susceptibility and changes in population immunity could affect the applicability of the study results.

3.1.10 Gao et al, 2023, Molnupiravir for treatment of adults with mild or moderate COVID-19: a systematic review and meta-analysis of randomised controlled trials [17].

Purpose: The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of MOV in adult patients with mild or moderate COVID-19.

Design: Systematic review and meta-analysis of RCTs where the intervention was MOV compared with standard care/placebo. Search results were obtained up to 27 December 2022.

Outcomes measured: Mortality, hospital admission, viral clearance, time to viral clearance, time to symptom resolution or clinical improvement, any adverse events, and serious adverse events.

Method: Articles were sourced from PubMed, Embase, CENTRAL, Web of Science, and WHO COVID-19 database until 27 December 2022. Authors used RoB-2-criteria to assess risk bias. Studies were included that enrolled patients aged 18-years and older with confirmed mild/moderate COVID-19. Authors performed DerSimonian-Laird random effects meta-analyses to summarise the evidence and evaluated the certainty of evidence using the GRADE approach.

Results: Nine RCTs enrolling 30,472 patients proved eligible. Majority of patients were outpatients, with the mean age ranging from 35 to 56.6 years. In adult patients with mild or moderate COVID-19, MOV probably reduces mortality (relative risk (RR) 0.43, 95% CI 0.20 to 0.94, risk difference (RD) 0.1% fewer; moderate certainty) and the risk of hospital admission (RR 0.67, 95% CI 0.45 to 0.99, RD 1.4% fewer; moderate certainty), and may reduce time to viral clearance (MD -1.81 days, 95% CI -3.31 to -0.31; low certainty) and time to symptom resolution or clinical improvement (MD -2.39 days, 95% CI -3.71 to -1.07; low certainty). MOV probably increases rate of viral clearance (RR 3.47, 95% CI 2.43 to 4.96, RD 16.1% more; moderate certainty) at 7 days (± 3 days) and likely does not increase serious adverse events (RR 0.84, 95% CI 0.61 to 1.15, RD 0.1% fewer; moderate certainty).

Discussion/conclusion: In adult patients with mild or moderate COVID-19, MOV likely reduces mortality and risk of hospital admission probably without increasing serious adverse events.

Comments:

This article is undergoing review and has not been published. Three of the RCTs included in this systematic review have been discussed in this paper (Bernal et al, Butler et al, and Khoo et al).

3.1.11 Huang et al, 2023, Clinical efficacy and safety of molnupiravir for non-hospitalised and hospitalised patients with COVID-19: a systematic review and meta-analysis of randomised control trials [18].

Abstract: The efficacy of MOV in treating patients with COVID-19 has been inconsistent across RCTs. Thus, this meta-analysis was conducted to clarify the literature. A literature search of electronic databases—PubMed, Embase, and Cochrane Library—was performed to identify relevant articles published up to December 31, 2022. Only RCTs that investigated the clinical efficacy and safety of MOV for patients with COVID-19 were included.

The primary outcome was all-cause mortality at 28–30 days. This pooled analysis of nine RCTs did not reveal a significant difference in all-cause mortality between MOV and control groups (risk ratio [RR], 0.43; 95% confidence interval [CI], 0.10–1.77) for overall patients. However, the risks of mortality and hospitalisation were lower in the MOV group than in the control group (mortality: RR, 0.28; 95% CI, 0.10–0.79; hospitalization: RR, 0.67; 95% CI, 0.45–0.99) among non-hospitalised patients.

In addition, MOV use was associated with a borderline higher virological eradication rate relative to the control (RR, 1.05; 95% CI, 1.00–1.11). Finally, no significant difference in adverse event risk was discovered between the groups (RR, 0.98; 95% CI, 0.89–1.08).

Comments:

A full text version of this article was not available at the time of preparing this report.

Overall, the findings suggest a clinical benefits of MOV for non-hospitalised patients with COVID-19 (reduced risk of hospitalisation). The findings also suggest that MOV may not improve the clinical outcomes of hospitalised patients. Given MOV is not indicated for hospitalised patients, this finding is not relevant for its use in New Zealand.

3.2 Company reports

[redacted]

3.3 CARM data

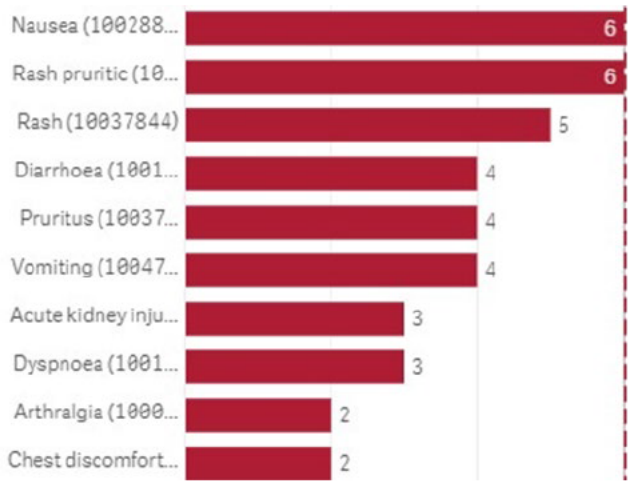
Up to 20 April 2023, the Centre for Adverse Reactions Monitoring (CARM) have received 41 ADR reports where the suspect medicine is MOV. The ten most commonly reported MedDRA Preferred Terms (PTs) are shown in Figure 6.

The majority of ADR reports were non-serious, however there are eight reports which are classified as serious [redacted] A summary of these cases is provided in Table 13.

Table 13. Serious ADR reports for MOV reported to CARM, up to 20 April 2023.

CARM ID Number, patient age, gender, ethnicity	PTs reported	Comments
144322 **43y, female,** [redacted]	Pruritis Dermatitis bullous Pain	Concomitant medicines included vildagliptin, allopurinol, ticagrelor, candesartan, furosemide, aspirin, calcitriol, atorvastatin, alutab, renal mvite, iron polymaltose, bisoprolol, gabapentin, calcitab. [redacted]
145323 **76y, female,** [redacted]	Chest discomfort Hypertension Dyspnoea Cough ECG QT prolonged	Concomitant medicines included omeprazole, budesonide+formoterol, Bendroflumethiazide, amlodipine [redacted]
145402 **75y, male,** [redacted]	Acute kidney injury	Concomitant medicines include thiamine, multivitamin [redacted]
145491 **72y, female,** [redacted]	Pancreatitis	Concomitant medicines include cefaclor [redacted]
145756 **73y, male,** [redacted]	Lip swelling	Concomitant medicines include metoprolol [redacted]
146022 **62y, female,** [redacted]	Anxiety Confused state Diarrhoea Nausea Restlessness	[redacted]
146341 **53y, male,** [redacted]	Sudden death	Concomitant medicines include atorvastatin [redacted]
146499 **70y, male,** [redacted]	Vomiting Diarrhoea Acute kidney injury Nausea	[redacted]

Figure 6. MedDRA PTs reported in MOV ADR reports received by CARM up to 20 April 2023. Source: Qlik App.



Comments:

In terms of the serious CARM reports, most patients had medical conditions that may have contributed to their ADR. The non-serious ADRs reported are consistent with what was reported in clinical trials and those reported in the post-market setting. No new safety concerns have been identified from post-market reports in New Zealand.

4 DISCUSSION AND CONCLUSIONS

MOV is an oral antiviral indicated for the treatment of mild-to-moderate COVID-19 disease in adults at risk of progressing to severe disease. It remains provisionally approved by Medsafe and at the time of this report, it is a funded treatment option in New Zealand's COVID-19 treatment portfolio [2, 6]. The usage of MOV is significantly less than Paxlovid which is the preferred oral antiviral treatment option for COVID-19. However, MOV may be more suitable for those with severe renal impairment and people with contraindicated medicine interactions that cannot be managed by withholding the offending medicine.

Concerns have been raised over the efficacy of MOV. Results from the PANORAMIC trial, a large multicentre open label, prospective, platform adaptive randomised controlled trial in the UK suggest that MOV does not reduce the frequency of COVID-19 associated hospitalisations or death among vaccinated adults with at least one risk factor for progressing to severe disease. Benefits of MOV in this study related to improvement in patient self-rated wellness and lessened symptom severity [8]. [redacted]

Section 3 of this paper provides a summary of literature relating to MOV efficacy. Observational studies in unvaccinated patients suggest a -3% difference in hospitalisation or death at day 28 compared with placebo [9]. The remaining observational studies were conducted in vaccinated and unvaccinated participants predominantly during an omicron dominant phase of infection. The results of MOV efficacy vary between the studies, with Xie et al reporting an absolute risk reduction of 1.1% in MOV users compared to placebo for the outcomes hospitalisation or death at 28 days. Wong et al reports that MOV treated patients had a lower risk of death and disease progression (HR 0.76 and 0.57 respectively), and Khoo et al report MOV patients to have a faster time to negative PCR tests with the probability of MOV being superior to placebo being 75.4%.

This report contained three systematic reviews with meta-analysis. The review by Malin et al does not suggest a statistically significant benefit of MOV on the risk of hospitalisation or death (RR 0.27, 95%CI 0.07–1.02) [16].

The remaining two reviews by Gao et al and Huang et al suggest a slightly positive effect of MOV. However, these results were of low-moderate certainty [17, 18].

Additionally the CHMP of the EMA has decided to refuse marketing authorisation for MOV in February 2023. The sponsor has requested a re-examination of this decision which will be communicated at a later date. MOV is not currently used in the EU. It is unknown what evidence the CHMP reviewed when making their decision. To date, the approval of MOV has not been contested by other medicine regulators. However, treatment guidelines in some countries have changed towards not recommend use or only use when there is no suitable alternative.

In terms of safety information, MOV is generally well-tolerated. Hypersensitivity and angioedema have been reported in the post-marketing setting and these ADRs have been added to section 4.4 and 4.8 of the data sheet. No other serious safety concerns have been identified; New Zealand ADR reports are consistent with the known safety profile.

From the currently available information, it seems that MOV may have some benefits in reducing hospitalisation or symptom severity in both unvaccinated and vaccinated patients with risk factors of severe Covid disease. The patients included in the studies were infected with several different SARS-CoV-2 variants, had comorbidities that increased their risk of severe disease (diabetes, cardiovascular disease), and were generally older. Trial participants share common traits with the population eligible for MOV use in New Zealand. Overall MOV was generally well tolerated in these trials with minimal numbers of people withdrawing from a trial due to ADRs.

The safety and efficacy of MOV and COVID-19 treatments is an everchanging area with new evidence emerging rapidly. There are several challenges when conducting research in this space, new SARS-CoV-2 variants, changes in vaccination status, antiviral eligibility, data collection methods, and patient demographic changes will influence study findings and generalisability of the results.

5 ADVICE SOUGHT

The Committee is asked to advise:

- If the evidence on efficacy is strong enough to support the use of molnupiravir for its current approved indication?
- If no, are further regulatory actions required?
- Whether any communication on this issue in addition to MARC's Remarks is needed?

6 ANNEXES

1. Lagevrio Medsafe Clinical Evaluation Report, NMA, Application ID: 116911

2. Butler et al, 2023, Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open label platform adaptive randomised controlled trial.

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