

In brief

Molnupiravir

9 November 2022

Summary

- [Molnupiravir](#) (MK-4482/EIDD-2801) is an antiviral medication that is administered orally.¹
- [Molnupiravir](#) is a potent ribonucleoside analogue that inhibits the viral replication of SARS-CoV-2 (or other viruses that employ RNA-dependant RNA polymerase) by introducing errors in the viral genome.²
- Despite some evidence of risk reduction associated with molnupiravir treatment in non-hospitalised unvaccinated adults with mild to moderate COVID-19 symptoms pre-Omicron, a more recent clinical trial (pre-print) from the Omicron predominant period has suggested no risk reduction in all-cause hospitalisation or mortality among non-hospitalised vaccinated adults.^{3, 4}
- In hospitalised patients, treatment with molnupiravir did not demonstrate a clinical benefit of reducing the risk for disease progression or mortality in one clinical trial (pre-Omicron).⁵
- Molnupiravir was associated with a faster decline in viral load and reduced time to viral clearance, although one trial concluded that a virological response superiority over non-treatment was inconclusive based on a priori threshold (the probability of molnupiravir being superior to placebo > 80%).^{4, 6, 7}
- In real-world studies from the Omicron predominant period, molnupiravir reduced the risk of disease progression in hospitalised patients not requiring oxygen therapy on admission and who are older than 65 or not fully vaccinated.⁸ In community-dwelling outpatients with mild symptoms who are at a higher risk of progressing to severe disease, molnupiravir treatment was associated with reduced risk of all-cause mortality, hospitalisation and in-hospital disease progression in patients older than 60 only.⁹
- Molnupiravir retained its antiviral activity against Omicron sub-lineages including BA.2.12.1, BA.4 and BA.5 in an in-vitro study.¹⁰
- COVID-19 rebound (resurgence of detectable virus or symptoms after initial recovery) has been recorded after molnupiravir treatment in pre-print studies, and in untreated patients, particularly after infection with the Omicron variant.^{11, 12 13}

Regulatory context: Australia

- 1 March 2022: molnupiravir (Lagevrio) was listed on the [Pharmaceutical Benefits Scheme](#).¹⁴
- 18 January 2022: Molnupiravir was granted provisional approval by the [Therapeutic Goods Administration](#) (TGA).¹⁵

Regulatory context: International

- 23 December 2021: [U.S. Food and Drug Administration](#) authorised molnupiravir for treatment of COVID-19.¹⁶

- 4 November 2021: [Medicines and Healthcare products Regulatory Agency \(MHRA\)](#), UK, approved molnupiravir (Lagevrio) for use in people who have mild to moderate COVID-19 and at least one risk factor for developing severe illness.¹⁷

Research evidence

- October 2022: A [randomised, placebo-controlled, double-blind study](#) (Delta and Omicron predominant) from the UK, showed that both vaccinated and unvaccinated outpatients with mild-to-moderate infection and treated with molnupiravir had a faster median time from randomisation to negative PCR compared to the placebo group (8 days versus 11 days, hazard ratio: 1.3). However, the probability of molnupiravir being superior to placebo (hazard ratio >1) was 75.4%, which was less than the predefined threshold of 80% to conclude a virological response superiority over the placebo.⁷
- October 2022: A multicentre, open label [randomised controlled trial](#) (pre-print, Omicron-predominant period, PANORAMIC trial) in the UK, concluded that molnupiravir did not reduce the rates of hospitalisation and mortality among vaccinated adults in the community with comorbidities. The outcomes for molnupiravir plus usual care versus usual care are as follows:
 - All-cause hospitalisation or mortality rate within 28 days: 0.8% versus 0.8%
 - Observed median time-to-first-recovery from randomisation: 9 days versus 15 days
 - Estimated median time-to-first-recovery: 10.3 days versus 14.5 days
 - Rates of viral detection at day seven: 79% versus 97%
 - Mean viral load (\log_{10}) at day seven: 3.82 versus 4.93
 - Participants experiencing serious adverse events: 0.4% versus 0.4%⁴
- October 2022: In a [real-world study from Hong Kong](#) (Omicron-predominant period), treatment with molnupiravir in community dwelling outpatients with mild symptoms at a higher risk of progressing to severe disease was associated with a significantly lower risk of all-cause mortality (hazard ratio: 0.76) and in-hospital disease progression (hazard ratio: 0.57). The risk of hospitalisation was similar to the control group (hazard ratio: 0.98)
 - Crude incidence rate per 10,000 person-days for the outcomes in the molnupiravir group versus control:
 - All-cause mortality: 17.9 versus 22.1
 - Hospitalisation: 107.6 versus 104.0
 - In-hospital disease progression: 10.2 versus 16.8⁹
 - In sub-group analysis, treatment with molnupiravir reduced the risk of all-cause mortality in patient aged over 60 only, regardless of the vaccination status. Molnupiravir treatment reduced the risk of hospitalisation only in patients aged over 60; and reduced the risk of in-hospital disease progression on in patients without full vaccination or aged over 60.
- September 2022: A [real-world study from Israel \(preprint, Omicron-predominant period\)](#) suggested that in outpatients who are at a higher risk for disease progression, treatment with molnupiravir was associated with the reduced rate for clinical deterioration (3.92% versus 7.46%), even after propensity matching and independent of vaccination status.¹⁸
- August 2022: In a [real-world study from Hong Kong](#) (Omicron-predominant period), treatment with molnupiravir in hospitalised and mild to moderate COVID-19 patients was associated with a significantly lower risk of all-cause mortality (hazard ratio: 0.48); disease progression (hazard ratio: 0.60) and the need for oxygen therapy (hazard ratio: 0.69).

- Crude incidence rate per 10,000 person-days for the outcomes in the molnupiravir group versus control:
 - All-cause mortality: 19.98 versus 38.07
 - Invasive mechanical ventilation: 0.93 versus 2.20
 - Intensive care unit admission: 0.13 versus 0.26
 - Need for oxygen therapy: 31.76 versus 44.35
 - Composite disease progression outcome: 44.49 versus 69.87
- According to subgroup analysis, treatment with molnupiravir did not have a significant benefit with regards to all-cause mortality, invasive mechanical ventilation, need for oxygen therapy, and composite progression outcome among patients aged 65 or under, or those who are fully vaccinated.⁸
- August 2022: A [real-world study from Poland](#) reported that hospitalised patients (mean age 67.4) who received molnupiravir treatment during the Omicron-predominant period had significantly lower mortality rate at 28-day follow-up compared to control (9.9% versus 16.3%).
 - Among patients over the age of 80 who were treated within the first five days of the disease, the absolute risk reduction of mortality compared to control was 20.6% (14.6% versus 35.2%).¹⁹
- July 2022: In another real-world study from Italy (Omicron-predominant period), among 192 patients treated with molnupiravir (mean age of 70.4 ± 15.4 years, with mild to moderate symptoms but with a high risk of disease progression), 20 (10.4%) showed a disease progression.
 - Adverse events were reported in 6.8% of treated patients and are mostly diarrhea, dizziness, nausea, and rash.
 - Early start of treatment was associated with a reduced risk of disease progression.²⁰
- August 2022: An in-vitro study suggests that molnupiravir remains susceptible to Omicron subvariants BA.2.12.1, BA.4 and BA.5 at a similar level to that of the ancestral strain.¹⁰
- August 2022: A [meta-analysis](#) based on five randomised controlled trials published until March 2022 suggests that molnupiravir, as compared to placebo, reduced the risk of mortality in non-hospitalised patients (risk ratio: 0.12; 95% CI: 0.03–0.54). No benefit was observed in hospitalised patients. The risk of hospitalisation was also less in patients receiving molnupiravir (risk ratio 0.67; 95% CI: 0.49–0.92).²¹
- July 2022: A [meta-analysis](#) based on three randomised clinical trials (published up to April 2022) reported that molnupiravir reduced the risk of mortality (10.9 fewer deaths per 1000), hospitalisation (16.3 fewer hospitalisation per 1000) and need for mechanical ventilation (13 fewer deaths per 1000). The relative risk reduction for mortality was 82%. Treatment with molnupiravir did not lead to an increase in adverse events.²²
- July 2022: In terms of [cost-effectiveness](#), a phase 3, double-blind, randomised, placebo-controlled trial shows that the use of molnupiravir led to an increase in quality-adjusted life-years (QALYs) and decrease in direct total medical costs (-\$895) per patient across a lifetime horizon, compared with best supportive care in COVID-19 outpatients.²³
- April and February 2022: In reference to two separate reviews, molnupiravir showed beneficial effects for mild to moderate COVID-19 patients, with a favourable safety profile.^{24, 25}
- February 2022: Analysis of a phase 3 study on molnupiravir ([MOVE-OUT trial; pre-Omicron](#)) found that, in at-risk, non-hospitalised adult patients with mild-to-moderate COVID-19,

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molnupiravir reduced the risk of hospitalisation or death by approximately 50%. At day 29 following randomisation:

- 6.8% of patients (48 out of 709) who received molnupiravir were either hospitalised (n=28) or died (n=0)
- 9.7% of patients (68 out of 699) who received placebo were either hospitalised (n=45) or died (n=8)
- the incidence of any adverse event was similar in the molnupiravir and placebo groups (35% versus 40%)
- the incidence of drug-related adverse events was similar in the molnupiravir and placebo groups (12% versus 11%)³
- January 2022: [A phase 2a clinical trial](#) reported that, in non-hospitalised COVID-19-infected patients with symptom onset within seven days; when compared with subjects who received placebo treatment, subjects who received molnupiravir twice-daily for five days experienced the following:
 - At day 3 and 800mg dosage: significantly lower rates of infectious virus isolation (1.9% versus 16.7%; p=0.02)
 - At day 5 and either 400mg or 800mg dosage: significantly lower rates of virus isolation (0% versus 11.1%; p=0.03)
 - Time to clearance of viral RNA at 800mg dosage: significantly lower median time to clearance (14 days versus 27 days; p=0.001)
 - Change in viral load at 800mg dosage: greater decrease in viral RNA from baseline to day 3 to 28
 - SARS-CoV-2 antibody detection at either 200mg, 400mg or 800mg dosage: greater proportion of antibodies by day 28 (99.2% versus 96.5%)
 - Molnupiravir was well tolerated with no increase in treatment-related or serious adverse events⁶
- December 2021: Analysis of a phase 2/3 trial in adults ([MOVE-IN trial, both pre-Omicron and Omicron period](#)) concluded that for adult patients requiring in-hospital treatment for COVID-19, a five-day course of molnupiravir up to 800 mg twice daily was not associated with dose-limiting side effects or adverse events. It did not demonstrate a clinical benefit of reducing the risk for disease progression or mortality.
 - Adverse events were reported in 121 of 218 (55.5%) molnupiravir-treated participants compared to 46 of 75 (61.3%) placebo-treated participants.
 - Treatment group and the placebo group had a similar median time to sustained recovery (both nine days) and recovery rates at 29 days (ranging from 81.5% to 85.2%).⁵
- November 2021: A phase 1, open-label, dose-escalating [randomised controlled study](#) reported that, among patients with COVID-19 (within five days since symptom onset), molnupiravir was well tolerated at 300mg, 600mg and 800mg doses. No serious or severe adverse events occurred.²⁶
- April 2021: In a first-in-human phase 1 [randomised, double-blind, placebo-controlled study](#) in healthy volunteers, molnupiravir was well tolerated at doses of 50 to 800mg; administered twice a day for 5.5 days and at single doses up to 1,600mg. The most frequent adverse events were headache and diarrhoea. However, the incidence rates for these adverse events were less than, or same as, the placebo-treatment group (12.5% versus 18.8% for headache; 7.1% versus 7.1% for diarrhoea).²⁷

COVID-19 rebound after treatment

- June 2022: A [retrospective cohort study](#) of electronic health records (pre-print; Omicron period) of 2374 patients who took molnupiravir within five days of their COVID-19 infection during the Omicron-predominant period, reported the following for the rebound rates at seven days and 30 days after the last day of treatment:¹³
 - COVID-19 infection: 5.86% and 8.59%
 - COVID-19 symptoms: 3.75% and 8.21%
 - COVID-19 hospitalisation: 0.84% and 1.39%
 - Patients with COVID-19 rebound had significantly higher prevalence of underlying medical conditions than those without

To inform this brief, PubMed and Google searches were conducted using terms related to molnupiravir on the 1 November, 6 October 2021, and 31 August 2022.

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