

In brief

Molnupiravir

24 November 2021

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
- There are currently four clinical trials underway to explore the use of molnupiravir. These include interim results from a phase 3 trial, a pre-print phase 2 trial and two phase 1 trials with small numbers of participants.
- In these trials, results are promising with molnupiravir reducing the risk of hospitalisation or death by approximately 50%, with no serious adverse events. In the phase 2a trial, the intervention arm had a significantly lower median time for the virus to clear.

Regulatory context: Australia

- On 10 August 2021, molnupiravir was granted provisional determination by the [Therapeutic Goods Administration](#) (TGA).³
- On 5 October 2021, it was reported the [Australian federal government](#) had ordered 300,000 courses of molnupiravir.⁴ Whilst some news articles are reporting 300,000 'doses' have been ordered; the [official Australian Government media release](#) specifies it is 300,000 'courses'.

Regulatory context: International

- On 9 June 2021, the [US Department of Health and Human Services](#) announced procurement of approximately 1.7 million courses of molnupiravir.⁵
- On 13 August 2021, [Merck Canada](#) initiated a rolling submission to Health Canada for molnupiravir.⁶ The submission is currently [under review](#).⁷
- On 1 October 2021, Merck announced plans to submit an application for Emergency Use Authorization (EUA) to the [US Food and Drug Administration \(FDA\)](#) as soon as possible.¹
- On 6 October 2021, news articles reported the [European Medicines Agency](#) will consider starting an accelerated 'rolling review' in the coming days.⁸

Research evidence

- Interim analysis of a phase 3 study on molnupiravir ([MOVE-OUT trial](#)) found that, in at-risk, non-hospitalised adult patients with mild-to-moderate COVID-19, molnupiravir reduced the risk of hospitalisation or death by approximately 50%. At day 29 following randomisation:
 - 7.3% of patients (28 out of 385) who received molnupiravir were either hospitalised (n=28) or died (n=0)

- 14.1% of patients (53 out of 377) 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%).¹
- A phase 1, open-label, dose-escalating [randomised controlled study](#) reported that, among patients with COVID-19 (and within five days since symptom onset), molnupiravir was well tolerated at 300mg, 600mg and 800mg doses with no serious or severe adverse events.⁹
- 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).¹⁰
- A [pre-print phase 2a 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 events.¹¹
- Molnupiravir is proposed to inhibit viral replication by a mechanism known as '[lethal mutagenesis](#)'.² Reassuringly, two recent studies found that mitochondrial function over 14 days was not significantly inhibited, and there was not an observed mutagenesis of host mRNA.^{12, 13}

Animal studies

- Animal studies found that treating infected animals ([ferrets](#), [hamsters](#)) with molnupiravir reduced the viral load in the upper respiratory tract and lung tissue, and suppressed the spread of the virus to untreated contact animals.^{14, 15} One [animal study](#) found molnupiravir to be effective against infection with variants of concern (B.1.1.7 and B.1.351) and has the potential to maintain its effectiveness against emerging variants of concern.¹⁴
- In one study, when infected hamsters were [treated with a combination of suboptimal doses of molnupiravir and favipiravir](#) at the time of infection, or six or 24 hours after infection, the virus titers in the lungs were reduced by more than 4.5 log₁₀, 3.1 log₁₀ and 2.4 log₁₀, respectively.¹⁶ Treatment of infected animals nearly completely suppressed the spread of the virus to co-housed untreated sentinels.¹⁶

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

References

1. Merck. Merck and Ridgeback's investigational oral antiviral molnupiravir reduced the risk of hospitalization or death by approximately 50 percent compared to placebo for patients with mild or moderate COVID-19 in positive interim analysis of phase 3 study [Internet]. US: Merck Sharp & Dohme Corp.; 1 October 2021 [cited 6 October 2021]. Available from: <https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderate/>.
2. Malone B, Campbell EA. Molnupiravir: coding for catastrophe. *Nat Struct Mol Biol.* 2021 Sep;28(9):706-8. DOI: 10.1038/s41594-021-00657-8
3. Therapeutic Goods Administration. TGA grants provisional determination to Merck Sharp & Dohme's antiviral COVID-19 treatment Molnupiravir [Internet]. Australia: TGA; 10 August 2021 [cited 6 October 2021]. Available from: <https://www.tga.gov.au/media-release/tga-grants-provisional-determination-merck-sharp-dohmes-antiviral-covid-19-treatment-molnupiravir>.
4. Lowrey T. Federal government buys 300,000 doses of Merck COVID-19 treatment drug molnupiravir that has not yet been approved [Internet]. ABC News; 5 October 2021 [cited 6 October 2021]. Available from: <https://www.abc.net.au/news/2021-10-05/government-buys-merck-covid-antiviral-pill-molnupiravir/100513410>.
5. US Department of Health and Human Services. Biden Administration announces U.S. government procurement of Merck's investigational antiviral medicine for COVID-19 treatment [Internet]. HHS.gov; 9 June 2021 [cited 6 October 2021]. Available from: <https://www.hhs.gov/about/news/2021/06/09/biden-administration-announces-us-government-procurement-mercks-investigational-antiviral-medicine-covid-19-treatment.html>.
6. Merck Canada. Merck Canada initiates rolling submission to Health Canada for molnupiravir, an investigational oral therapeutic agent for the treatment of COVID-19 [Internet]. Canada: Merck Canada Inc.; 13 August 2021 [cited 6 October 2021]. Available from: https://www.merck.ca/static/pdf/Molnupiravir_Rolling_Submission_EN.pdf.
7. Government of Canada. Drug and vaccine authorizations for COVID-19: List of applications received [Internet]. 1 October 2021 [cited 6 October 2021]. Available from: <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/authorization/applications.html>.
8. Reuters. EMA to consider rolling review for Merck's molnupiravir in coming days [Internet]. US: Reuters; 5 October 2021 [cited 6 October 2021]. Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/ema-consider-rolling-review-mercks-molnupiravir-coming-days-2021-10-05/>.
9. van Kampen JJA, van de Vijver DAMC, Fraaij PLA, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). *Nat Commun.* 2021;12(1):267. DOI: 10.1038/s41467-020-20568-4
10. Painter WP, Holman W, Bush JA, et al. Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity Against SARS-CoV-2. *Antimicrobial agents and chemotherapy.* 2021;65(5):e02428-20. DOI: 10.1128/AAC.02428-20
11. Fischer W, Eron JJ, Holman W, et al. Molnupiravir, an Oral Antiviral Treatment for COVID-19. *medRxiv.* 2021. DOI: 10.1101/2021.06.17.21258639
12. Sheahan TP, Sims AC, Zhou S, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Science translational medicine.* 2020;12(541).
13. Sticher ZM, Lu G, Mitchell DG, et al. Analysis of the potential for N 4-hydroxycytidine to inhibit mitochondrial replication and function. *Antimicrobial agents and chemotherapy.* 2020;64(2):e01719-19.

14. Abdelnabi R, Foo CS, De Jonghe S, et al. Molnupiravir Inhibits Replication of the Emerging SARS-CoV-2 Variants of Concern in a Hamster Infection Model. *The Journal of Infectious Diseases*. 2021;224(5):749-53. DOI: 10.1093/infdis/jiab361
15. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol*. 2021 Jan;6(1):11-8. DOI: 10.1038/s41564-020-00835-2
16. Abdelnabi R, Foo CS, Kaptein SJF, et al. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. *EBioMedicine*. 2021;72. DOI: 10.1016/j.ebiom.2021.103595

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