Oral Antiviral Drug Cuts COVID-19 Hospitalization [UPDATED]

Molnupiravir reduces severe illness and death, but it must be started within days after developing symptoms.

November 26, 2021 By Liz Highleyman

UPDATE: On November 26, Merck announced that molnupiravir reduced the risk of COVID-19 hospitalization by 30% in a larger analysis, substantially below the 50% previously reported. An FDA advisory committee will consider authorization of molnupiravir on November 30. Briefing documents for the meeting are available here.

UPDATE: On October 11, Merck submitted an Emergency Use Authorization application to the Food and Drug Administration for the use of molnupiravir to treat adults with mild-to-moderate COVID-19 who are at risk of progressing to more severe disease or hospitalization.

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Molnupirvair, an experimental oral antiviral, reduced the chances of hospitalization or death by about 50% among people with mild to moderate COVID-19 in an international trial, according to an announcement from Merck and Ridgeback Biotherapeutics. The study was halted early and the companies plan to request Food and Drug Administration (FDA) authorization soon.

“The data are impressive,” Anthony Fauci, MD, director of the National Institute of Allergy and Infectious Diseases, said at a White House COVID-19 Response Team briefing. That’s “very important and very good news.”

> Tune in now for this morning’s COVID-19 briefing with Dr. Fauci, Dr. Murthy, Dr. Walensky, and Jeff Zients.
>
> https://t.co/9kOajmBe5U
>
> — White House COVID-19 Response Team

(@WHCOVIDResponse) October 1, 2021

Despite the availability of highly effective COVID-19 vaccines, there is currently no oral treatment for early disease. Monoclonal antibodies are used to prevent disease progression, but they require IV infusion or injection. Other medications, including remdesivir (Veklury) and dexamethasone, are used to treat hospitalized patients with more severe disease.

“With the virus continuing to circulate widely, and because therapeutic options currently available are infused and/or require access to a healthcare facility, antiviral treatments that can be taken at home to keep people with COVID-19 out of the hospital are critically needed,” Ridgeback CEO Wendy Holman said in the compaies’ statement.

Molnupiravir, formerly known as EIDD-2801 or MK-4482, is a nucleoside/nucleotide analogue, in the same broad class as remdesivir, reverse transcriptase inhibitors for HIV and polymerase inhibitor direct-acting antivirals for hepatitis C. Perhaps the best comparison is oseltamivir (Tamiflu) for the early treatment of influenza. These drugs interfere with viral replication by acting as defective RNA or DNA building blocks. Molnupiravir leads to the accumulation of so many mutations in the genome of SARS-CoV-2 (the coronavirus that causes COVID-19) that the virus in unable to replicate.

Early research showed that molnupiravir is active against Venezuelan equine encephalitis virus (a potential biological warfare agent), hepatitis C virus, influenza viruses and the coronaviruses that cause SARS and MERS. It stopped SARS-CoV-2 replication in human lung cells in laboratory studies and reduced viral load in hamsters. Data from a Phase II clinical trial presented at this year’s Conference on Retroviruses and Opportunistic Infections showed that daily treatment with molnupiravir for five days eliminated SARS-CoV-2 in the nasopharnyx (back of the nose and throat). Further data presented this week at the IDWeek conference showed that the drug works against SARS-CoV-2 variants.

The Phase III MOVe-OUT trial (NCT04575597) included 775 unvaccinated, nonhospitalized adults in the United States and all regions of the world who had mild to moderate COVID-19 symptoms for no more than five days, tested positive for SARS-CoV-2 and had least one risk factor associated with poor disease outcomes, such as older age or underlying health conditions. Most participants had the SARS-CoV-2 delta, gamma or mu variants. They were randomly assigned to receive molnupiravir or placebo pills (four capsules twice daily) for five days.

On October 1, Merck and Ridgeback released results from an interim analysis showing that 7.3% of molnupiravir recipients were hospitalized or died within a month, compared with 14.1% of placebo recipients. In fact, there were no deaths in the molnupiravir group versus eight in the placebo group. However, the treatment was not as effective as monoclonal antibodies, which reduce hospitalization and death for high-risk patients by 70% or more.

The treatment was well tolerated and side effects were comparable in the molnupiravir and placebo groups, according to the companies; 12% and 11%, respectively, experienced drug-related adverse events. Some experts caution that the drug's ability to cause genetic mutations may mean it will be unsafe for pregnant people. However, side effects and drug resistance are less of a concern for a medication taken for only five days, unlike drugs used for lifelong HIV treatment.

Although these latest results have not yet been published in a peer-reviewed journal or presented at a medical meeting, the interim findings were promising enough that a data and safety monitoring board, in consultation with the FDA, recommended that the trial be stopped ahead of schedule. This typically happens when early results show that a therapy is either ineffective or so effective that it would be unethical to continue giving some participants a placebo.

A group of independent experts saw the data and said "we've seen enough"

And stopped the trial because the drug was clearly working

That's important verification

It also makes me far more optimistic about other similar therapies being studies for COVID will pan out

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— Ashish K. Jha, MD, MPH (@ashishkjha) October 1, 2021

Merck indicated that it plans to file for FDA emergency use authorization as soon as possible. The cost of molnupiravir is expected to be $700 for a five-day course, compared with around $2,000 for a course of monoclonal antibodies or around $3,000 for remdesivir.

Questions remain about appropriate use and access to molnupiravir. Should it be available for everyone with early COVID-19 or only those at high risk for disease progression? Is it appropriate for vaccinated individuals with breakthrough infection, who were not included in the study? Will people be able to get tested soon enough to fall within the five-day window after developing symptoms? And will it be accessible regardless of income and insurance status in the U.S. and widely available in lower-income countries where many people still do not have access to COVID-19 vaccines?

Merck said it expects to produce 10 million courses of molnupiravir by the end of 2021. The U.S. government has agreed to purchase approximately 1.7 million courses if the drug receives emergency use authorization or approval. The company has also made supply and purchase agreements with other governments worldwide. Merck indicated that it plans to implement a tiered pricing approach to reflect countries' relative ability to pay, and it has entered into voluntary licensing agreements with several generic manufacturers to accelerate availability in low- and middle-income countries.

"We are committed to making sure that there is access to this drug," Merck vice president Daria Hazuda, PhD, said during a media conference call.

Another question is whether healthy people might stockpile molnupiravir in case they become infected in the future. The drug is also being studied for post-exposure prophylaxis in the MOVe-AHEAD trial (NCT04939428), which is evaluating whether it can prevent COVID-19 in exposed household members.

Molnupiravir is not the only oral antiviral under study as an early treatment for COVID-19. Atea Pharmaceuticals and Roche are developing AT-527, another nucleoside/nucleotide analogue SARS-CoV-2 polymerase inhibitor. Pfizer is testing PF-07321332 (Paxlovid), a SARS-CoV-2 protease inhibitor that is administered with low-dose ritonavir (like some HIV protease inhibitors). The drug is being studied in people with early COVID-19 symptoms and as post-exposure prophylaxis in the EPIC-PEP trial.

But as new antivirals emerge from the pipeline, health officials emphasize that they are not a substitute for vaccines.

"The right way to think about this is this is a potential additional tool in our toolbox to protect people from the worst outcomes of COVID," White House coronavirus adviser Jeff Zients said at the October 1 briefing. Vaccination "remains far and away our best tool against COVID-19…we want to prevent infections, not just treat them when they happen."

Click here for more news about COVID-19 treatment.