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FDA Advisors Recommend Antiviral Pill for Early COVID Treatment

Molnupiravir, the first oral antiviral for COVID-19, reduces the risk of hospitalization or death if started within five days.

December 1, 2021 By Liz Highleyman

A Food and Drug Administration (FDA) advisory committee has recommended emergency use authorization of molnupirvair (brand names Lagevrio or Legebrio), Merck and Ridgeback Biotherapeutics' oral antiviral for the early treatment of COVID-19, but the panel expressed concerns about its modest effectiveness and potential risks.

Despite the availability of highly effective COVID-19 vaccines, there is currently no oral treatment for early infection. Monoclonal antibodies can 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.

Molnupiravir (formerly known as EIDD-2801 or MK-4482) is a nucleoside/nucleotide analogue, in the same broad class as some reverse transcriptase inhibitors for HIV and direct-acting antivirals for hepatitis C. The drug leads to the accumulation of so many mutations in the genetic material of SARS-CoV-2, the coronavirus that causes COVID-19, that the virus is unable to replicate. Early research showed that it stopped SARS-CoV-2 replication in human lung cells in the laboratory and reduced viral load in hamsters.

The Phase III MOVe-OUT trial (NCT04575597) included 775 unvaccinated, nonhospitalized adults 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 for poor disease outcomes, such as older age or underlying health conditions. They were randomly assigned to receive molnupiravir or placebo pills for five days.

As previously reported, in early October, Merck announced results from a interim analysis showing that 7.3% of molnupiravir recipients were hospitalized or died within a month, compared with 14.1% of placebo recipients—a nearly 50% risk reduction. In fact, there were no deaths in the molnupiravir group versus eight in the placebo group.

However, further analysis of a larger group of 1,433 study participants showed that 6.8% of molnupiravir recipients and 9.7% of placebo recipients were hospitalized or died, for a 30% risk

reduction. Although the effectiveness was substantially lower than previously reported, there was just one death in the molnupiravir group compared with nine in the placebo group.

The findings, which have not yet been peer-reviewed or published, took some of the shine off the enthusiasm for molnupiravir. In comparison, monoclonal antibodies reduce the risk of hospitalization and death for high-risk patients by around 70% or more, while Pfizer's oral antiviral Paxlovid, a SARS-CoV-2 protease inhibitor, reduced the risk by 89%.

The treatment was well tolerated and side effects were comparable in the molnupiravir and placebo groups (12% and 11%, respectively). Unlike Paxlovid, which is given with a small dose of ritonavir to boost drug levels, molnupiravir is not expected to interact with other drugs. But some experts are worried about whether the drug could cause genetic mutations in human DNA, although animal studies did not raise red flags. Another concern is that, by causing so many viral mutations, molnupiravir could promote the emergence of resistant strains or even new variants.

Meeting on November 30, the FDA's Antimicrobial Drugs Advisory Committee voted by a narrow 13 to 10 margin to recommend emergency use authorization of molnupiravir for adults with mild to moderate COVID-19 who are at high risk for progressing to severe COVID-19. The full FDA is not required to accept the committee's recommendation, but it usually does so.

> FDA AMDAC has voted 13 yes, 10 no for EUA for Merck's molnupiravir COVID-19 drug. I voted no. Inclusive data on mutagenic potential and concerns over generating troublesome SARS-CoV2 variants were not addressed to my satisfaction. Drug has modest 30% reduction in COVID-19 risk.
>
> — James E.K. Hildreth (@JamesEKHildreth) November 30, 2021

Some committee members were skeptical about the drug's modest effectiveness, and Merck representatives were unable to explain why efficacy dropped off between the interim and final analyses. Others expressed concerned that molnupiravir could cause birth defects if used during pregnancy.

The meeting took place just days after health officials in South Africa announced the identification of a new SARS-CoV-2 variant dubbed Omicron. Although little is known yet about the new variant, it has more than 30 spike protein mutations, which is expected to reduce the effectiveness of vaccines and monoclonal antibodies. But antivirals like molnupiravir and Paxlovid should still work.

"Because they work differently from the majority of COVID-19 vaccines, which teach the immune system to identify and attack the coronavirus's characteristic spike protein, the antivirals remain effective against mutant variants whose spike proteins are harder for immune cells to recognize," Monica Gandhi, MD, MPH, of the University of California at San Francisco, wrote in The Atlantic. "Designing, manufacturing and distributing vaccines updated for new variants will take time, so the availability of antivirals will be all the more essential."

> "These miraculous drugs arrived with minimal fanfare but represent the biggest advance yet in treating patients already infected with COVID-19," @MonicaGandhi9 writes. https://t.co/amunabuyPs
>
> — The Atlantic (@TheAtlantic) November 29, 2021

Some have suggested that oral antivirals like molnupiravir and Paxlovid could be game-changers, but questions remain about how widely accessible they will be and how best to use them.

Merck stated in a press release that it expects to produce 10 million courses of molnupiravir by the end of 2021 and at least 20 million courses in 2022. The cost is expected to be about $700 per course, compared with around $1,250 plus administration fees for a course of monoclonal antibodies. The U.S. government has agreed to purchase 3.1 million courses upon authorization. The company said it plans to implement a tiered pricing structure, has entered a licensing agreement with the Medicines Patent Pool and has entered nonexclusive voluntary licensing agreements with generic manufacturers to increase access for people in low- and middle-income countries.

The MOVe-OUT study enrolled only unvaccinated people, but there's no reason to think molnupiravir wouldn't also work for vaccinated individuals with breakthrough infections. Limiting the drug's indication to the former group could give the appearance of "punishing" people who have done the right thing.

Both molnupiravir and Paxlovid must be started very early, just three to five days after a person first develops symptoms. This raises concerns about whether people will be able to get tested for

SARS-CoV-2 and receive a prescription in a timely manner, which could further widen disparities for those who cannot pay for expensive tests or do not have a regular health care provider. A new Health and Human Services rule would make it easier to get a rapid test, a prescription and the drugs at a pharmacy. While people with resources may be inclined to keep rapid antigen tests and a course of the meds on hand "just in case," widespread use by those at no real risk for progression to severe illness could lead to drug resistance.

Some wonder whether combining antivirals that work by different mechanisms could improve their effectiveness and reduce the likelihood of resistance—the approach used for lifelong HIV treatment and months-long hepatitis C treatment. But this increases side effects and cost and may not be necessary for such short-term therapy.

Preventive use of antivirals, either before or after exposure, could also be a possibility. Molnupiravir post-exposure prophylaxis, or PEP, is being studied in the MOVe-AHEAD trial (NCT04939428), evaluating whether the drug can prevent COVID-19 in exposed household members.

Health officials stress that antivirals should not be considered a substitute for vaccination, and all eligible individuals should receive their initial vaccines and boosters as soon as they can. But COVID-19 pre-exposure prophylaxis (PrEP) using antiviral pills or monoclonal antibodies could potentially be a life-saving option for immunocompromised people who do not respond well to the vaccines.

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