Merck announces promising new pill to treat COVID infections

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On Friday morning, Merck, the pharmaceutical giant, announced significant positive results for their antiviral drug Molnupiravir (EIDD-2801) to treat people infected with early COVID-19 experiencing mild to moderate symptoms. According to the press release, their "oral antiviral" drug reduced the risk of hospitalization and death by around 50 percent.

In fact, the phase three trial was stopped early on the recommendation by the independent data monitoring committee, in consultation with the Food and Drug Administration (FDA), on these significant findings. The oversight committees are responsible for the conduct and integrity of such trials. If during a planned interim analysis of the data the review committee finds the drug to be efficacious, it can recommend stopping the trial, as not to further delay using these drugs that can benefit patients.

The analysis showed that the COVID-19 pill reduced hospitalizations and death down from 14 percent in the group taking a placebo to 7 percent in those that were given the active ingredient. When the interim data was broken down further, the reduction in hospitalizations was only 39 percent. But more impressive was the reduction in deaths, from eight in the placebo group to zero taking the actual medication.

The final analysis of all the data is anticipated shortly and peer-reviewed publication of the report will be important to ensure confidence in the process. But such a development is welcome news and an urgently-needed addition to the fight against the coronavirus. It is only an addition, however, and no substitute for an aggressive campaign to eradicate the virus using every possible public health measure, including lockdowns.

Merck has indicated they have already proceeded with an application to the FDA to obtain emergency use authorization (EUA). Pending this approval, the positive findings mean that there is now, for the first time in the course of the pandemic, a COVID-19 treatment that can be administered by mouth. The pharmaceutical company expects to produce 10 million treatment courses by the end of the year and many more doses in 2022.

In June 2021, the Biden administration signed an agreement with Merck for 1.7 million courses of treatment (one pill twice a day for five days) for a total price tag of $1.2 billion, or $700 for each course. The drug is expected to generate revenues up to $7 billion by year's end. The company has said it has agreements with several governments but has not shared these details. As it stands, Molnupiravir will be catapulted into the profit stratosphere as one of the most lucrative drugs ever made.

An effective oral antiviral treatment is a game-changer. Ease of delivery and storage makes it ideal in a situation when there can be considerable delay in symptom onset and confirmatory testing of COVID-19. Both Remdesivir (a broad-spectrum antiviral drug) and Regeneron (a monoclonal antibody) must be administered intravenously, requiring skilled health care workers and additional supplies. Remdesivir's data has also been criticized for tepid results in three trials that suggest it only modestly improves time to recovery by a few days.

In brief, the phase three MOVe-OUT trial was an international randomized, blinded study that compared Molnupiravir to a placebo in non-hospitalized adults diagnosed with mild to moderate COVID-19. Patients had to have one or more risk factors associated with poor outcomes. Symptom onset could not have lasted for more than five days to participate in the trial. The primary endpoint was the percentage of participants who were hospitalized and/or died through 29 days after being randomized into the study.

The main risk factors for severe disease among subjects were obesity, age at or over 60, diabetes, and heart disease. The Delta, gamma, and Mu variants accounted for 80 percent of sequenced infections. With more than 170 sites involved, 55 percent of participants were from Latin America, 23 percent from Europe, and 15 percent from Africa. The adverse effects of the medication were comparable to the placebo arm of the trial. Fewer people discontinued their treatment in the Molnupiravir arm than in the placebo group.

In the early stages of the pandemic, in the effort to find anything that could work to treat infected patients, many older drugs sitting on laboratory shelves and benches were resurrected and tested for their response against SARS-CoV-2. In this regard, Molnupiravir, a broad-based antiviral drug, was as likely a candidate as any. It proved to provide impressive results against the coronavirus in human lung cell cultures.

Molnupiravir (EIDD-2081) has, like many chemical compounds, a convoluted history. Several years before the pandemic, Emory University was awarded a $10 million contract through the Defense Threat Reduction Agency to develop new drugs to treat infections caused by emerging and fabricated viral threats—in other words, it originates as a byproduct of the Pentagon's germ warfare program.

According to an article published in *Chemical & Engineering News* on May 5, 2020, Dr. George Painter, director of the Emory

Institute for Drug Development, and his team screened molecules that were analogues to those used in antiviral drugs, seeking a compound that had a high barrier to resistance, which means that despite a virus's ability to mutate, the drug would remain effective. Also, the molecule had to penetrate the blood-brain barrier because these viral threats attacked the brain.

Their efforts zeroed in on an obscure molecule called N4-Hydroxyctidine (NHC), which they dubbed EIDD-1931, which had broad and intriguing antiviral properties that seemed to fulfill each of their requirements. It had first been looked at in the 1970s by Russian and Polish scientists working on treatment against smallpox infection. Subsequently, many laboratories had used the compound in their experiments on elucidating viral replication mechanisms.

Once the molecule is incorporated into the RNA by the virus's replicating enzyme, NHC is recognized as either Cytidine or Uracil (two of four nucleotides in the building blocks of RNA). In other words, NHC can exist, through a chemical reaction called *tautomerization*, as two forms rapidly flipping back and forth from one to the other. When the virus attempts to replicate again, multiple errors are incorporated as a result of the change in forms in NHC during RNA strand replication, leading to a lethal mutation that leaves the virus unable to infect or reproduce.

The researchers also found the drug had tremendous activity against coronaviruses, including SARS and MERS in mice and dog animal models. However, testing in monkeys revealed it was getting trapped in the cells that line their guts and unable to fight the infection, making its potential use in humans problematic. This then led to the current prodrug formulation, EIDD-2081, that allows the drug to reach the bloodstream before metabolizing to its active form.

It was in early 2020, when the team from Emory University was considering a new drug application with the FDA for EIDD-2081 as a treatment for influenza, that the outbreak in Wuhan, China, began making the front pages of every news channel across the globe.

In early March 2020, EIDD-2081was tested in human cell cultures infected with SARS-CoV-2 and proved exceptionally adept at stopping viral replication. It was also effective at killing the viruses that became resistant to Remdesivir. Virologist Juliet Morrison of the University of California, Riverside, commented at the time that the cell culture studies had been very promising. Still, if these drugs are to work in people, they would need to be administered early in the course of an infection. The team moved quickly to get EIDD-2081 into clinical studies.

On March 19, 2020, Miami-based Ridgeback Biotherapeutics, founded in 2016 as a company focused on developing therapies against emerging infectious diseases, licensed EIDD-2081 from Emory for an undisclosed amount, according to the *Washington Post*.

The *Post* wrote on June 25, 2020, "But what the tiny Miami company did have was a growing team with experience in pharmaceutical development and research and a willingness from its wealthy owners—chief executive Wendy Holman and her husband, hedge fund manager Wayne Holman—to place a bet on the treatment in the midst of the coronavirus pandemic. That wager paid off with extraordinary speed in May when, just two months after acquiring the antiviral therapy called EIDD-2081 from Emory, Ridgeback sold exclusive worldwide rights to drug giant Merck."

As Dr. Aaron Kesselheim, a physician at Brigham and Women's Hospital in Boston and specialist in drug development, noted at the time, "I would think that universities … would not normally transfer products to basically a house flipper. I wouldn't think they would have to engage with speculators, like it appears that Ridgeback Biotherapeutic is."

As significant as the positive data released on Merck's COVID pill is, it begs the question why it has taken so long to initiate and conduct these trials? Clearly there had been little hope placed in pharmaceuticals for the treatment of COVID. Additionally, the vaccines were at the front and center of the response to the pandemic. It is certain more information will be forthcoming in the weeks and months ahead, but it would be safe to assume that financial deliberations were behind these maneuverings.

In this competition, much is currently in advanced development. Pfizer has recently commenced a large phase 2/3 trial testing their investigational oral antiviral agent, a novel protease inhibitor (PF-07321332). Meanwhile, Roche reported in mid-August that they were making amendments to their phase two trial with their experimental drug AT-527, which has been shown to reduce viral replication in hospitalized patients.

However, caution needs to be raised that the antiviral pill and the next generation of therapeutics are not a panacea and do not obviate the need for a global eradication strategy. The ruling elites will now further mobilize their efforts to push to make the virus endemic. Meanwhile, all federal and state public health measures are being abandoned and privatized. The COVID pandemic has provided the impetus for the complete abrogation of all responsibility by the government for the safety and well-being of its population.