The ‘very, very bad look’ of remdesivir, the first FDA-approved COVID-19 drug

By Jon Cohen, Kai KupferschmidtOct. 28, 2020 , 7:05 PM

President Donald Trump and Food and Drug Administration Commissioner Stephen Hahn (right) met with Daniel O’Day (left), CEO of Gilead Sciences, when remdesivir received an emergency use authorization in May.

AP Photo/Alex Brandon

October was a good month for Gilead Sciences, the giant manufacturer of antivirals headquartered in Foster City, California. On 8 October, the company inked an agreement to supply the European Union with its drug remdesivir as a treatment for COVID-19—a deal potentially worth more than $1 billion. Two weeks later, on 22 October, the U.S. Food and Drug Administration (FDA) approved remdesivir for use against the pandemic coronavirus SARS-CoV-2 in the United States—the first drug to receive that status. The EU and U.S. decisions pave the way for Gilead’s drug into two major markets, both with soaring COVID-19 cases.

But both decisions baffled scientists who have closely watched the clinical trials of remdesivir unfold over the past 6 months—and who have many questions about remdesivir’s worth. At best, one large, well-designed study found remdesivir modestly reduced the time to recover from COVID-19 in hospitalized patients with severe illness. A few smaller studies found no impact of treatment on the disease whatsoever. Then, on 15 October—in this month’s decidedly unfavorable news for Gilead—the fourth and largest controlled study delivered what some

believed was a coup de grâce: The World Health Organization’s (WHO’s) Solidarity trial showed that remdesivir does not reduce mortality or the time COVID-19 patients take to recover.

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Science has learned that both FDA’s decision and the EU deal came about under unusual circumstances that gave the company important advantages. FDA never consulted a group of outside experts that it has at the ready to weigh in on complicated antiviral drug issues. That group, the Antimicrobial Drugs Advisory Committee (AMDAC), mixes infectious disease clinicians with biostatisticians, pharmacists, and a consumer representative to review all available data on experimental treatments and make recommendations to FDA about drug approvals—yet it has not convened once during the pandemic.

The European Union, meanwhile, decided to settle on the remdesivir pricing exactly 1 week before the disappointing Solidarity trial results came out. It was unaware of those results, although Gilead, having donated remdesivir to the trial, was informed of the data on 23 September and knew the trial was a bust.

“This is a very, very bad look for the FDA, and the dealings between Gilead and EU make it another layer of badness,” says Eric Topol, a cardiologist at the Scripps Research Translational

Institute who objected to remdesivir’s FDA approval.

FDA has no obligation to convene outside panels for its decisions, stresses AMDAC member David Hardy, an HIV/AIDS scientist of the University of California, Los Angeles. Yet the agency often does so for tricky drug approvals and Hardy is “amazed” the agency didn’t consult the panel in this case. “This sets the standard for the first COVID-19 antiviral,” he says. “When it comes to the point of giving pharmaceutical companies exclusive marketing rights in this area, that really is something that’s very, very important. And there does need to be more than just governmental input.”

FDA did not respond to *Science*’s request to discuss why it opted against convening the committee, noting only that it is “at the discretion” of division directors. But FDA’s inaction stands in sharp contrast to its handling of potential COVID-19 vaccines. Last week, the agency convened an advisory group to discuss the mere possibility of such a vaccine passing regulatory muster.

As to the EU agreement, Gilead confirmed to *Science* that WHO in “late September” provided the company with a manuscript about the study results, but a spokesperson for the European Commission, the EU executive arm, said these weren’t revealed during its negotiations. The company has aggressively called into question the validity of the Solidarity data, in part because the study was carried out in vastly different countries around the world with different health care standards. In a 15 October statement, Gilead went so far as to say “it is unclear if any conclusive findings can be drawn from the study results.”

That criticism has angered investigators in the Solidarity study, including Marie-Paule Kieny, director of research at the French medical research agency INSERM and a former WHO officer. “It’s appalling to see how Gilead tries to badmouth the Solidarity trial,” Kieny says. “Pretending the trial has no value because it is in low-income countries is just prejudice.”

Disappointing trials

On 10 January, 2 days after SARS-CoV-2 was proved to be the cause of COVID-19, researchers published a study in *Nature Communications* that showed remdesivir had powerful inhibitory effects in both test tube and mouse studies on the related coronavirus that is responsible for Middle East respiratory syndrome. Two weeks later, doctors treated the first confirmed case of COVID-19 in the United States with the drug and reported that the 35-year-old man improved rapidly.

An interim analysis from a large-scale, placebo-controlled clinical trial carried out by the National Institutes of Health (NIH), announced on 29 April, tempered expectations but also emphasized that remdesivir had promise. The drug reduced the median time that severely ill, hospitalized COVID-19 patients took to recover from 15 days to 11 days. It was a modest gain, but NIH noted in a press release that treated patients “had a 31% faster time to recovery than those who received placebo.” Remdesivir, which must be repeatedly infused intravenously, also seemed to lower the risk of death, but that difference could have arisen by chance. (A peer-reviewed, final report of the study published 8 October in *The New England Journal of Medicine* reduced the time to recovery for the 531 treated patients to 10 days.)

A second, smaller placebo-controlled study of remdesivir on hospitalized COVID-19 patients in China, published online by *The Lancet* also on 29 April, found no statistically significant benefit

from the treatment—and the antiviral surprisingly had no impact on levels of the coronavirus.

Two days after the results from China and the United States came out, FDA granted remdesivir an emergency use authorization (EUA)—a temporary status that is far from full approval—for use in severe COVID-19 patients. The agency cited the NIH trial data, but not the other study. President Donald Trump praised the EUA in an Oval Office press event with Daniel O’Day, CEO of Gilead.

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On 21 August, a Gilead-sponsored study published online in *JAMA* compared hospitalized COVID-19 patients with moderate pneumonia who received remdesivir for 5 days or 10 days versus those treated with the standard of care. The 5-day remdesivir group improved more quickly, but, oddly, the 10-day group did not. (An earlier published study sponsored by Gilead found no difference between the two treatment courses.)

The next week, FDA expanded remdesivir’s EUA to include all hospitalized COVID-19 patients. That led Topol to publish a scathing open letter to FDA Commissioner Stephen Hahn on Medscape, a popular medical website of which Topol is editor-in-chief. Under the headline “Tell the Truth or Resign,” Topol lumped the decision together with heavily criticized EUAs issued earlier for the malaria drug hydroxychloroquine—which the agency later rescinded—and antibody-rich “convalescent” plasma obtained from the blood of recovered COVID-19 patients. “These repeated breaches demonstrate your willingness to ignore the lack of scientific evidence, and to be complicit with the Trump Administration’s politicization of America’s healthcare institutions,” Topol wrote.

Debating the evidence

WHO’s Solidarity trial, conducted in 405 hospitals in 30 countries, is about three times as large as the other three trials together and many scientists expected it to better resolve remdesivir’s worth. Solidarity did not use a placebo, but instead compared remdesivir and three other repurposed drugs with each other and the standard of care. The Solidarity trial investigators described the study results to FDA representatives on 10 October and posted a preprint on them on medRxiv 5 days later. Solidarity mainly aimed to determine whether the drugs lowered mortality among hospitalized COVID-19 patients, which none of them did. The researchers also noted that remdesivir did not affect “the duration of hospitalization” or whether COVID-19 patients required ventilators, which are only used when people advance to very serious disease.

The release of the Solidarity data has triggered a fresh debate about the relative value of each remdesivir trial—and whether FDA should have aired that discussion in public instead of weighing the data privately. In its review that recommended remdesivir’s approval, the agency only included data from three trials: the NIH study and two Gilead-sponsored trials, ignoring the Solidarity data as well as the findings from the other placebo-controlled trial in China.

That infuriated the Solidarity team. “The mantra I’ve always heard as a joke about the FDA is that they say ‘In God we trust, everyone else has to provide data,’” Kieny says. “So look at all the data.”

As far as Gilead is concerned, the Solidarity data should not play an important role. “We are concerned that the data from this open-label global trial have not undergone the rigorous review required to allow for constructive scientific discussion, particularly given the limitations of the trial design,” the company wrote in its statement.

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Gilead Chief Medical Officer Merdad Parsey wrote in an open letter posted the day of FDA’s remdesivir approval that Solidarity “does not negate other study results—particularly from a trial designed with the strictest of scientific standards, as is the case with” NIH’s study. Gilead has also raised questions about the availability of Solidarity’s data, telling *Science* it has requested from WHO, but has yet to receive, “the underlying data sets or statistical analysis plan” for the trial.

WHO counters that Gilead knew the statistical analysis plan before joining the trial and will receive the full data set once the study is complete. It does not matter that the data have not yet been peer reviewed, WHO scientists say, because FDA traditionally reviews all available data, including unpublished findings. As to the disparity in health systems that Gilead cites as a confounding factor in Solidarity’s findings, WHO’s chief scientist, Soumya Swaminathan, notes that 50% of the 2750 patients who received remdesivir in the trial were from Canada and Europe, places recognized for high-quality health care. And she stresses that the other participating countries do not necessarily have substandard care.

Clifford Lane of the National Institute of Allergy and Infectious Diseases, who helped run the NIH study, says its main difference with Solidarity is “the degree of granularity” of the analyses of subgroups that may have benefited. “I think the Solidarity data are fine,” Lane says. “It’s a very large study and it has a very robust endpoint.”

Martin Landray of the University of Oxford, who is co-leading the world’s largest study of various COVID-19 treatments, says remdesivir “definitely doesn’t work in the sickest patients where the biggest gains would be” but might help people at earlier stages of disease. Further complicating the matter, most people infected with SARS-CoV-2 recover without any intervention. “The argument that the earlier you use it the better is great until you realize what the implications of that are: You won’t save many lives, and you’ll have to treat a lot of patients,” Landray says. “It’s very inconvenient, and it’ll cost you a fortune.”

Questions have also arisen about the potential of remdesivir to do harm. WHO has a regular overview of possible adverse drug events related to COVID-19 treatments. In late August it noted a disproportionately high number of reports of liver and kidney problems in patients receiving remdesivir compared with patients receiving other drugs for COVID-19. The European Medicines Agency (EMA) also announced this month that its safety committee had started a review to assess reports of acute kidney injuries in some patients taking remdesivir.

Gilead Sciences’s remdesivir has become part of the standard of care for many COVID-19 patients in the United States and the company has been increasing production of the antiviral to meet increasing demand.

Gilead

Many researchers point out that another crucial piece of data is missing entirely from FDA’s statement on remdesivir’s approval: evidence the drug reduces the amount of SARS-CoV-2 in the body, the viral load. “I’ve been working in antivirals for 30 years. Every time you study an antiviral, you show an effect on the virus and you publish it,” says Andrew Hill, a clinical pharmacologist at the University of Liverpool. “Surely Gilead has done that. Where are the data? It is very, very strange.”

Richard Peto, an Oxford statistician and epidemiologist who helped design Solidarity and analyze the data, stresses that the WHO trial cannot prove whether remdesivir has zero benefit for COVID-19. “Trials produce confidence intervals, not just point estimates and this is actually the difficulty in trying to discuss this,” Peto says. “Gilead and the FDA have sort of maneuvered us into a position where we’re being asked to try and prove remdesivir does nothing rather than asking the usual way round, which is, ‘Can the manufacturers prove it does something?’”

To many scientists, such complexities underscore that FDA should have consulted ADAC, its panel of outside experts, for a vigorous debate. It could have “elevated the discussion,” says ADAC Chair Lindsey Baden, an infectious disease specialist at Brigham and Women’s Hospital. “Hydroxychloroquine, convalescent plasma, remdesivir—these are complicated decisions given the imperfect nature of the data upon which the decisions are being made, and the urgency of the clinical use gives all the more reasons to have an open discussion,” says Baden, whose group last met in October 2019.

“This was not a straightforward approval and this is not an ordinary time,” adds Luciana Borio, a former acting chief scientist at FDA who now works at a not-for-profit venture capital firm. “It would have been helpful to have a public discussion on the matter.”

Georgetown University’s Jesse Goodman, a former chief scientist at FDA, notes that it is complicated to organize advisory committee meetings, but adds that the agency obviously just arranged one for COVID-19 vaccines. “Although it’s a pandemic and everybody is super busy, it’s something … you can do virtually,” he says. “It would have been an opportunity to make clear publicly the rationale and their risk-benefit assessment.”

European Commission in the dark

EMA, Europe’s FDA counterpart, in July gave “conditional approval” to remdesivir—which is similar to an EUA—but it has yet to give its full blessing. The European Union nevertheless has negotiated a “joint procurement agreement” with Gilead that offers 500,000 treatment courses over the next 6 months for $1.2 billion. A spokesperson of the Commission confirms to *Science* it was not informed of the drug’s failure in the Solidarity trial until the day after the new contract was signed on 8 October.

“The Commission became aware of the results of the Solidarity trial on 9 October from the reporting of [EMA] at the COVID task force meeting on the same day,” the spokesperson says. “There was no discussion with WHO about the ongoing study prior to signing the contract with Gilead.”

When *Science* asked Gilead why it didn’t disclose the Solidarity data during its negotiations with the Commission, the company acknowledged it received a draft manuscript from WHO in late September but said it was “heavily redacted.” WHO says the only information blacked out was results relating to the other drugs used in the trial because of confidentiality agreements with their manufacturers.

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Although the agreement with Gilead locks EU members into a price of about $2400 for a full course of remdesivir, it does not obligate any countries to purchase the drug, the Commission spokesperson tells *Science*. “The EU needs to publish the deal with Gilead,” says Yannis Natsis of the nonprofit European Public Health Alliance. “It should at least renegotiate the volume of the doses and the price per treatment.” Gilead says it doesn’t plan to adjust its negotiated price in the wake of the Solidarity data.

Kieny says it’s an “enormous” waste for EU countries to invest in remdesivir based on the idea that it might help a small subset of patients. “You can always say, ‘OK, now, if I disaggregate the population and if I take only those who have a blue eye and a wooden leg, maybe this is very effective,’” she says.

Indeed, some advocates of remdesivir point to analyses of Solidarity patient subgroups that suggest a mortality benefit in those who received supplemental oxygen but were not on ventilators. But accepting that would also mean accepting that remdesivir harmed those who were on ventilators, Hill says. “You can’t do a subgroup analysis and only believe half the story.”

The bottom line from the trials so far is there simply isn’t enough evidence that remdesivir works, says Jason Pogue, a University of Michigan, Ann Arbor, researcher who is president of the Society of Infectious Diseases Pharmacists. Pogue believes FDA made a mistake and, unless more data emerge, EMA should not give the drug full approval. “There are more questions than answers about the efficacy of remdesivir in hospitalized patients,” he says.

***Correction, 30 October, noon:** An earlier version of this story incorrectly stated that Gilead was the sponsor of the Solidarity trial. It has been corrected to note that the company supported the study by donating the drug.*