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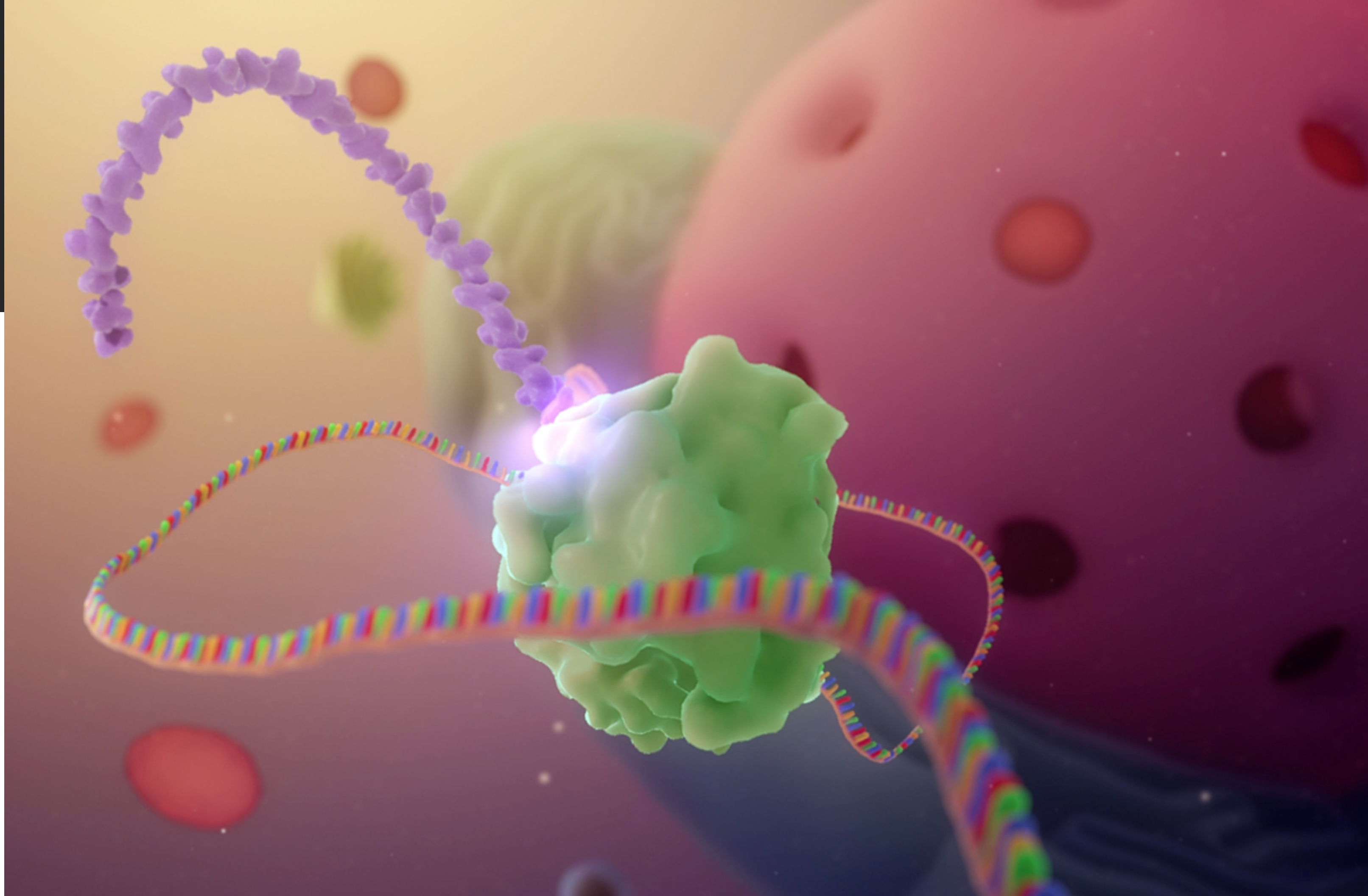
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SCIENCEINSIDER HEALTH

An mRNA vaccine with a twist—it copies itself—protects against COVID-19

Company's limited data release backs promise of new, lower dose vaccine designed to be easier to distribute and cheaper

21 APR 2022 · 6:35 PM · BY JON COHEN



The Arcturus Therapeutics COVID-19 vaccine contains a strand of messenger RNA (multicolored) that self-amplifies after injection and then is translated by cells into the viral spike protein (purple). ARCTURUS THERAPEUTICS

A third messenger RNA (mRNA) vaccine appears to have proved its worth against COVID-19. And although it is more than a year behind the Moderna and Pfizer-BioNTech vaccines now seen as gold standards, the new vaccine may come with significant advantages: easier storage, along with lower cost because its "self-amplifying" design allows for smaller doses.

Arcturus Therapeutics of San Diego, which staged a placebo-controlled trial of its candidate in more than 17,000 participants in Vietnam, **announced yesterday in a press release** that the vaccine had 55% efficacy against symptomatic COVID-19 and provided 95% efficacy against severe illness and death. "It's a huge accomplishment that for the first time a self-amplifying RNA vaccine has been shown to be safe and effective," says Deborah Fuller, a vaccinologist at the University of Washington School of Medicine who is an adviser to HDT Bio, which has its own self-amplifying COVID-19 mRNA vaccine in human studies.

Arcturus's success may also help make mRNA vaccines more broadly accessible. Its candidate incorporates a freeze-drying process to transform the mRNA-filled solution into a powder that can be stored at room temperature, then rehydrated. This has far simpler cold-chain requirements than the conventional, liquid mRNA vaccines in use. And Vietnam's Vinbiocare Biotechnology, which collaborated with Arcturus on the trial and has submitted the efficacy data to the country's regulators for emergency use authorization, hopes to manufacture the product there.

The Pfizer-BioNTech and Moderna vaccines contain mRNA that codes for the SARS-CoV-2 spike protein. When the vaccines are injected, they deliver the mRNA to cells, which make copies of spike and then clear the foreign genetic material within a few days. Arcturus's self-amplifying vaccine and others in development include enzymes from alphaviruses to repeatedly copy the genetic strand inside a cell and stay in the body for more than twice as long.

Some researchers have cautioned that self-amplifying vaccines cannot use an mRNA modification that is key to the Moderna and Pfizer-BioNTech vaccines: the replacement of the natural RNA building block uridine with pseudouridine. Studies have shown the swap leads to higher levels of the spike protein and lower production of immune chemicals called cytokines that can cause side effects. A conventional mRNA vaccine made by CureVac failed in an efficacy trial last year, and **some scientists suggested** this may have been because it didn't use pseudouridine. But Arcturus says the efficacy findings refute those concerns. "It's a big deal for the field," says Pad Chivukula, the company's chief scientific officer.

The trial, which began in August 2021, gave participants two doses, each containing 5 micrograms of the self-amplifying mRNA, spaced 28 days apart. The Pfizer-BioNTech and Moderna vaccines use 30-microgram and 100-microgram doses, respectively, for the first two shots.



Like most COVID-19 vaccinemakers with fresh efficacy trial results, Arcturus only released a peek at the findings. The bottom line against symptomatic infection—55% efficacy—is below the 90% to 95% seen in trials of the first two mRNA vaccines. But those vaccines faced the original SARS-CoV-2 virus. The Arcturus candidate, based on a similar strain, had to protect against the Delta and Omicron variants that were circulating in Vietnam during the trial, which have evolved dramatically from the ancestral strain, decreasing the power of vaccine-triggered antibodies. Fuller says the current real-world effectiveness of existing mRNA vaccines may be in the same ballpark. Of the 43 severe cases of COVID-19 recorded by Arcturus during the trial, only two were in the vaccinated group, and nine of the 10 people with COVID-19 who died received the placebo.

"These are indeed exciting results," says chemist Benjamin Pierce, who is helping run a Ugandan trial of a self-amplifying mRNA COVID-19 vaccine made by Imperial College London. "The low dose used here—six to 20 times lower than approved RNA vaccines—further indicates that self-amplifying RNA technology has such potential. I look forward to seeing more of the data from the trial."

Fuller says a self-amplifying mRNA COVID-19 vaccine ideally would replace the two primary doses, giving it an even clearer benefit over its conventional relatives. A booster months later might still be warranted, as is encouraged now for the current mRNA vaccines. But self-amplifying mRNAs could also lead to more durable immune responses, Fuller suggests.

When the Arcturus trial began, less than 15% of the eligible Vietnamese population had received even a single shot of a COVID-19 vaccine. Now, the figure is 80%, which raises the question of how the vaccine will perform in the vast majority of people who have already been vaccinated or naturally exposed to SARS-CoV-2. Arcturus hopes to soon launch a 2400-person trial to assess its value as a booster shot. This trial will aim to show the vaccine boosts antibody responses that other studies have shown **correlate with protection**—though no new COVID-19 vaccine has yet received authorization from strict U.S. or European regulators based on "immunobridging" data.

The Pfizer-BioNTech collaboration and Moderna have received intense criticism for not quickly sharing their manufacturing skills and intellectual property with developing countries, which have had relatively little access to their mRNA vaccines. Arcturus, in contrast, **in August 2021** agreed to a technology transfer deal with Vinbiocare, which is building a plant in Hanoi to manufacture the vaccine.

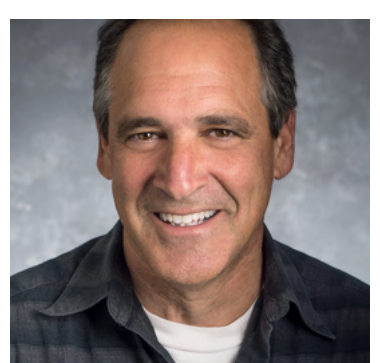
But with much of the world vaccinated, the Arcturus vaccine may be making its debut too late, at least for primary vaccination. Chivukula is confident it will find a market in countries that have far lower vaccination rates than Vietnam and stresses it will be at "a price point that everyone can afford."

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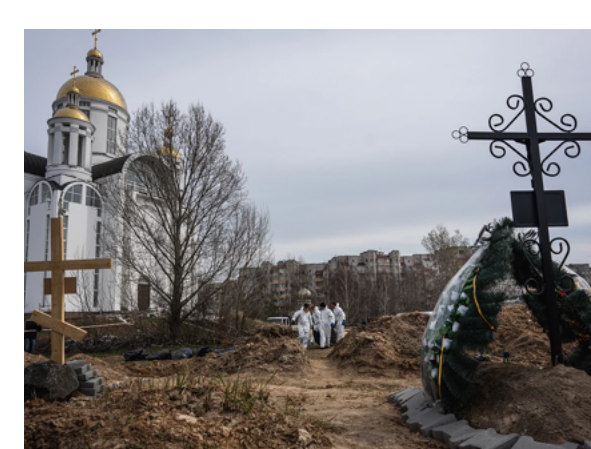
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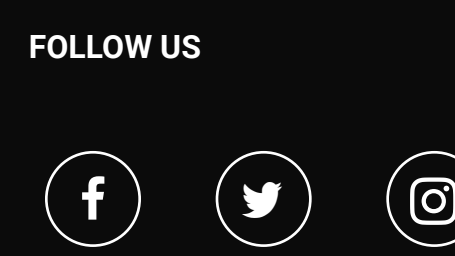
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