The New York Times

# *AstraZeneca, Under Fire for Vaccine Safety, Releases Trial Blueprints*

Experts are concerned that the company has not been more forthcoming about two participants who became seriously ill after getting its experimental vaccine.

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- Published Sept. 19, 2020Updated Sept. 20, 2020, 10:03 a.m. ET

AstraZeneca revealed details of its large coronavirus vaccine trials on Saturday, the third in a wave of rare disclosures by drug companies under pressure to be more transparent about how they are testing products that are the world's best hope for ending the pandemic.

Polls are finding Americans increasingly wary of accepting a coronavirus vaccine. And scientists inside and outside the government are worried that regulators, pressured by the president for results before Election Day on Nov. 3, might release an unproven or unsafe vaccine.

"The release of these protocols seems to reflect some public pressure to do so," said Natalie Dean, a biostatistician and expert in clinical trial design for vaccines at the University of Florida. "This is an unprecedented situation, and public confidence is such a huge part of the success of this endeavor."

Experts have been particularly concerned about AstraZeneca's vaccine trials, which began in April in Britain, because of the company's refusal to provide details about serious neurological illnesses in two participants, both women, who received its experimental vaccine in Britain. Those cases spurred the company to halt its trials twice, the second time earlier this month. The studies have resumed in Britain, Brazil, India and South Africa, but are still on pause in the U.S. About 18,000 people worldwide have received AstraZeneca's vaccine so far.

AstraZeneca's 111-page trial blueprint, known as a protocol, states that its goal is a vaccine with 50 percent effectiveness — the same threshold that the Food and Drug Administration has set in its guidance for coronavirus vaccines. To determine with statistical confidence whether the company has met that target, there will have to be 150 people ill with confirmed coronavirus among participants who were vaccinated or received placebo shots.

However, the plan anticipates that a safety board will perform an early analysis after there have been just 75 cases. If the vaccine is 50 percent effective at that point, it might

be possible for the company to stop the trial early and apply for authorization from the government to release the vaccine for emergency use.

In allowing only one such interim analysis, AstraZeneca's plan is more rigorous than the others that have been released, from Moderna and Pfizer, Dr. Eric Topol, a clinical trials expert at Scripps Research in San Diego, said in an interview. Moderna allows two such analyses, and Pfizer four.

Such plans are not usually shared with the public "due to the importance of maintaining confidentiality and integrity of trials," Michele Meixell, a spokeswoman for AstraZeneca, said in a statement.

The company has released few details about the two cases of serious illness in its trial. The first participant received one dose of the vaccine before developing inflammation of the spinal cord, known as transverse myelitis, according to a participant information sheet for AstraZeneca's vaccine from July. The condition can cause weakness in the arms and legs, paralysis, pain and bowel and bladder problems.

The case prompted a pause in AstraZeneca's vaccine trials to allow for a safety review by independent experts. A company spokeswoman told the Times last week that the volunteer was later determined to have a previously undiagnosed case of multiple sclerosis, unrelated to the vaccine, and that the trial resumed shortly thereafter.

Transverse myelitis can sometimes be the first sign of multiple sclerosis, which involves more complex symptoms. But the myelitis alone can also occur after the body encounters an infectious agent like a virus.

The company said it had not confirmed a diagnosis in the second case, a participant who got sick after the second dose of the vaccine. A person familiar with the situation who spoke with The Times on the condition of anonymity said the participant's illness had been pinpointed as transverse myelitis. The trial was paused again on Sept. 6 after she fell ill.

The condition is rare, but serious, and experts said that finding even one case among thousands of trial participants could be a red flag. Multiple confirmed cases, they said, could be enough to halt AstraZeneca's vaccine bid entirely.

"If there are two cases, then this starts to look like a dangerous pattern," said Mark Slifka, a vaccine expert at Oregon Health and Science University. "If a third case of neurological disease pops up in the vaccine group, then this vaccine may be done."

A participant information sheet dated Sept. 11 on AstraZeneca's trial in Britain lumped the two volunteers' cases together, stating the illnesses were "unlikely to be associated with the vaccine or there was insufficient evidence to say for certain that the illnesses were or were not related to the vaccine," based on safety reviews. The next day, AstraZeneca announced that it had resumed the trial in Britain.

But the F.D.A. has so far not allowed the company to start up again in the United States.

A spokesman for the F.D.A. declined to comment. The National Institutes of Health said in a statement that it "remains to be seen" whether the onset of illness in trial participants was coincidental or tied to the vaccine, adding that "pausing to allow for further evaluation is consistent with standard practice."

Dr. Mark Goldberger, an infectious disease expert at the Global Antibiotic Research and Development Partnership and a former F.D.A. official, said he found the rapid restarting of trials abroad to be "a little disturbing," especially given the lack of details around the patients' symptoms and the ambiguity around their connection to the vaccine. "Maybe this is the best they could do — it may not be possible to get more certainty at this time," he said. "It is a question mark as to what's going on."

The company did not immediately inform the public about the neurological problems of either participant. Nor did it promptly alert the F.D.A. that it was again pausing its trials after the second U.K. volunteer developed illness and an independent safety board called for a temporary halt, according to multiple people familiar with the situation. The company's chief executive told investors about the problems but did not discuss them publicly until the information was leaked and reported by STAT.

"The communication around it has been horrible and unacceptable," said Dr. Peter Jay Hotez, a virologist with Baylor College of Medicine in Houston. "This is not how the American people should be hearing about this."

Dr. Hotez also criticized obtuse statements released by government officials, including U.K. regulators who he said failed to supply a rationale for resuming their trials.

"Tell us why you came to that decision," he said.

Dr. Paul Offit, a professor at the University of Pennsylvania and a member of the F.D.A.'s advisory committee on vaccines, said that it's unclear how the company — or the U.K. government — determined that the second case was not related to the vaccine.

He and other experts noted that transverse myelitis is rare, diagnosed in only about one in 236,000 Americans a year. The trial in Britain involved only about 8,000 volunteers, a spokesman for the Oxford researchers said last month.

The vaccine being developed by AstraZeneca, which formed a partnership with Oxford University scientists, uses a virus meant to carry coronavirus genes into human cells and trigger an immune response that will protect people from the coronavirus. This so-called vector is a modified form of an adenovirus that causes common colds in chimpanzees but is considered safe for people. Several other companies, including Johnson & Johnson and CanSino, are pursuing similar adenovirus-based approaches, although there are multiple types of adenoviruses, and specific ingredients differ from vaccine to vaccine.

While other adenovirus-based products have seen some success in the past, they have also been linked to serious adverse events. The most famous was the case of 18-year-old Jesse Gelsinger, who died in 1999 after receiving gene therapy through an adenovirus that sparked a lethal inflammatory response from his immune system.

If a serious side effect was definitively linked to AstraZeneca's vaccine, scientists would need to determine if its root cause stemmed from the adenovirus vector, or perhaps the coronavirus genes it carried — connections that could raise concerns about other companies' products that rely on the same components.