6 Hospitalized, One of Them Brain-Dead, After Drug Trial in France

By SEWELL CHANJAN. 15, 2016

LONDON — Six men were hospitalized — and one of them was pronounced brain-dead — after a drug trial in northwestern France, the country's health minister said on Friday.

Marisol Touraine, the minister for social affairs, health and women's rights, said in a statement that her office was informed Thursday evening about a "serious accident" that resulted in the hospitalization of the six men, at the Centre Hospitalier Universitaire de Rennes, in eastern Brittany.

Calling the incident "unprecedented" at a news conference in Rennes, Ms. Touraine said: "I have no knowledge of a comparable event."

The patients, all men, were ages 28 to 49, she said. The head of the hospital's neurology department said that three men may have suffered irreversible brain damage, based on magnetic resonance imaging scans, but cautioned that the scans were not conclusive.

"I was deeply moved by their suffering," Ms. Touraine said after visiting the patients and their families.

The drug was administered orally to healthy volunteers as part of a Phase 1 clinical trial by Biotrial, a drug evaluation company based in Rennes, on behalf of a Portuguese drug manufacturer, Bial. The drug is intended to help with mood, anxiety and motor problems linked to neurodegenerative diseases by having an effect on the endocannabinoid system, a set of brain receptors. Of 128 participants, 90 were given the drug, and the rest a placebo.

Photo

Six men have been hospitalized during Phase 1 of clinical trial by Biotrial, a drug-evaluation company based in Rennes, France. Credit David Vincent/Associated Press
Experts in clinical trials said serious injuries involving early-stage clinical trials were rare but must be thoroughly investigated since they typically involve healthy subjects who would not otherwise have fallen ill.

Carl Elliott, a bioethicist at the University of Minnesota, said investigators should look into questions like how much the men were paid and whether they properly consented to the trial. “Many Phase 1 trial volunteers are poor and unemployed, and they volunteer for trials like this because they are desperate for money,” he said. “This means they are easily exploited.”

In a statement, Biotrial acknowledged “serious adverse effects” in a trial, adding: “The trial has been conducted in full compliance with the international regulations, and Biotrial’s procedures were followed at every stage throughout the trial, in particular the emergency procedures for the transfer of subjects to the hospital. We are in close and regular contact with the health authorities and ministry in France.”

Bial, based in Coronado, Portugal, also said that it had followed all guidelines and regulations for clinical trials. The company, it said, “is strongly committed to ensuring, first of all, the well-being of the participants in this trial and to determine thoroughly and exhaustively the causes which are at the origin of this situation.”

Biotrial submitted its application to conduct the trial on April 30, Ms. Touraine said. The French Agency for the Safety of Health Products, the country’s drug regulator, authorized the trial on June 26, and it began on July 9. Biotrial, which recently announced that it was building a clinical trial site in Newark, had been subjected to two “routine” inspections in 2014, she said, which did not find any problems.

Ms. Touraine said the drug had previously been tested on animals, including chimpanzees, and was administered to 90 people under the trial. The six men received the drug several times, starting on Jan. 4. The first symptoms appeared in one man on Sunday. He was quickly hospitalized, and the others followed. The trial was halted the next day.

Contrary to several reports in the French news media, the drug was not a cannabis-based painkiller, Ms. Touraine said.

Bial identified the drug as an inhibitor of an enzyme known as FAAH, or fatty acid amide hydrolase. Other FAAH inhibitors have been tested safely in Phase 1 and Phase 2 clinical trials, said Andrea G. Hohmann, a professor of neuroscience at Indiana University who studies the endocannabinoid system and pain.

Daniele Piomelli, professor of anatomy and neurobiology, pharmacology and biological chemistry at the University of California, Irvine, said it was difficult to comment on the drug because its structure and pharmacological properties were unknown.

He said in an email that the main problem with other FAAH inhibitors, which have been tested by Pfizer, Sanofi, Organon and others, was that they did not work very well, not that they were unsafe.

Along with the French drug regulation agency, the country's General Inspectorate of Social Affairs, the Rennes prosecutor's office and the health branch of the Paris prosecutor's office have opened investigations.

Deaths or serious adverse reactions during Phase 1 clinical trials are rare.

In March 2006, six previously healthy young men fell ill and spent weeks in intensive care, with severe damage to their immune systems, at Northwick Park Hospital in London after being injected with an immune-system stimulant, known as TGN1412, during a Phase 1 trial.

Despite its potency, the drug, which was held up as a potential treatment for multiple sclerosis, leukemia and rheumatoid arthritis, was tested under much the same standards as those governing ordinary pharmaceuticals. British regulators approved the trial in just 17 days, and the testing company, based in Massachusetts, did not have an adequate response plan in the event of a disastrous adverse reaction, British investigators concluded.

"Toxicity deaths in Phase 1 trials are rare," said Daniel P. Carpenter, a professor of government at Harvard and an authority on the United States Food and Drug Administration. Some deaths were reported in Phase 1 trials early in the effort to treat AIDS, he said, but "nothing like this in a long time."

A meta-analysis of noncancer Phase 1 drug trials, published last year in The British Medical Journal, found serious adverse events in only 0.31 percent of participants, and no deaths.