Many See Hope in Parkinson's Drug Pulled From Testing

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With his condition deteriorating from Parkinson's disease last year, Steve Kaufman gave up making improvements to his home in Algonquin, Ill. "I couldn't even hold a nail stable," he recalled.

Earlier this year, after taking an experimental drug in a clinical trial, Mr. Kaufman built new kitchen cabinets and an outdoor deck. He was so steady he could walk across a narrow piece of lumber like an Olympic gymnast on the balance beam.

The drug, however, is no longer available to Mr. Kaufman or other Parkinson's patients in clinical trials. In June, its developer, Amgen, announced that the drug, which is called glial cell line-derived neurotrophic factor, or GDNF, had not proved better than a placebo. Two months later, the company said that safety issues had been discovered and it abruptly ordered all patients taken off the drug.

Amgen's move has provoked an outcry from patients who say the company is robbing them of their only hope. "It's almost the same thing as a diabetic losing their insulin," said Mr. Kaufman, who is 50 and has had Parkinson's for 10 years.

The story of Amgen's drug shows the clash between the faith of patients and the cold logic of science and business. At a time when public debate is focused on whether unsafe drugs like Vioxx are remaining on the market too long, this story shows patients who are more than willing to accept risks to get a drug. Their willingness also raises an ethical question: If a company stops developing a drug for safety or efficacy reasons, is it obligated to continue supplying it to patients from its clinical trials?

A complicating factor in the clinical trials is the nature of Parkinson's, a disease that chokes off the supply of dopamine, a signaling chemical, in the brain. Some studies have suggested that mere anticipation of treatment can induce a patient's brain to produce more dopamine, which alleviates the symptoms. The patients not only feel better, they are better - at least for a time. In fact, some of patients in the GDNF trial who improved the most had received a placebo.

Patients and their families have written letters to Amgen, imploring the company to continue providing the drug. Some of the most poignant have come from England, where the drug has been tested the longest, since 2001.

"To quote a headline that my daughter used in a story she wrote for a national women's magazine - GDNF has given me my dad back," wrote Stephen Waite, who had used the drug

for more than three years. In a telephone interview, Mr. Waite, 60, began crying when talking about the loss of the drug. "I would sign a disclaimer, anything, in order to continue," he said.

Another family told Amgen how the drug allowed their mother to shop, dance and go on vacation for the first time in three years. "GDNF deserves more time, and so does our mother," they wrote.

And Neil Shadwick wrote, "My whole world collapsed around me," when he learned the drug would be stopped. "My first thought was I don't want to be a shaking helpless man at 44."

But while Amgen executives say they empathize with the four dozen patients who have participated in the trials, they also say they cannot keep giving them a drug that does not work and might be dangerous. "How can we ethically justify administering this drug?" said Roger Perlmutter, executive vice president for research and development.

In August, the company's studies found that high doses of the drug damaged some monkey brains. It also found that a few patients had developed antibodies against the drug, posing a potential danger.

Kevin Sharer, the chief executive, called the failed trial a "tragedy" and "the single most disappointing" one in his 12 years at the company.

Some of the doctors involved in the clinical trial have criticized Amgen, saying the trial failed because it was poorly designed, not because GDNF does not work. "I don't think there's ever been a trial like this where so many investigators were so indignant about the way things were handled," said Michael Hutchinson, an associate professor of neurology at New York University who was involved in the trial.

Critics also say the safety concerns are not serious. Some even suspect Amgen is killing the drug because it believes it will not be a big seller. But Mr. Sharer denied that business considerations were behind the company's decision, noting that Amgen had spent hundreds of millions of dollars over 10 years on the drug's development.

GDNF had been considered one of the most promising approaches to a disease that affects 500,000 to 1.5 million Americans. Parkinson's, marked by severe tremors and rigidity, stems from the death of brain cells that make dopamine, a signaling chemical. Existing drugs augment the brain's dopamine supply but do not stop the death of the brain cells.

GDNF is one of a class of natural human proteins called nerve growth factors that can protect brain cells from death and induce them to grow. It has been shown in animals to spur growth of dopamine-producing cells. "This is the

first drug that we might have that might influence the course of the disease and that's why it's important that it not be killed," said Richard Penn, a neurosurgeon at the University of Chicago.

Amgen obtained GDNF in 1994 when it paid $240 million to acquire Synergen, a Colorado biotechnology company that made the protein using genetic engineering. Synergen had tested the drug in monkeys and filmed some dramatic results.

"We looked at that movie and said, 'Buy this company,' " Mr. Sharer said. "Literally."

The drawback of GDNF is that it cannot pass from the blood into the brain, so it cannot be given by injection like other protein drugs. It must be put directly into the brain.

Amgen first tested the drug by injecting it into the fluid-filled cavity in the center of patients' brains. The trial failed and the company abandoned development in 1999.

But some academic scientists refused to give up. Steven S. Gill at Frenchay Hospital in Bristol, England, designed a way to deliver the drug directly to the part of the brain where it is needed. The procedure requires drilling two holes in the skull and implanting narrow catheters. The catheters are threaded just under the skin from the head through the neck and chest to the abdomen, where two pumps are implanted to deliver the drug to the brain.

The procedure is surgically cumbersome and raises the risk of infections. But five patients treated by Dr. Gill all showed improvement. Indeed, a video that Amgen used to present to investors shows Mr. Waite, before treatment, barely able to get out of a chair and hobble. After a few months of treatment, he stands up easily and strides across the room.

The success in England was followed by a test at the University of Kentucky. "We had 10 out of 10 patients showing benefit at six months," said Don M. Gash, chairman of anatomy and neurobiology.

Barbara A. Allen, a schoolteacher from Salyersville, Ky., wrote in a letter to Amgen that with GDNF, "I could once again perform simple tasks like folding towels and buttoning a shirt. I could interact with my family and friends. I could smile at a stranger."

But in both trials, the patients knew they were getting the drug, meaning it was possible they were experiencing a placebo effect.

"There's a long history of dramatic placebo effects in Parkinson's," Dr. Perlmutter of Amgen said. Implants of fetal cells into patients' brains, for example, were also

once hailed as a Parkinson's treatment, he said. But controlled clinical trials ultimately proved that those implants did not work.

To control for the placebo effect, Amgen began a 34-patient trial last year in which all the patients had the pumps and catheters implanted but for the first six months half got GDNF and the other half saline solution. The results, announced in June, showed that while the group getting GDNF did somewhat better than the control group on a scale measuring the severity of symptoms, the difference in the results was not statistically significant.

Moreover, said Anthony E. Lang, a neurologist at the University of Toronto and a trial investigator, "Many of the patients who believed they were doing extremely well were on placebo."

Amgen says it believes that the striking results in the earlier trials were probably a placebo effect, too. Yet even Mr. Sharer said he found that conclusion hard to believe. He recalled that a patient in England, who said GDNF had restored his ability to paint, had sent him a painting in gratitude. "Is that placebo?" Mr. Sharer asked. "The data says it is."

But several of the scientists say they think the earlier results were too consistent and long lasting to be placebo effect. Dr. Gill said several patients in England, who have been off the drug for nearly three months, have not deteriorated as might have been expected with a placebo effect.

Dr. Hutchinson said that calling all the results a placebo effect was "a slap in the face" to the patients and to the researchers who had conducted the earlier trials. He said the drug worked in the latest trial in the sicker patients, but the effect was masked by less certain results in patients who were not so ill.

Dr. Gill said the catheter Amgen used did not deliver the drug as efficiently as the ones used in England and Kentucky. Also, he said, the dose Amgen used was at the low end of the various doses used in the English trial, a dose later shown to be ineffective.

But Dr. Lang of Toronto said the study was well designed. He also said the drug was never going to be a big breakthrough anyway, as long as Parkinson's patients would need brain surgery and pumps.

In early August, Amgen met with investigators in Chicago and discussed trying a higher dose. After all, even when it announced the drug had not worked, Amgen said it had been "safe and well tolerated" and that all the placebo patients had switched to the drug after six months.

But by the end of August the drug went from safe to dangerous. The company told trial participants that it had

discovered two serious safety issues. It had approached regulators, who agreed with the company's decision to stop all human testing by Sept. 1.

The company said 4 out of 70 monkeys given the drug had suffered damage to the cerebellum, the area of the brain involved in coordinated movement. Amgen called this a "completely new finding never seen before in any of the previous studies."

The second problem was that a handful of patients had developed antibodies that attacked the drug as if it were a germ. The danger, Amgen said, is that such antibodies might also attack the patients' own GDNF, with unknown but possibly harmful effects.

But the doctors who support the drug said the cerebellum damage was not seen in people. They said the monkey damage might not have been caused by the drug and, in any case, the monkeys got a dose several times higher than people got, even though their brains are less than a 12th the size of human brains.

They also said that the formation of antibodies was not uncommon with protein drugs and that so far none of the patients seems to have been harmed.

To try to determine a path forward, the Michael J. Fox Foundation for Parkinson's Research held a two-day meeting on the drug in October. Amgen then met with the investigators on Nov. 11 near its headquarters in Thousand Oaks, Calif. But sharp disputes persist.

Amgen said it is willing for now only to provide the drug for laboratory and animal studies of the safety issues or of better ways to deliver the drug, such as by gene therapy or cell transplants.

"If we can find a path forward, we'll take it," Mr. Sharer said. "We just don't see one right now."

Some doctors and patients want Amgen to license the drug to another company or a university willing to continue trials. But Mr. Sharer said Amgen could not do so because it would still be liable if safety problems arose.

The doctors and patients also want Amgen to provide the drug as a compassionate gesture to the patients from the clinical trials under rules of the Food and Drug Administration. Amgen says the drug does not qualify for compassionate use distribution because it is not under development and has safety problems. Some of the doctors plan to plead their case to the F.D.A.

And in an act that is part defiance, part desperation, many patients and their doctors have refused to shut off the pumps, as Amgen had requested, because once stopped the pumps might not restart. Saline solution is running through the pumps to keep them primed and so that any drug still

stuck in the tubes will dribble into the patients' brains.

Mr. Kaufman in Illinois said after several weeks off the drug, he already feels his stamina slipping and his shaking becoming more pronounced. "I don't think we were given a fair chance," he said.

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