Pfizer had clues its blockbuster drug could prevent Alzheimer’s. Why didn’t it tell the world?

By Christopher Rowland

June 4

A team of researchers inside Pfizer made a startling find in 2015: The company’s blockbuster rheumatoid arthritis therapy Enbrel, a powerful anti-inflammatory drug, appeared to reduce the risk of Alzheimer’s disease by 64 percent.

The results were from an analysis of hundreds of thousands of insurance claims. Verifying that the drug would actually have that effect in people would require a costly clinical trial — and after several years of internal discussion, Pfizer opted against further investigation and chose not to make the data public, the company confirmed.

Researchers in the company’s division of inflammation and immunology urged Pfizer to conduct a clinical trial on thousands of patients, which they estimated would cost $80 million, to see if the signal contained in the data was real, according to an internal company document obtained by The Washington Post.

“Enbrel could potentially safely prevent, treat and slow progression of Alzheimer’s disease,” said the document, a PowerPoint slide show that was prepared for review by an internal Pfizer committee in February 2018.

The company told The Post that it decided during its three years of internal reviews that Enbrel did not show promise for Alzheimer’s prevention because the drug does not directly reach brain tissue. It deemed the likelihood of a successful clinical trial to be low. A synopsis of its statistical findings prepared for outside publication, it says, did not meet its “rigorous scientific standards.”

Science was the sole determining factor against moving forward, company spokesman Ed Harnaga said.

Likewise, Pfizer said it opted against publication of its data because of its doubts about the results. It said publishing the information might have led outside scientists down an invalid pathway.

Pfizer’s deliberations, which previously have not been disclosed, offer a rare window into the frustrating search for Alzheimer’s treatments inside one of the world’s largest drug companies. Despite billions spent on research, Alzheimer’s remains a stubbornly prevalent disease with no effective prevention or treatment.

Some outside scientists disagree with Pfizer’s assessment that studying Enbrel’s potential in Alzheimer’s prevention is a scientific dead end. Rather, they say, it could hold important clues to combating the disease and slowing cognitive decline in its earliest stages.

Pfizer did share the data privately with at least one prominent scientist, but outside researchers contacted by The Post believe Pfizer also should at least have published its data, making the findings broadly available to researchers.

“Of course they should. Why not?” said Rudolph E. Tanzi, a leading Alzheimer’s researcher and professor at Harvard Medical School and Massachusetts General Hospital.

“It would benefit the scientific community to have that data out there,” said Keenan Walker, an assistant professor of medicine at Johns Hopkins who is studying how inflammation contributes to Alzheimer’s. “Whether it was positive data or negative data, it gives us more information to make better informed decisions.”

Internal discussions about possible new uses of drugs are common in pharmaceutical companies. In this case, Pfizer’s deliberations show how decisions made by industry executives — who are ultimately accountable to shareholders — can have an impact well beyond corporate board rooms.

As its Enbrel deliberations ended early last year, Pfizer was getting out of Alzheimer’s research. It announced in January 2018 that it would be shutting down its neurology division, where Alzheimer’s treatments were explored, and laying off 300 employees.

Meanwhile, Enbrel has reached the end of its patent life. Profits are dwindling as generic competition emerges, diminishing financial incentives for further research into Enbrel and other drugs in its class.

“I’m frustrated myself really by the whole thing,” said Clive Holmes, a professor of biological psychiatry at the University of Southampton in Great Britain who has received past support from Pfizer for Enbrel research in Alzheimer’s, a separate 2015 trial in 41 patients that proved inconclusive.

He said Pfizer and other companies do not want to invest heavily in further research only to have their markets undermined by generic competition.

“Someone can pop up and say, ‘Look, I’ve got a me-too drug here,’” Holmes said, referring to the advent of generic versions of Enbrel. “I think that is what this is all about.”

Enbrel’s ‘life cycle’
The broader market forces that critics say discouraged Pfizer from investing in Alzheimer’s clinical trials are rooted in Enbrel’s “life cycle,” the 20-year period of patent exclusivity when a brand manufacturer reaps monopoly profits from a drug. By industry standards, Enbrel, an injectable biologic drug, is relatively old, with FDA approval for rheumatoid arthritis in 1998. It also has been approved to treat psoriasis.

Pfizer got rights to market it internationally when it acquired drugmaker Wyeth in 2009. But Enbrel, which earned Pfizer $2.1 billion in 2018, now faces generic competition.

Drug companies often are criticized for extending the patent life of a drug — and winning new profits — by merely tweaking a drug’s molecule or changing the method of delivery into the body. But it is a “heavy lift” for a company to win regulatory approval to use a drug for a completely different disease, said Robert I. Field, a professor of law and health care management at Drexel University.

“Our patent laws do not provide the appropriate incentives,” Field said. Drug therapy for early Alzheimer’s “would be a godsend for American patients, so we should be doing everything we can as a country to encourage development of treatments. It’s frustrating that there may be a missed opportunity.”

As Enbrel’s life cycle winds down, Pfizer has introduced a new rheumatoid arthritis drug, Xeljanz, that works differently from Enbrel. Pfizer is putting its marketing muscle behind the new treatment. While Enbrel revenue is shrinking, Xeljanz revenue is growing. The Xeljanz patent expires in 2025 in the United States and 2028 in Europe, according to Pfizer’s public disclosures. The drug is on track to make Pfizer billions more each year for the foreseeable future.

Wagering money on a clinical trial of Enbrel for an entirely different disease, especially when Pfizer had doubts about the validity of its internal analysis, made little business sense, said a former Pfizer executive who was aware of the internal debate and spoke on the condition of anonymity to discuss internal Pfizer matters.

“It probably was high risk, very costly, very long term drug development that was off-strategy,” the former executive said.

Another former executive, who also spoke on the condition of anonymity to discuss Pfizer operations, said Pfizer offered virtually no explanation internally for opting against further investigation in early 2018, when the internal debate ended.

“I think the financial case is they won’t be making any money off of it,” the second former executive said.

Impeding research

Drug companies frequently have been pilloried for not fully disclosing negative side effects of their drugs. What happens when the opposite is the case? What obligation does a company have to spread potentially beneficial information about a drug, especially when the benefits in question could improve the outlook for treating Alzheimer’s, a disease that afflicts at least 500,000 new patients per year?

A medical ethics expert argued that Pfizer has a responsibility to publicize positive findings, although it is not as strong as an imperative to disclose negative findings.

“Having acquired the knowledge, refusing to disclose it to those who might act upon it hides a potential benefit, and thereby wrongs and probably harms those at risk of developing Alzheimer’s by impeding research,” said Bobbie Farsides, professor of clinical and biomedical ethics at Brighton and Sussex Medical School in the United Kingdom.

Another health-care ethics specialist cautioned that the demand for drug company disclosure should remain focused on information collected during clinical trials.

“I do think you have to draw some limits, and say that not every piece of information they have in their files has to be disclosed with others,” said Marc A. Rodwin, a law professor at Suffolk University Law School in Boston.

Pfizer markets Enbrel outside North America. Another drug company, Amgen, which holds rights to market Enbrel in the United States and Canada, says it knew of the Pfizer data and similarly decided the findings held little promise. Amgen said market factors played no role in its deliberations.

“Unfortunately, our exploratory work did not yield results strong enough to warrant further studies,” Amgen said.

Analyzing insurance claims

Sometimes doctors prescribe drugs for uses that have not been approved by the Food and Drug Administration. But none of the experts interviewed for this story said such “off-label” use of Enbrel would be appropriate for Alzheimer’s, because of the very limited nature of the data thus far. Nor, they said, do they believe such prescribing is happening to any significant extent.

The role of brain inflammation in Alzheimer’s recently has been getting closer attention among academics after the failure of multiple experimental drugs that targeted the buildup of plaques on brain tissue. In 2016, researchers from Dartmouth and Harvard universities published a study of insurance claims data — similar to Pfizer’s internal findings — that showed a potential benefit of Enbrel. Enbrel “shows promise as a potential treatment” for Alzheimer’s, the study found.

Pfizer’s analysis about potential Enbrel benefits in the brain sprang from the company’s division of immunology and inflammation, based in a large Pfizer office complex in Collegeville, Pa.
Statisticians in 2015 analyzed real world data, hundreds of thousands of medical insurance claims involving people with rheumatoid arthritis and other inflammatory diseases, according to the Pfizer PowerPoint obtained by The Post.

They divided those anonymous patients into two equal groups of 127,000 each, one of patients with an Alzheimer’s diagnosis and one of patients without. Then they checked for Enbrel treatment. There were more people, 302, treated with Enbrel in the group without Alzheimer’s diagnosis. In the group with Alzheimer’s, 110 had been treated with Enbrel.

The numbers may seem small, but they were mirrored in the same proportion when the researchers checked insurance claims information from another database. The Pfizer team also produced closely similar numbers for Humira, a drug marketed by AbbVie that works like Enbrel. The positive results also showed up when checked for “memory loss” and “mild cognitive impairment,” indicating Enbrel may have benefit for treating the earliest stages of Alzheimer’s.

A clinical trial to prove the hypothesis would take four years and involve 3,000 to 4,000 patients, according to the Pfizer document that recommended a trial. The document said Pfizer would gain a positive public relations “halo effect” by investigating an Alzheimer’s treatment.

Enbrel reduces inflammation by targeting a specific protein called TNF-a. The Pfizer claims data analysis added to a growing body of evidence that broadly targeting TNF-a in the body has the potential to prevent Alzheimer’s, said Holmes, the professor of biological psychiatry at the University of Southampton.

Holmes is among the few researchers who has gained access to the Pfizer data; he won the company’s permission to use it in a grant application for a small clinical trial he is undertaking in England.

“If it’s true in reality, if you did it in a clinical trial setting, it’s massive — it would be huge,” Holmes said. “That’s why it’s so exciting.”

One reason for caution: another class of anti-inflammatory therapies, called non-steroidal anti-inflammatory drugs (NSAIDS), showed no effect against mild-to-moderate Alzheimer’s in several clinical trials a decade ago. Still, a long-term follow-up of one of those trials indicated a benefit if NSAID use began when the brain was still normal, suggesting the timing of therapy could be key.

Pfizer said it also was skeptical because Enbrel has only a limited effect on the brain. The Enbrel molecule is too large to pass through the “blood-brain barrier” and directly target TNF-a in brain tissue, the company said.

Yet Alzheimer’s researchers believe inflammation outside the brain — called peripheral inflammation — influences inflammation within the brain.

“There is a lot of evidence suggesting that peripheral or systemic inflammation may be a driver of Alzheimer’s disease,” said Walker, the Johns Hopkins researcher. It is a fair hypothesis that fighting inflammation outside the brain with Enbrel will have a similar effect inside the brain, he said.

“I don’t believe Enbrel would need to cross the blood brain barrier to modulate the inflammatory/immune response within the brain,” Walker said.

“There is increasing evidence that peripheral inflammation can influence brain function,” said rheumatologist Christopher Edwards, of the University of Southampton in Britain.

“It’s important that that’s published, and in the public domain,” Edward added of the Pfizer data. “It needs to be out there.”

Correction: An earlier version of this story misstated the location of the Brighton and Sussex Medical School.