

Bial incident raises FAAH suspicions

One volunteer for a phase 1 trial of the oral analgesic BIA 10-2474 died and five others were hospitalized at Rennes University Hospital in France with serious neurological symptoms in January. The trial testing a drug from Bial-Portela of São Mamede do Coronado, Portugal, in healthy volunteers was halted on January 11. The incident has cast a pall over inhibitors of fatty acid amide hydrolase (FAAH), the drug class to which the compound belongs. Although it is still unclear what may have caused the neurological damage, the Bial trial has prompted Janssen, a research unit of Johnson & Johnson, based in New Brunswick, New Jersey, to suspend its own phase 2 trials of a different FAAH inhibitor as a precaution.

French authorities, in a report published on January 29, faulted Biotrial, the Rennes-based contract research organization conducting the BIA 10-2474 trial. French health minister Marisol Touraine stated that the contract researchers continued to administer the highest dose of the drug after the first volunteer fell ill, failed to notify the authorities promptly and kept the incident from the remaining volunteers. Bial said 90 volunteers received varying doses of BIA 10-2474 starting in the summer of 2015. The six hospitalized volunteers, one of whom did not show any symptoms but was under observation, were in the group receiving the highest dose.

BIA 10-2474 is a small-molecule FAAH inhibitor. FAAH is an enzyme that degrades endocannabinoids, the best known of which is anandamide. Blocking the enzyme could slow the breakdown of such endogenous cannabinoids, which could help treat pain as well as other conditions including, anxiety, multiple sclerosis and motor problems in Parkinson's disease.

The preliminary report did not investigate the role of the compound itself. Even if the class is cleared, patients may remain wary of FAAH inhibitors. "If it is indeed a class effect, then FAAH inhibitors are doomed," says Christopher Fowler, a professor of pharmacology, at Umeå University in Umeå, Sweden. "It may be damaging regardless of how this turns out." Johnson & Johnson has suspended two phase 2 clinical trials of its FAAH inhibitor JNJ-42165279 in patients with social anxiety disorder and in major depressive disorder with anxious distress "as a precaution." The company said it did not receive reports of adverse events in its tests of the compound.

The disastrous outcome of the Biotrial study was unexpected. Previous early-stage clinical trials of FAAH inhibitors showed no such effects,



Marisol Touraine, French health minister, holds a press conference on February 4 about the Bial affair.

according to Steve Alexander, associate professor of molecular pharmacology at the University of Nottingham. "What we don't have is clarity; it is possible that this is an off-target effect."

At least five other compounds targeting FAAH have been developed with limited success over the past several years. New York-based Pfizer had begun testing an FAAH inhibitor PF-04457845 in patients with osteoarthritis of the knee in 2009. Although there were no untoward effects, the drug was no better than a sugar pill in controlling pain. The company abandoned mid-stage studies of the drug in patients with Tourette syndrome and as a cannabis withdrawal treatment due to business reasons, says Susanne Straetmans, a Pfizer spokeswoman based in Berlin. In August 2014, the venture capital firm TVM Capital, based in Munich and Montreal, established FAAH Pharma in Montreal to develop FAAH inhibitor IPI-940, in-licensed from Infinity Pharmaceuticals of Cambridge, Massachusetts. Commenting on the impact these recent events may have on the biotech's future, Hubert Birner, a TVM Capital managing partner, says, "What happened was very tragic, and we are still in the middle of evaluating our options." The compound is currently in preclinical trials.

Another FAAH inhibitor, V158866 from Winnersh, UK-based Vernalis, in August 2015 missed the primary endpoint in a phase 2 study to treat neuropathic pain resulting from spinal cord injury. Vernalis, which once valued the drug at annual peak sales of over \$500 million, will cease further investments into the treatment. Mike Wood, the company's research director, declined to comment on the future of the compound "until the facts are clear."

Touraine expects a complete report on the incident from France's General Inspectorate of Social Affairs before the end of March.

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Seed spy pleads guilty

A Chinese man accused of stealing trade secrets from three US biotech seed companies pleaded guilty in an Iowa federal court in January. Prosecutors had alleged that the man, Mo Hailong, also known as Robert Mo, stole proprietary seeds from Monsanto, DuPont Pioneer and LG Seeds in an attempt to benefit his Chinese conglomerate, Beijing Dabeinong Technology Group Company (DBN Group) (*Nat. Biotechnol.* **32**, 607–608, 2014). Mo was one of seven people connected to DBN who were accused of agricultural espionage. US prosecutors say the group was after the seed companies' 'inbred' or 'parent' lines of corn, which can take five to eight years and millions of dollars to develop. Seed companies take many precautions to protect this technology, but open fields present a security challenge. Mo in May 2011 was found digging in a field in rural Iowa where inbred seeds belonging to Johnston, Iowa-based DuPont Pioneer had been planted the day before, prosecutors said. "The guilty plea was a small win for the industry, but I doubt it prevents it from happening again," says Kendall Lamkey, a professor of agronomy at Iowa State University in Ames, who consulted with US attorneys on seed production and corn breeding. The performance of corn in China lags the US considerably, and the Chinese company appeared to be trying to catch up by stealing the seeds, he says. Charla Lord, a spokesperson for St. Louis-based Monsanto, says the company is pleased the matter is concluded. "Monsanto appreciates all of the efforts that have been taken by the US government to protect our intellectual property," she says. In exchange for Mo pleading guilty to conspiracy to steal trade secrets, the government agreed to dismiss a theft charge levied against him, and to cut his maximum possible jail sentence to five years. "This is a complicated case with many gray areas, legally and factually, but today Robert Mo takes complete responsibility for his unlawful conduct in this case," says Mo's attorney Mark Weinhardt at Weinhardt & Logan in Des Moines, Iowa. Mo is a US permanent resident, and has a wife and two children who are US citizens. Five of his alleged conspirators remain fugitives, and charges against one other—Mo's sister Mo Yun—were dropped.

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“Hard to accept that these imbeciles represent the people in our government.” Martin Shkreli

tweeted after his appearance at a US House of Representatives hearing on drug pricing. Shkreli did not testify at the hearing, on the advice of his lawyers, as he is under indictment for securities fraud, but couldn't resist slamming the US Congress as he left the committee room. (STAT, 4 February 2016)