프랑스서 신약 임상시험 참가자 1명 사망…정부 조사 착수(종합)

파리=연합뉴스) 박성진 특파원 = 프랑스에서 신약 임상시험에 참가했다가 뇌사 상태에 빠진 남성이 17일(현지시간) 사망했다.
프랑스 렌 병원은 "뇌사자가 오늘 숨졌으며 다른 5명 환자는 안정적인 상태다"라고 발표했다고 현지 BFM TV가 보도했다. 렌 병원에는 최근 프랑스 비오트리알 연구소에서 진행한 신약 임상시험에 참가했다가 부작용이 생긴 환자 6명이 치료받고 있었다. 참가자들은 포르투갈 제약회사 비알이 개발하는 신약을 지난 7일 투약한 후 사흘이 지나고서부터 몸에 이상이 생겼다고 보고했다.

비알은 불안 등 정서 장애 치료제를 개발 중이었다. 이 신약 임상시험에는 28~48세의 건강한 프랑스 성인 90명이 참가해 약을 복용했다. 사망한 뇌사자 이외에도 3명이 회복 불가능한 뇌 손상을 입는 등 총 6명이 부작용으로 입원했다. 병원 측은 "약에 노출된 다른 지원자 84명을 접촉했으며 이 중 10명이 검사를 받았으나 이상한 점은 없었다"고 밝혔다. 프랑스 국립의약품건강제품안전청(ANSM)은 신약 임상시험 과정에서 의료 사고를 낸 비오트리알 연구소 등에 대한 조사에 착수했다. 비오트리알은 "조사에 협조하고 있다"면서 "자체 조사에서는 임상시험 과정에서 절차상 문제를 발견하지 못했다"고 밝혔다.

제조사인 비알도 성명에서 "신약 개발 과정에서 국제적 관행을 준수했다"고 발표했다. 비오트리알은 업계 관행에 따라 임상시험 참가자에게 100~4천500유로(약 13만~595만원)를 줘 왔다.

프랑스 정부는 신약 자체에 결함이 있었는지 아니면 임상시험 과정에서 잘못이 있었는지 밝혀낼 계획이다. 마리솔 투렌 보건복지부 장관은 "이례적으로 심각한 일이 벌어졌다"면서 "진상을 철저히 밝히겠다"고 말했다. 프랑스에서는 매년 수천 명이 참가비를 받고 신약 임상시험에 참가하고 있다. 앞서 2006년에는 영국에서 백혈병 신약 임상시험에 참가했던 6명이 부작용으로 입원했던 적이 있다.

2016/01/18 00:13
연합뉴스
http://www.yonhapnews.co.kr/bulletin/2016/01/18/0200000000AKR20160118000500081.HTML?input=1195m

얀센, FAAH 저해제 실험약 임상 시험 자발적 중단

프랑스 사망자 발생 약물과 같은 계열, 예비적 차원 결정

얀센은 프랑스에서 사망자가 발생된 FAAH 저해제와 같은 계열 실험 약물의 2상 임상 시험 2건을 예비적 차원에서 중단한다고 지난 18일 밝혔다.

얀센의 FAAH 저해제 약물인 JNJ-42165279는 1상 임상 시험에서 완화한 부작용이 보고된 바 있다. 따라서 얀센은 불안 장애로 인한 주요 우울 증상 환자에 대한 2상 임상을 시작한 바 있다. 포르투갈 제약사인 바이알의 약물은 1상 임상 시험에서 15건의 중증 부작용이 발생했다.

그러나 얀센과 화이자가 개발 중인 FAAH 저해제 약물은 1상과 2상 임상에서 상당히 안전한 것으로 나타났다. 화이자의 실험 약물은 PF-04457845이다. 따라서 분석가들은 프랑스에서 발생한 사고가 약리학적 문제는 아니며 약물이 목표 지점 이외에 작용해 발생한 것으로 추정하고 있다.

얀센의 실험 약물인 JNJ-42165279는 2015년 ACS Medicinal Chemistry Letters에 발표된 논문에서 선택성이 매우 높은 것으로 나타났다.

화이자의 약물은 골괴사증 환자에 대한 2상 임상에서 위약보다 더 우수한 진통 효과를 보이지 못했다. 이외에도 사노피와 베날리스(Vernalis)가 FAAH 저해제 약물을 개발 중이다.

얀센은 관련 약물에 대한 추가적인 정보가 나올 경우 임상 시험 중단 결정을 다시 평가하게 될 것이라고 말했다.

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데일리팜
http://www.dailypharm.com/News/207932

프랑스 임상 시험서 1명 사망, 3명 뇌손상 발생

포르투갈 제약사 바이알, 진통제 1상 임상 시험

포르투갈 제약사인 바이알(Bial)의 진통제 실험 약물에 대한 임상 시험에서 대상자 1명이 사망했다고 17일 보도됐다.

프랑스에서 진행된 임상 시험에는 90명이 참여했으며 이중 1명은 뇌사 상태이며 5명은 병원에 입원한 것으로 지난 15일 보도됐다. 그러나 뇌사 상태에 빠진 환자가 17일 사망했다. 나머지 5명은 안정된 상태이지만 이중 3명은 뇌 손상등으로 중증 후유증이 우려된다.

이번 사건의 정확한 원인은 알려지지 않았으며 현재 프랑스 정부의 조사가 진행되고 있다. 관련 임상 시험은 모두 중단됐으며 임상에 참여한 모든 환자에 대해 연락을 취하고 있다.

문제가 된 약물은 FAAH 저해제 계열 약물로 신체내 endocannabinoid 시스템에 작용한다. 임상 시험은 지난 7일 시작됐으며 건강한 사람을 대상으로 1상 임상이 진행됐다.

프랑스 보건부 장관은 약물이 통증 이외에 신경퇴행성(neurodegenerative) 질환과 연관된 운동 장애와 우울증등 감정 변화를 조절하는 목적으로도 개발됐다고 설명했다. 그러나 실험 약물이 대마초를 기반으로 한 약물은 아니라고 말했다.

바이알은 독성 실험 이후 지난해 6월 약물에 대한 임상 시험을 이미 실시했었으며 당시 임상에 참여한 건강한 대상자 108명은 중증 부작용 및 반응을 보이지 않았었다.

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http://www.dailypharm.com/News/207801

프랑스서 실사판 영화 '돌연변이'… 신약 임상시험 부작용으로 뇌사자 등 5명 입원

약을 먹고 잠 자면 돈을 준다는 임상실험의 부작용을 소재로 다룬 영화 '돌연변이'. 영화에서나 나올 것 같았던 일이 실제로 프랑스에서 발생했다.

프랑스에서 신약 임상시험을 하던 5명이 임상시험의 부작용으로 입원했다. 이 중 1명은 뇌사 상태에 빠진 것으로 알려졌다.

현지 일간지 르피가로는 마리솔 투렌 보건복지부 장관의 말을 빌려 "15일(현지시간) 프랑스 서북부 렌 부근의 민간 연구소에서 임상시험 중 이런 심각한 사고가 일어났다"고 보도했다.

투렌 장관은 "임상시험은 중단됐으며 시험에 참가한 지원자들을 불러 검사하고 있다"고 덧붙였다.

연구소는 대마 성분을 이용한 진통제의 임상시험을 하고 있었다고 현지 언론은 보도했다.

투렌 장관은 현장을 방문해 기자 회견을 열 예정이다.

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국제신문
http://www.kookje.co.kr/news2011/asp/newsbody.asp?code=0400&key=20160115.99002202648

프랑스 신약 임상시험 참가자 6명 병원행, 1명 뇌사 3명 위독

프랑스에서 신약 임상시험에 참가한 사람 중 6명이 심각한 부작용으로 병원에서 치료를 받고 있으며 이중 한명은 뇌사 상태에 빠졌다.

프랑스 일간지인 르피가로에 따르면 마리솔 투렌 보건복지부 장관은 15일(현지시간) "(프랑스 서북부) 렌 부근의 민간 연구소에서 임상시험 중 심각한 사고가 일어났다"고 알렸다.

환자를 치료하고 있는 렌 병원은 "뇌사 상태 환자 이외에도 3명이 회복이 어려울 수 있는 장애를 겪고 있지만 신약 부작용을 없애는 해독제는 없다"고 우려했다.

투렌 장관은 환자들이 지난 7일 임상 시험에 참가해 약을 복용하기 전에는 건강한 상태였다고 설명했다.

문제의 신약은 포르투갈 제약회사 비알이 개발 중인 진통제이다.
이를 프랑스 연구소인 비오트리알에서 임상시험 중이었다.
투렌 장관은 '신약에 대마 성분이 있다'는 일부 보도에 대해 부인했다.

임상시험에는 90명이 참가했으며 보건부는 다른 참가자들에게는 부작용이 없는지 검사하고 있다.

2016-01-16 09:55:02
세계일보
http://www.segye.com/content/html/2016/01/16/20160116000480.html?OutUrl=naver

Drug trial participant dies, 5 others hospitalized in France

By Jen Christensen, CNN
Updated 1036 GMT (1836 HKT) January 18, 2016 | Video Source: CNN

*(CNN)*A man has died in France after participating in a clinical drug trial, the University Hospital of Rennes said in a statement Sunday.
The conditions of five other volunteers have been improved to stable.
The French Health Ministry is investigating what it calls a "serious accident."
Four of the patients may be permanently disabled with neurological damage, doctors in the northwestern city of Rennes said. One other person doesn't have symptoms but remains under medical surveillance.
The company conducting the testing said on its website the trial was administered "in full compliance with the international regulations and Biotrial's procedures were followed at every stage throughout the trial."
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Biotrial International said it was "in close and regular contact with the Health Authorities and Ministry in France."
The first patients to get sick started to show symptoms January 10 and were hospitalized in Rennes. The testing has been stopped, Health Minister Marisol Touraine said in a news conference Friday, and health authorities have been reaching out to the rest of the volunteers to let them know about these adverse effects.

French Social Affairs and Health Minister Marisol Touraine and professor Gilles Edan hold a news conference Friday.
The drug being tested is a painkiller meant to treat anxiety and motor disorders, and was designed to work on the body's endogenous cannabinoid system, which deals with pain. Earlier reports said the drug was related to cannabis, but Touraine insisted that the drug -- developed by the Portuguese science group Bial -- does not contain cannabis or cannabis extracts.
A total of 128 volunteers took part in the drug test. The subjects were between the ages of 18 to 55 and were considered healthy. Ninety people were given different level dosages of the drug and the rest got the placebo.
Volunteers began taking the drug on January 7 in early testing known in the industry as Phase I, in which it's determined if the drug is safe for human consumption. Scientists also measure the effectiveness of a drug at this phase and can watch to see how it reacts at different doses in the human body.

Earlier testing of the drug in question involved animals, the health minister said. While animals can react similarly to humans, their bodies can process substances differently. In order for any drug to get to market, it must go through several government-approved steps along the way that involve human subjects.

Such extreme adverse reactions to drugs in these early phases of drug trails are incredibly rare.

Bial pharmaceutical said in statement that throughout this trial, the new drug had already been administered to 108 patients "without any moderate or serious adverse reaction."

The French health ministry said it immediately sent agents to the medical facility to determine if all the rules had been followed in the testing and if the facility where the patients were staying during the trial maintained sanitary conditions. The facility was inspected in 2014 and the ministry said it had favorable inspections.

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CNN's Kellie Morgan contributed to this report.

http://edition.cnn.com/2016/01/18/health/france-drug-trial-participant-dies/

French drug trial leaves one brain dead and three facing permanent damage

Government promises to investigate 'unprecedented' accident as six volunteers remain in hospital after trial for pharmaceutical company Bial

One man is brain dead and three others could face irreversible neurological damage after they volunteered to take part in a drugs trial in western France.
Six volunteers remain in hospital in Rennes, Brittany, after taking part in the Phase 1 trial for a new experimental medication designed to treat mood disorders such as anxiety, which was under development by the Portuguese pharmaceutical company Bial.
The French government promised to investigate the "tragic circumstances" of what it called an unprecedented and exceptionally serious accident which has sent shockwaves through the pharmaceutical industry.

The six men, aged between 28 and 49, had been pronounced fit and healthy when they arrived at the Biotrial private clinic at the start of the drug trial on 4 January.
As paid volunteers , they spent over a week at the approved clinic where they tested the drug by regularly taking increased doses by mouth. Approximately 90 people had taken the drug while about 30 others received a placebo.
The six men who were hospitalised were the group who had taken the drug regularly and had taken the most.
Contrary to earlier reports, the health minister Marisol Touraine stressed that the drug did not contain cannabis or any element derived from cannabis. The minister said the drug was meant to act on the body's endocannabinoid system. It had an impact on receptors which regulate pain, mood or appetite.
The men began taking the drug on 7 January after being checked for health and fitness. The first volunteer was admitted to the neurology department at the nearby hospital in Rennes three days later.
Pierre-Gilles Edan, head of the neurology department, said the man had come in with acute symptoms similar to a stroke and was now in a brain-dead state. The other volunteers were admitted to hospital shortly after. He said four men were suffering from neurological problems, three of whom might face permanent damage. A sixth volunteer was being monitored in hospital.

A judicial investigation has been opened by the French state prosecutor as well as two separate state-run inquiries. After visiting the men and their families in hospital, Touraine, promising to shed light on who was responsible, said: "Their distress is immense. Their lives have been brutally turned upside down ... The shock is even greater given the fact that the people taking part in clinical trials are healthy."

In the initial Phase 1 stage of clinical testing, a drug is given to healthy volunteers to see how it is handled by the body and what is the right dose to give to patients.

Cases of early-stage clinical trials going wrong are rare but not unheard of. There was a similar incident in Britain in 2006, when six previously healthy men were treated for organ failure only hours after being given an experimental drug targeting the immune system.

The six men who received the drug suffered a severe immune reaction which caused swelling and widespread organ failure. One patient was described as looking like the "elephant man" after his head swelled up; another has since required surgery to remove fingers and toes, and all the volunteers have been told they face a heightened risk of cancer and immunological disorders in later life. The catastrophe happened even though trials in animals suggested the drug was safe.

The incident prompted a review of procedures and resulted in the UK regulatory agency imposing new testing standards, including recommendations to use the lowest possible dose and to test new drugs only in one person at a time.

The French health ministry urged calm and said no drug currently on the market was implicated in the failed trial.

Friday 15 January 2016 19.13 GMT

http://www.theguardian.com/science/2016/jan/15/six-volunteers-in-hospital-after-unprecedented-accident-in-french-drug-trial

Botched Drug Trial Leaves 1 Brain Dead, 5 in Hospital

By thomas adamson, associated press
PARIS — Jan 15, 2016, 5:41 PM ET

One man was brain dead and three others faced possible permanent brain damage after volunteering to take part in a drug trial for a painkiller based on a natural brain compound similar to the active ingredient in marijuana, French authorities said Friday.

The Paris prosecutor's office opened an investigation into what French Health Minister Marisol Touraine called "an accident of exceptional gravity" at a clinical trial lab in the western French city of Rennes.

The trial involved 90 healthy volunteers who were given the experimental drug in varying doses at different times, she told reporters at a news conference in Rennes.

Six male volunteers between 28 and 49 years old have since been hospitalized, including one man now classified as brain dead, Touraine said, adding that the other 83 volunteers were being contacted.

Calling the case "unprecedented," Touraine said she was "deeply moved" by the suffering of the victims, who she met with earlier Friday, along with their families. "We'll do everything to understand what happened," she said. "I don't know of any other event like this."

The drug trial for the six hospitalized men began on Jan. 7 and was halted Monday, a day after the first volunteer fell ill.

The chief neuroscientist at the hospital in Rennes, Dr. Gilles Edan, said in addition to the brain-dead man, three other men could have "irreversible" brain damage. A fifth man is suffering from neurological problems and a sixth man is being kept in the hospital but is in less critical condition, he said.

Edan said there's no known way to reverse the effects of the experimental drug, which was given orally to healthy volunteers as part of a Phase 1 trial by Biotrial, a drug evaluation company based in Rennes, on behalf of the Portuguese pharmaceutical company Bial.

Touraine said that in addition to treating pain, the drug was intended to ease mood and anxiety troubles as well as motor problems linked to neurodegenerative illnesses by acting on the endocannabinoid system. In this system, natural brain compounds act on specific receptors to exert their effects. The experimental drug is based on a natural brain compound similar to the active ingredient in marijuana.

Touraine said the drug was not based on marijuana itself, as some media reports had claimed.

"This drug is not cannabis. It is not derived from cannabis. It works on the natural system that helps fight pain," she said, adding that no drug currently on the market was implicated in the failed trial.

Bial, the Portuguese drug producer, said Friday that 108 healthy people had already taken part in trials involving the drug and had no moderate or serious reactions. Bial added that initial testing for the drug started in June following toxicology tests.

For the French volunteers, it was meant to be a way to earn extra money and help develop a drug to treat people with pain and anxiety. Adults volunteering for Biotrial tests can earn between 100 euros and 4,500 euros ($110 to $4,920).

It's rare for volunteers to fall seriously ill during Phase 1 trials, which study safe usage, side effects and other measures on healthy volunteers, rather than drug effectiveness. Researchers generally start with the lowest possible dose after extensive tests in animals, and Touraine said the drug had previously been tested on chimpanzees and other animals.

Biotrial, which also has offices in London and Newark, New Jersey, says it has over 25 years of experience in clinical trials and uses "state-of-the-art facilities."

In 2006, Britain saw a similar incident, when six previously healthy men were treated for organ failure only hours after being given an experimental drug targeting the immune system. That prompted a review of procedures and resulted in the U.K. regulatory agency imposing new testing standards, including recommendations to use the lowest possible dose and to test new drugs only on one person at a time.

The six men in Britain now apparently have a higher risk of cancer and autoimmune diseases tied to their exposure to the experimental drug.

Dr. Ben Whalley, a neuropharmacology professor at Britain's University of Reading, said standardized regulations for clinical trials are "largely the same" across Europe.

"However, like any safeguard, these minimize risk rather than abolish it," Whalley said in a statement. "There is an inherent risk in exposing people to any new compound."

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Associated Press writers Elaine Ganley in Paris, Barry Hatton in Lisbon and medical writer Maria Cheng in London contributed to this report.

http://abcnews.go.com/Technology/wireStory/fall-ill-france-participating-clinical-trial-36309158

Researchers question design of fatal French clinical trial

UK's Royal Statistical Society among those demanding more information after the release of trial's protocol.

Ewen Callaway & Declan Butler

22 January 2016

Scientists are voicing concerns over the design of a French drug trial that left one participant dead and several others with severe health problems — and they are calling for more information to be released.

The researchers, including those in the UK's Royal Statistical Society (RSS), have examined a document that describes how the trial was conducted, and say that major pieces of information are still missing.

In particular, the researchers note a lack of information about whether the design included adequate time intervals between the individuals given the multiple-dose regimen of the drug that caused the problems. Such intervals allow investigators to watch for possible side effects in one volunteer before they expose subsequent volunteers to the drug. The incorporation of such delays was identified as important both by an RSS working group and the European Medicines Agency, after a clinical trial went disastrously wrong in the United Kingdom in 2006.

"A key aspect is a proper interval of time between dosing of successive volunteers," says biostatistician Sheila Bird of the Medical Research Council Biostatistics Unit at the University of Cambridge, UK, who is a member of the RSS working group, which focuses on 'first-in-human' clinical trials.

The RSS is now calling on the Portuguese company Bial, which sponsored the trial (conducted by French contract-research oranization Biotrial in Rennes), to release further information about its design and the tests that preceded it.

Bial spokesperson Susana Vasconcelos told *Nature* that the company denounces the release of the protocol, as well as "discussion on this subject without knowing the results of the current investigations and all clinical data regarding the volunteers of the clinical trial".

Protocol released

In the days after the trial went wrong — the first public acknowledgement of the incidents came on 15 January — little information was available, frustrating those who wanted to understand what had happened. Then, on 22 January, France's

National Agency for Medicines and Health Products Safety (ANSM) released the protocol of the drug trial, after the newspaper *Le Figaro* published a version of the same document.
The document identifies, for the first time, the chemical makeup of the drug — which was aimed at treating anxiety and motor disorders associated with Parkinson's disease, and chronic pain in people with cancer and other conditions — and the regimen that the study volunteers followed. But it still leaves many questions unanswered.

Such phase I trials are conducted in healthy volunteers to determine the safety and dosing of a drug, before moving on to studies that test the effectiveness of drugs in people with a particular condition.
In the study, the first volunteers received either just a single dose of the oral drug, which is known as BIA 10-2474, or a placebo. After this, different volunteers were given a single administration of increasingly higher doses of the drug. The six volunteers who were hospitalised — some with severe symptoms such as bleeding or dying tissue in the brain — were the first to receive multiple doses of the drug, administered on successive days. (The first patient to fall ill died on 17 January; one other has recovered sufficiently to be discharged from hospital, and the health of the remaining patients has improved.)

Basic facts about the trial

- The trial recruited 128 healthy volunteers aged 18–55, who were paid €1,900 (US$2,060) each.
- Ninety people received different doses of the drug, and the remainder a placebo.
- The trial had tested escalating single doses of the drug without observing any serious adverse side effects.
- The six participants who fell ill were the first to receive repeat higher doses over the course of several days.
- The first participant to fall ill experienced adverse symptoms on 10 January and died on 17 January.
- Biotrial halted the trial on 11 January; the other five affected people were hospitalized in the days that followed.
- At least one of these patients has since been discharged, and the health of the remaining patients has improved.
- Of the 84 other subjects who received lower doses of the drug, 28 have been given neurological check-ups since the accident, and none has shown any of the symptoms seen in those hospitalized.
- Biotrial filed an application for the trial to the French National Agency for

Medicines and Health Products Safety (ANSM) on 30 April last year and the agency authorized it on 26 June, with the final sign off given by the French equivalent of a local institutional review board (Comité de Protection des Personnes) in Brest on 3 July.

- The trial began on 9 July in Biotrial's clinical facilities in Rennes.

According to the newly released protocol, the participants in this part of the trial were to receive one dose of the drug each day for ten consecutive days. But Bird says that the protocol does not state whether there was any interval between the individuals who were beginning this regimen, or the dosage that these participants received.

Intervals recommended

After the 2006 UK trial of the antibody treatment TGN1412, which led to the hospitalization of six volunteers, Bird's working group recommended that such intervals be included in the design of phase I trials. Guidelines drafted by the EMA after that disaster also underscores the importance of these intervals and says that their length should be justified by previous data collected in humans and animals.

According to the timeline detailed by France's health minister, Marisol Touraine, those who fell ill had begun to take the experimental treatment on the same day, 7 January, and adverse symptoms appeared in the first subject – who was hospitalized with brain death – on 10 January. The trial was halted on 11 January, and the five others were hospitalized in the days that followed.

Catherine Hill, a biostatistician who previously served on the ANSM's scientific advisory board, says that it was "a big mistake" to begin giving the six volunteers the drug on the same day. She says that the trial should have incorporated a delay between volunteers as they started the multiple-dose regimen. "You have to do things reasonably, and I think it's an unreasonable protocol," she says.

Bial's Vasconcelos says: "We reiterate that the development of this molecule has been conducted since the beginning in accordance with all the good international practices, with the completion of tests and preclinical trials, particularly in the area of toxicology. The results obtained in accordance with international guidelines have permitted the start of the clinical trials in humans."

In a statement on 22 January, the RSS called for the publication of the 'investigator brochure', which details the preclinical studies that led up to the trial. According to the ANSM, Bial declined to publish the brochure and another document, citing French laws that protect the release of trade secrets.

Bird says that the release of such information is important to ensure the safety of

participants in other clinical studies. “There are other studies going on around the world right now, and we want to know what the design problems were.”
On the same day, the British Pharmacological Society published a statement calling for improved early access to data from catastrophic clinical trials, following the recent disaster in France.

Nature
DOI:10.1038/nature.2016.19221
http://www.nature.com/news/researchers-question-design-of-fatal-french-clinical-trial-1.19221

Scientists Speculate On What Caused The Bial Drug Testing Tragedy In France

A Phase 1 drug trial in France has now left one volunteer dead and five others hospitalized- four with neurological damage- at the University of Rennes Central Hospital (CHU Rennes).

A Phase 1 drug trial is the first time an experimental drug is given to humans after a series of exhaustive laboratory and animal studies. Phase 1 trials are conducted in healthy volunteers-those without the medical condition in question- and 84 other patients had safely received the drug since the trial began in July. Biotrial, a clinical research organization with a 150-bed research unit in Rennes, has been the trial site.

The drug in question, code named BIA 10-2474, is under development by Portugal-based pharmaceutical company Bial-Portela & Ca., S.A., for pain relief, a therapeutic area where non-addictive drugs are in great need. Unlike oxycodone working on opioid receptors or naproxen inhibiting cyclooxygenase enzymes, BIA 10-2474 is an inhibitor of an enzyme called fatty acid amide hydrolase, or FAAH.

What's so important about FAAH? Our bodies make several fatty acid amides that include anandamide, a natural stimulator of the cannabinoid receptors upon which chemicals in the marijuana plant act. Anandamide is referred to as an endocannabinoid. The rationale is that a drug blocking FAAH will allow naturally-occurring anandamide to accumulate and act on cannabinoid receptors in a manner that won't produce the psychoactive effects of cannabis.

Other pharmaceutical companies have been developing their own FAAH inhibitors, such as Janssen/Johnson & Johnson's JNJ-42165279 for social anxiety disorder, Merck's MK-4409, and Pfizer's PF-04457845 against osteoarthritis pain, insomnia, Tourette syndrome, and cannabis withdrawal, and Vernalis' V158866.

Related - Janssen Voluntarily Suspends Two Phase 2 FAAH Inhibitor Trials Out of Caution, More Details On Bial Tragedy

The diversity of indications reflects the spectrum of actions endocannabinoids have in animal research models. But none of these drugs have been associated with any type of brain injury in human research volunteers.

Few details, best-informed speculation

How and why this tragedy occurred has been a focus of considerable speculation in the scientific and medical communities. But crucial details on the drug involved, such as in vitro and animal studies, are lacking. As of this morning, PubMed lists no publications of any type from Bial on any FAAH inhibitor.

And even the clinical information on the patient death and severe adverse reactions in others is too general to make any significant interpretations. CHU Rennes neurology department head Dr. Pierre-Gilles Edan described MRIs of the patients' brains: The worst showing cerebral hemorrhage and necrosis, "with three others were suffering a 'handicap that could be irreversible' and another also had neurological problems."

Amsterdam-based writer for Science, Martin Enserink, has two reports with the greatest medical details to date. Update: Enserink corrected me on Tuesday morning that while the five surviving men in Rennes are hospitalized, one is without symptoms. That's perhaps the only bright spot in this tragedy and will certainly be valuable in the investigation.

The Bial website does feature the company's commitment to transparency of clinical trial information and data sharing upon completion of human studies. To their credit, they have registered 93 of their drug trials at clinicaltrials.gov, mostly those that have been completed or terminated. Many are with their drug for epilepsy, eslicarbazepine acetate (BIA 2-093), that was approved in the United States in November 2013 and sold under the brand name Aptiom by Sunovion Pharma. However, no trials with BIA 10-2474 are listed.

The Paris prosecutor's office has opened an investigation, according to Agence France-Presse, so any further technical information on the drug is unlikely to be made public.

What we do know can be gleaned from 1) the drug's likely chemical structure and 2) the development and testing of other FAAH inhibitors that have progressed to clinical trials.

Drug is an irreversible FAAH inhibitor

Chemical informatics expert Christopher Southan has been the best source of the most-likely chemical structure of BIA 10-2474, having examined patents and patent applications from Bial (although he notes that an anonymous Wikipedian posted the structure prior to him). Southan cites the comment thread at In the Pipeline, the highly-read blog by industrial medicinal chemist Derek Lowe, PhD, at Science Translational Medicine. One discussion point has been that the drug is likely to be an irreversible FAAH inhibitor, meaning that the drug makes chemical bonds with the enzyme to inactivate it.

Irreversible inhibitors are not necessarily a bad thing-that's how aspirin works. In fact, scientists writing in a 2011 paper in Nature Reviews Drug Discovery discussed a resurgence in this covalent binding class of drugs across therapeutic areas.

But any time a small molecule is designed to irreversibly bind to an enzyme, an opportunity arise for the immune system to recognize it as foreign. In rare cases, the immune system will mount an inflammatory response against it, but also against regions of the normal enzyme surrounding where the drug binds. This response can result in a hypersensitivity or autoimmune reaction in a subset of individuals whereby the immune system attacks everywhere the enzyme is present.

One example of an autoimmune drug reaction is the liver damage that can occur with the old inhaled anesthetic, halothane. The liver metabolizes halothane to a compound that forms covalent chemical bonds with liver proteins and, in a very small subset of patients, the immune system attacks the liver.

A similar reaction can occur with people who are hypersensitive to some types of penicillins.

But none of these reactions have been observed in the brain, as with BIA 10-2474.

Most drug hypersensitivity reactions occur in the liver, the skin, and in the bone marrow, where some drugs can cause potentially-fatal aplastic anemia.

Scientists at Merck who developed their FAAH inhibitor, called MK-4409, made a case against developing an irreversible inhibitor in a 2014 ACS Medicinal Chemistry Letters publication,

"More recently, however, several scaffolds have been disclosed as reversible noncovalent modifying inhibitors of FAAH. Aminopyrimidine and sulfonamide are chief among these novel classes of FAAH inhibitors. This approach, in our view, would decrease potential safety concerns over the creation of a long-lived covalent adduct between a compound and the FAAH enzyme. [emphasis mine]

"Off-target" effects

Several writers, including Forbes contributor Judy Stone, MD, have pointed to so-called off-target effects that may have led to brain injury in this group of trial volunteers. What's meant by this is that the drug may have had effects on an unintended biochemical process. For example, FAAH belongs to a family of 200 enzymes called serine hydrolases, some whose function is not yet understood. In addition to binding these other enzymes at higher doses, the drug might bind to other cellular proteins that affect blood flow in the brain.

The potential for these off-target effects has clearly been well-appreciated by Janssen/J&J and Pfizer research teams with their respective drugs. For example, Janssen tested their FAAH inhibitor against 50 enzymes, receptors, transporters, and ion-channels as well as the major drug-metabolizing enzymes of the cytochrome P450 (CYP) family.

Pfizer and their collaborators were even more comprehensive in making sure their drug didn't attack proteins other than FAAH at concentrations higher than would be expected in the body. PF-04457845 was examined against in the serine hydrolase superfamily, several CYP drug-metabolizing enzymes, and a panel of 68 receptors using an in vitro pharmacology screening service offered by the French company, CEREP.

Sean Ekins, PhD, who writes at Collaborative Chemistry, has run the BIA 10-2474 structure through two computational algorithms to identify potential protein targets other than FAAH to which the drug might bind. While he stresses that these are simply computational analyses that have not been confirmed experimentally, Ekins writes

"These high scores for many protein targets in humans could suggest the molecule is highly promiscuous and there may not be a single pathway interfered with. Vesicular acetylcholine transporter is slightly lower down in the list which also makes you wonder how many GPCRs might be impacted too. For now this is all idle speculation until we hear more about exactly what happened. Perhaps this compound could be profiled both computationally and experimentally to answer these questions of what the target/s of the toxicity are."

If Bial performed similar experiments for their drug-biochemical or computational-no similar data has been published or otherwise made available publicly.

Other possibilities: Drug impurities?

This speculation is mine entirely and derives from a close examination of the U.S. patent application that most commentators believe is for BIA 10-2474. The inventors at Bial describe that in the chemical synthesis of their top FAAH inhibitor (denoted "compound 23" and "Formula A" in the application), an additional purification step must be done to remove an "N-acetylated aniline impurity."

Aniline caught my eye because it was used in the manufacture of dyes and other industries. Occupational exposure to high concentrations of aniline can change hemoglobin to methemoglobin and impair oxygen delivery to tissues. As a result, acute aniline poisoning first affects organ systems with high oxygen requirements, such as the brain and the heart.

This is an intellectual leap, of course, but if a drug impurity were present in the batch of study drug used for this trial, those receiving the highest doses might have been exposed to an aniline relative capable of causing methemoglobinemia. One would expect that clinicians would have easily detected this since the patient's

skin would take on a blue hue.

Longtime British scientist at Pfizer, Dennis A. Smith, PhD, wrote in his textbook, Metabolism, Pharmacokinetics, and Toxicity of Functional Groups that,

"Compounds containing aromatic amines (anilines) induce a variety of toxicological responses including carcinogenicity and hepatotoxicity. Several drugs containing an aniline moiety, which have been withdrawn from the market, have a black box warning on their labels. Therefore, anilines have been put on the blacklist of functional groups that the medicinal chemists generally avoid."

BIA 10-2474 does not itself contain an aniline group (it's a phenylurea for those interested), it's possible that an N-acetyl aniline impurity could produce aniline toxicity. Again, this is pure speculation based on what is thought to be the patent application for the study drug. I contacted Bial for confirmation of the chemical structure of the drug but a response had not been received at the time this commentary was posted.

Other questions: Why did the study have a placebo group?

Forbes contributor Judy Stone, MD, raised an interesting point as to why a placebo group was included in a Phase 1 trial, a stage at which drug efficacy is not among the intended endpoints. One possible reason is that modulating endocannabinoid levels could produce psychoactive side effects, although this has not occurred with the Merck or Pfizer compounds. But since effects like agitation, confusion, dizziness, and headache are observed in a percentage of placebo participants in trials for any therapeutic area, the investigators may have wanted to have a baseline against which the study drug's effects could be compared.

In summary, this rare Phase 1 clinical trial tragedy has generated substantial scientific and medical interest in the precise cause of these severe neurological reactions that have led one patient dying. Even with spotty details on the drug, its intended target, and other clues, it's clear that investigators will have many possibilities to explore in determining why this tragedy occurred.

Forbes.com.