Letter on the article "The BIAL/Biotrial case of death of a human volunteer in the first-in-human study of BIA 10-2474: Are we missing the fundamentals?"

Correspondance à propos de l'article « The BIAL/Biotrial case of death of a human volunteer in the first-in-human study of BIA 10-2474: Are we missing the fundamentals? »

In Rennes, a man died during a phase 1 trial, trial in which a product is administered for the first time to a human being or First In Human (FIH) trial. This particular trial was conducted in healthy volunteers.

Most of the facts have been summarised by Funck-Brentano and Ménard [1], but they left out a few piece of information and they exonерated the investigators, possibly in relation to the declared conflicts of interest. They also downplayed the role of the investigative journalists involved. We present a different point of view.

The Portuguese drug company BIAL studied in animal models a Fatty Acid Amide Hydrolase inhibitor called BIA 10-2474 and contracted Biotrial in Rennes for the phase 1 study in human.

The protocol
The protocol of the phase 1 study [2] included four consecutive trials. It is only for the first trial (single ascending dose) that the doses were specified. The selection of the doses in the three other trials was left open in the protocol, which only specified that it would depend on the results previously accumulated. The protocol was submitted to the "Agence national de sécurité du médicament" (ANSM) and to the "Comité de protection des personnes" (CPP) in Brest, who endorsed it.

The conduct of the protocol
The first trial started on July 9, 2015 and included eight subjects at each dose level: 0.25 mg, 1.25 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg and 100 mg. Two of each eight subjects were given a placebo, 6 others were given BIA 10-2474. The first two subjects, one receiving a placebo and one 0.25 mg of the drug were treated first; the other 6 subjects of the 0.25 mg dose level were treated 24 hours later. At all other doses, all eight subjects were treated simultaneously. The second trial included 12 subjects receiving 40 mg twice separated by a fortnight, once while fasting and once with food.

The third trial included eight subjects, again two receiving a placebo, at each of the five first dose levels 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg, all eight subjects being treated simultaneously. The serious condition of a subject at the last of these dose levels led to stopping the trial. Precisely, on Sunday January 10, after receiving the fifth 50 mg dose, corresponding to a 250 mg cumulative dose never given to a human until then, a volunteer had blurred vision, swallowing difficulties and speech problems which led the medical doctor at Biotrial to send him to the emergency ward of the University Hospital in Rennes at 8:30 pm. During the night and on Monday morning, his condition deteriorated and around noon he was in a deep coma. He died a week later. Despite the hospitalisation of one subject on Sunday evening, the medical doctor in charge of drug administrations at Biotrial delivered a sixth dose to the seven other subjects at 8 am on Monday January 11.

On Tuesday, another subject had problems similar to those of the first patient: blurred and double vision, followed by violent headaches. He was hospitalised on Wednesday.

Three other volunteers, whose identity has not been revealed, have also had neurological problems and were hospitalised between Wednesday and Friday. The brain MRI performed at that time showed lesions. The ANSM was informed on Thursday. At the end of February, all volunteers from previous dose levels were invited to the University Hospital in Rennes for a control brain MRI.

The enquiries
The authorities conducted three administrative enquiries, two conducted by Temporary Specialised Scientific Committees (TSSC) appointed by ANSM, and one by the "Inspection générale des affaires sociales" (IGAS). A judicial investigation has been opened on June 14 [3] and on November 3 a team from the University Hospital in Rennes [9] described the condition of four of the volunteers exposed to the highest dose.

Overall, the administrative enquiries found little to criticise in the conduct of the trial. The first group of experts appointed by ANSM concluded in a 30 pages report [4], put on line on April 19, that the Bial product...
was the cause of the problem. The IGAS enquiry led to a two volumes report of 120 and 151 pages respectively [5], including a rebuttal of its critiques written by Biotrial (volume 1 pages 85 à 110 et 117 à 120, volume 2 pages 75 à 146).

The IGAS inspectors had been invited to audit the whole trial process, including the authorisation process, the selection of the subjects, the conduct of the trial, and the surveillance of side effects. However they only criticised the management of the crisis. So, “at the end of its investigations, the mission considers that there is no reason to call into question the authorisation delivered” while pointing out that “the overall design of the protocol and the latitude left for its implementation did not offer a sufficient framework to protect the subjects participating into the trial”. The three main criticisms concern the management of the accident by Biotrial: “not to have searched for information on the condition of the hospitalised patient before giving an extra dose to the other subjects on Monday morning”; “not to have informed the subjects nor obtained their consent to continue the trial on Monday”; “not to have informed before Thursday evening the health authority of the serious adverse event that occurred on Sunday” (page 3, synthesis volume 1).

Neither the Agence nationale de sécurité du médicament (ANSM) nor the Comité de protection des personnes (CPP) in Brest are questioned in the report, the protocol and its validation by these two instances being considered as respecting the regulations.

The paper from the University Hospital [9] described the condition of four of the volunteers exposed to the highest dose: one remains asymptomatic (did he actually swallowed the pills?), one has residual memory impairment, one has a residual cerebellar syndrome, and one died.

The second group of experts appointed by ANSM described the neurological symptoms and the radiological signs among 82 of the 84 volunteers exposed to lower doses and concluded that the nature and frequency of symptoms were different from those observed with the highest dose [10].

The journalists’ investigations

At first the ANSM refused to publish the protocol, arguing that is was the property of Bial, it is the daily newspaper Le Figaro which published it on line on January 21 2016. Facing the fait accompli, the ANSM then published the protocol on its website. The online investigative and opinion journal Médiapart revealed on May 24 that a healthy volunteer in the third dose level of the MAD phase, i.e. receiving 10 mg per day for 10 days in November 2015, suffered from visual problems twice during treatment. The control MRI performed in February at the University Hospital in Rennes was returned to him with a diagnosis of “non-recent stroke”. Le Figaro submitted this MRI to four experts who concluded that the stroke was very likely to have occurred during the subject exposure to BIA 10-2474, and was probably related to this exposure. Realizing its mistake, the University Hospital in Rennes has since sent a rectified interpretation of the MRI to the patient.

Médiapart published on June 1st, the facsimile of the letter from Biotrial medical doctor sent with the first patient to the University Hospital on Sunday night. This letter specifies “these symptoms are possibly related to the investigated product”.

Médiapart described on October 27 an extract from an enquiry conducted by ANSM on January 15 and 16 [6] which reported four cases of headaches and blurred vision, three in individuals exposed to 10 mg per day and one to 20 mg per day, all for 10 days. Le Figaro and Mediapart described and criticized the second TSSC report.

More general questions

The accident in Rennes raises more general questions on the conduct of phase 1 trials.

(1) How come one continues to give simultaneously to six subjects a new product at a dose never tested in humans, when this same practice led six young men into an intensive care unit in London in 2006? Following this accident, the Comité de protection des personnes in Marseilles in 2006 [7] and the European Medicine Agency in 2007 [8] recommended to include subjects one at a time. Despite this recommendation, both IGAS and ANSM consider this safety measure as optional, its application depending on the evaluation of the presupposed level of risk (“niveau de risque pressenti”, rapport IGAS tome 1, pages 23 et 24), an undefined concept. The rule should be to play it safe, and all exception to this rule ought to be explicitly justified.

(2) How can a medical team, who gave an individual a new product at a dose never tested in human, who later sent this individual to the emergency ward, and who is in charge of the safety of seven other persons, invoke the confidentiality of medical information (IGAS report volume 1 page 91) to justify its failure in finding out the condition of the transferred patient?

(3) How can the team invoke the fact that the causal relation between the drug and the side effect was not established (IGAS report volume 1 page 97, and volume 2 pages 81 to 87) to justify not informing the subjects? The volunteers should be given the benefit of the doubt, instead of protecting the protocol.

(4) Why did the IGAS auditors fail to obtain the medical file of the patient from the emergency ward on January 10? Their analysis is based on a narrative written by Biotrial, including a sequence of observations (IGAS report volume 1 pages 117–120) in which all symptoms have been systematically redacted, and replaced by . . . The letter from the Biotrial medical doctor that was sent to...
the hospital with the patient and was published by *Médiapart* allows filling in the blanks.

The descriptions of the communications between Biotrial and Rennes University Hospital on Sunday night are conflicting. Biotrial claims having received a call asking them if they could take care of the patient for the night, for want of a bed in the hospital, which Biotrial interpreted as implying that the condition of the patient was not serious. The hospital mentions no record of this phone call in its report, but it has been written by the administration. To explain the hospital request to send back the patient to Biotrial on Sunday night, Biotrial claimed that the hospital told them that the MRI was not available (IGAS report volume 1, page 89) whereas the University Hospital website indicates that an MRI is dedicated to the emergency unit 24/7. (5) The New England Journal of Medicine paper [9] described the condition of four of the volunteers exposed to 50 mg per day for 5 or 6 days: one remains asymptomatic (one wonders whether he actually swallowed the pills), one has residual memory impairment, one has a residual cerebellar syndrome, and one died. There is no mention of the condition of the other two individuals exposed to the same dose or of the 84 exposed to lower doses. The paper states "no clinical severe adverse event had been reported" at lower doses. This is technically correct but ignores both the stroke identified by the journalists in a patient receiving 10 mg per day for 10 days, and the headaches and blurred vision reported at 10 and 20 mg per day for 10 days. They report that 35% of the volunteers have had neurological symptoms, and consider this frequency as not alarming. However they also report that generally, in phase 1 trials, two-thirds of the volunteers report medical symptoms, 25% of these being neurological. This gives an expected frequency of 17% (2/3 × 25%) individuals with neurological symptoms. The volunteers exposed to BIA10-2474 have therefore a doubled risk of neurological symptoms and the excess is highly statistically significant (P < 0.001). The proportion of neurological symptoms among the symptoms reported by the volunteers is also much larger than the 25% expected from previous phase 1 trials and two volunteers reporting recurrent blurred vision constitute a signal by itself. Moreover, the TSSC report fails to take into account the design of the trial: volunteers who received 0.25 mg of BIA10-2474 are described together with those who received 10 times 20 mg of the drug, possibly because the Committee included no specialist of the design and analysis of trials. Such a specialist may also have recommended control MRIs in the volunteers having received the placebo. The conclusion of the report that the nature and frequency of symptoms are different from those observed with the highest dose is seriously hampered by the fact that the information was not reviewed similarly for the individuals exposed to the highest dose and for the other individuals: radiologists appointed by the TSSC failed to review blindly the MRI’s from the 6 volunteers exposed to the highest dose under the argument that these results had been published in the New England Journal of Medicine, but the publication included only data for 4 of them.

**Independence and conflict of interest**

The enquiries have been conducted by individuals appointed by ANSM and by employees of the Health Ministry, but ANSM and its supervising Ministry the Health Ministry are not independent since ANSM had approved the protocol. The inspectors from IGAS state candidly that they relied on ANSM expertise and it is no surprise, they found no fault to the protocol.

**Conclusion**

Phase 1 trials raise complex safety problems and the evaluation of their protocol requires multiple expertise. Following the accident in London in 2006, the EMA published a recommendation on the staggering of subject inclusion in phase 1 trials which was not compelling enough, and all Ethic Review Boards in France have not been informed of the problem. The phase 1 trial protocol for BIA 10-2474 was both complicated and imprecise, but the authorities considered that it was within acceptable limits, endorsing therefore the simultaneous inclusion of subjects at each dose level.

The death of a healthy volunteer in a phase 1 trial is a tragic event, and some risks are unforeseeable, however in the present trial the vigilance expected in First in Man trials seems to have been suboptimal.

However, Biotrial failed its duty to protect the volunteers by giving one extra dose to the seven other subjects after sending one to the hospital emergency ward, and the legalistic and regulatory arguments put forward by Biotrial do not diminish its responsibility.

To conclude, the lessons from this tragic event ought to be:

- the inclusion of subjects one at a time in FIH trials;
- the deletion from all texts on the conduct of phase 1 trials in healthy volunteers of the concept of adverse effect or "identified risk". Any serious event observed during a phase 1 trial must be considered as attributable to the experimental product, until proven otherwise.

**Disclosure of interest:** the authors declare that they have no competing interest.

**References**


[2] A double-blind, randomised, placebo-controlled, combined single and multiple ascending dose study including food interaction, to investigate
the safety, tolerability, pharmacokinetic and pharmacodynamic profile of BIA 10-2474, in healthy volunteers.


