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Broader Transparency on Risk-benefit Assessment of the Bial Trial in France

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Author's contribution

The sole author analyzed, interpreted and prepared the manuscript.

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Commentary

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ABSTRACT

On 11 January 2016, a Phase I trial of an experimental fatty acid amide hydrolase inhibitor for pain developed by Bial-Portela was halted after six healthy volunteers were admitted to the University of Rennes Hospital in France. One volunteer died and four suffered severe neurological injuries. It is a dreadful reminder of the Tenegero trial that also hospitalized six volunteers in 2006. Three major similarities were observed between the Tegenero and Bial trials. The first similarity is related to the dosing interval protocol. There is a lack of information about whether the multiple-dose regimen included adequate time intervals between individuals receiving the drug. The second similarity is on the dosing calculation that was based on the 'no adverse effect level' (NOAEL). The third similarity is observed in terms of how there was no prior publication of preclinical findings in the public domain before the start of both trials. There have been calls for the full release of the Investigation Medicinal Product Dossier and the Investigator's Brochure, as these data are critical to maximize patient safety in the future and should outweigh considerations of commercial confidentiality. Likewise, it is necessary for the Brest Regional Ethics Committee to release its documents, which captured the risk-benefit assessment in approving the Bial trial, for external scrutiny.

Keywords: Bial trial; first-in-human trial; ethical assessment; risk-benefit assessment; phase 1.

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1. INTRODUCTION

On January 11, 2016 a Phase I trial was halted after six volunteers were admitted to the University of Rennes Hospital in France with severe neurological injuries. The drug BIA 10-2474, an experimental fatty acid amide hydrolase (FAAH) inhibitor developed by Bial-Portela, a Portugese pharmaceutical company, had caused hemorrhagic and necrotic brain lesions in five out of the six men in a group who had received the multiple-dose regimen [1]. As approval and conduct of clinical trials are under the jurisdiction of European Union member states, the investigation of this incident is conducted by the French National Agency for Medicines and Health Products Safety (ANSM). It is a dreadful reminder of what happened 10 years ago in the UK - the unfortunate Tengero case, a trial that also hospitalized six people in the UK in 2006. The UK Medicines & Healthcare products Regulatory Agency has stated that both incidents have nothing in common in terms of protocols or how they were conducted [2]. Upon careful examination of the published clinical trial protocol [3], however, three major similarities can be observed between the Tegenero and Bial trials.

The first similarity relates to the dosing interval protocol. It was noted that there was a lack of information about whether the multiple-dose regimen allowed for adequate time intervals for the individuals who were given the drug [4]. As per the protocol, if there were any drug safety concerns, participant dosing would be staggered - a maximum of 4 participants dosed on the same day with 24 hours of follow-up necessary before dosing the remaining participants (under section "*2.1.3.4. Dose selection*", page 31 of study protocol BIA-I02474-101). However, the participants seemed to have been dosed simultaneously, as all the volunteers experienced their adverse effects three days after taking the drug orally. Although an interval of 10 minutes between each participant was mentioned in the study protocol, it remains unclear how this was justified as drug absorption after oral administration depends on the release of the drug substance from the capsule, the solubilization of the drug under physiological conditions, and the permeability across the gastrointestinal tract.

Under section "*4.6. Discussion of the Design*", page 36 of study protocol BIA-I02474-101, the description of single ascending dose (SAD) study design mentioned that the first group (eight participants) receiving a single oral dose of BIA 10-2474 will be scheduled to start with two participants (1 verum and 1 placebo). These two participants are to be dosed 24 h before the remaining six participants, and if the safety and tolerability results were acceptable, the remaining six participants (5 verum and 1 placebo) will be dosed. However, the same provision was not described for the multiple ascending dose (MAD). This resulted in simultaneous occurrence of the adverse events after six participants took the highest tested dose (50 mg) once daily for a planned 10 days. With the cause still unknown till today, the hypothesis is whether a sufficient gap between participants before incremental increases in dosing could have prevented or mitigated the outcome. Simultaneous rather than sequential administration was identified as being problematic in the Tegenero trial in 2006. It caused multiple organ failure in six participants [5].

A second similarity was the dosing calculation, which was based on the 'no adverse effect level' (NOAEL). Investigation into the Tegenero trial revealed that the calculation of an initial dose based on a fraction of the predicted NOAEL proved to have been dangerously wrong [6]. The third similarity observed was how there was no prior publication of preclinical findings available in the public domain before the start of both trials. However, this scenario is not just typical of the Tegenero and Bial trials; it is a known concern for all industry sponsored trials where the publishing of animal findings is not considered to be a priority in the industry.

2. QUESTIONING THE ETHICS COMMITTEE

The concern here then is whether this incident could potentially have been an avoidable event. Although risk science is a well-established transdisciplinary field of investigation, balancing that risk and the benefits in medicine remains an area of active research. A review of the initiatives on frameworks and methodologies between 2000 and 2013 showed there is still a lack of consensus regarding the most appropriate risk-benefit methodologies for stakeholders [7]. A survey conducted in 2013 reported that key decision-makers from both regulatory agencies and the pharma industry acknowledge that there is a lack of a universal and scientifically validated framework for performing benefit risk assessment on documentation and the

communication related to decision-making [8]. Another study has reported that ethics committee members described feeling less than fully competent to evaluate various aspects of clinical trial protocols (e.g., the originality and feasibility of a study, the adequacy of its methods, and the analysis procedures) [9].

These issues are just the symptoms of a much greater problem – the possible flaw in the current system in terms of how ethics committees actually conduct risk-benefit assessments for early human trials. An attempt to search online for information on the Brest Regional Ethics Committee, which approved the Bial trial in France, offered no relevant information. Interestingly, in 2009 it was reported that it was impossible to assess the quality/quantity of information provided on the website of the French Ethics Committee, as there was no specific website with Ethics Committee application guidance and no relevant information available in English on the Ethics Committee [10]. This lack of transparency and open access to basic information somehow contradicts the trademark and the goals of ethical research.

Both the British Pharmacological Society and the Royal Statistical Society have released statements urging the full release of the Investigation Medicinal Product Dossier (the basis for approval of clinical trials by the competent authorities in the EU) and the Investigator's Brochure (document containing a summary of the clinical and non-clinical data relating to an investigational medicinal product), as these data are critical [11,12]. It is important that priority for patient safety should outweigh all considerations of commercial confidentiality. Likewise, it is necessary for the Brest Regional Ethics Committee to release for external scrutiny its meeting minutes or any other documents that captured the risk-benefit assessment when approving the Bial trial. The committee should be held accountable for the reasons behind their decisions.

3. ETHICAL AND SCIENTIFIC JUSTIFICATIONS

Current Phase 1 recruitment practices of healthy volunteers raise questions about data quality [13]. Depending on the characteristics of the medicinal product, the recruitment of patients is sometimes more justifiable than the recruitment of healthy volunteers when studying agents of unknown toxicity and/or efficacy. In these circumstances, potential health benefits are a major justification for recruiting patients for Phase 1 trials that are deemed too risky for healthy people [13]. Further complications, however, can include informed consent forms that fail to highlight the differences between the study definition of a positive response and the way that patients define that type of response (i.e., knowledge benefits to society versus direct benefits to the participants) [13].

The primary objective of Phase 1 trials is to define the recommended dose and/or dosing schedule for further clinical trials. These trials are often ethically justified on the basis of overall social value because they do expose healthy people with limited economic opportunities and ill people with limited health options to potential harm for the benefit of others [13]. However, the irony is that with the given low number of Phase 1 trials that successfully have progressed to regulatory approval (~10%) [14], the question can be raised regarding whether Phase 1 trials are unethically justified as their risks are neither justified by therapeutic benefits nor the progressive value of future knowledge for society.

The basic assumption governing the design of Phase 1 trials is that for dose determination purposes, toxicity is an acceptable endpoint. A disconnect exists, however, between how these endpoints are chosen to determine the maximum tolerated dose (MTD) in Phase 1 and how the ethical principles of beneficence (i.e., do no harm) fit into the overall concept of maximizing benefits for the research and minimizing risks to all participants. If toxicity has traditionally been the primary endpoint for Phase 1 trials, are such risks then truly justified, including the risk of dying from a study? There are alternative endpoints that can be used to establish the recommended dose and schedule of targeted agents that will not produce immediate or consistent drug-related toxicity. These include (i) measuring the inhibition of a target; (ii) determining plasma drug levels that are biologically relevant (pharmacokinetics); and (iii) observing the surrogate markers of biologic activity [15,16]. A review of statistical, model-guided dose-escalation Phase I clinical trials has demonstrated that adaptive Phase I designs are efficient in terms of sample size and short trial duration; they locate the MTD rapidly and accurately, with most patients treated at or near the MTD [17,18]. Whether Bial adhered to the current accepted guiding principle for a dose escalation study is unclear at the moment.

To evaluate whether the Bial trial fulfilled all ethical requirements for clinical research, the clinical trial protocol was assessed using the seven ethical requirements set by Emanuel et al. (see Box 1) [19].

3.1 Social Value

The drug was a FAAH inhibitor that inhibits an enzyme produced in the brain and elsewhere and breaks down neurotransmitters called endocannabinoids. Modulating the activity of the endocannabinoid system has therapeutic promise for a wide range of disparate diseases and pathological conditions that range from mood and anxiety disorders, movement disorders like Parkinson's and Huntington's diseases, neuropathic pain, multiple sclerosis and spinal cord injuries, to cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity/metabolic syndrome, and osteoporosis. Therefore, in general, the potential impact of the clinical introduction of FAAH inhibitors is indeed large, and the study was deemed to have a high social value.

3.2 Scientific Validity

The study protocol stated that BIA 10-2474 is being developed for "the treatment of medical conditions in which there is an advantage in enhancing the levels of endogenous arachidonoyl ethanolamide or anandamide (AEA) and tonically increasing the drive of the endocannabinoid system" (under section "*2.1.2 BIA 10-2474*", page 26). This rather broad assignment of therapeutic indication requires equally broad panel of preclinical tests. The study protocol reported that the drug was subjected to an extensive preclinical test in three animal species – mice, dogs, and monkeys. No significant side effects were observed in the *in vivo* safety pharmacology studies, which studied a dose of up to 300 mg/kg/day. Repeated daily dosing of BIA 10-2474 for up to 13 weeks in mice, dogs, and monkeys and up to 26 weeks in rats also produced no signs of toxicity when tested up to the NOAEL. Based on this information, the scientific justification for proceeding with tests in healthy volunteers was reasonable. However, no description for the calculation of human NOAEL of 100 mg was provided. Neither calculations of receptor binding and occupancy, concentration-response curves *in vitro* in target cells nor any assessment of non-target binding interactions was presented as suggested by the European Medicine Agency Guideline for Phase 1 studies [21]. This level of information, however, would more likely have been presented in the Investigator's Brochure. Without access to the Investigator's Brochure, it would be difficult to make any further judgment on whether the scientific premise of the study was indeed valid.

3.3 Fair Participant Selection

The typical and widely accepted selection criteria for Phase 1 for healthy volunteers was described. The inclusion and exclusion criteria for the recruitment of participants seemed to satisfy the ethical norms. Healthy volunteers are expected to respond to tests performed under standardized conditions, thereby reducing the influence of confounding factors that are usually observed in a patient participant. Therefore the participation of healthy participants is justified when considering the expected benefits for the future targeted population.

Box 1. Seven requirements to determine whether a research trial is ethical *

Social value:	Is there a need to conduct research on FAAH inhibitors?
Scientific validity:	Was the experimental agent appropriate for human trials?
Fair subject selection:	Were subjects selected fairly without targeting vulnerable populations?
Favorable risk-benefit ratio:	Did the study have a favorable risk/benefit ratio?
Independent review:	Was the study reviewed by an independent body?
Informed consent:	Were research participants provided suitable informed consent forms and given a full chance to ask questions?
Respecting enrolled participants:	Were the participants closely monitored, and did they have their rights fully protected when conducting the research?

** The guiding questions were adapted from Emanuel EJ and Miller FG [20]*

3.4 Favorable Risk-benefit Ratio

As BIA 10-2474 increases exposure to anandamide, endocannabinoid effects, such as catalepsy, hypothermia, and hyperphagia, may be potentiated. However, none of these findings provided any explanation for the type and severity of events that were later observed in Rennes. Of particular interest, "few adverse events" were observed at the highest dose tested during the toxicology study. Any further description of these “few adverse events” was not elaborated on in the protocol. The drug was also characterized in rats and dogs as having a long apparent half-life (45 h and 104 h respectively). A report by Le Figaro, a French daily newspaper, said it had information suggesting a preclinical trial of the drug had left “a number” of dogs dead and others with neurological damage [22]. There is also reason to be concerned about administering the experimental agent to participants in close succession because no justification was provided as to why 10 minutes interval was deemed sufficient for an oral dosage form delivered in hard gelatin capsule. In retrospect of these observations, the potential clinical value of this drug did not offer any favorable risk/benefit ratio despite there being no significant safety concerns derived from the prior animal testing, as reported in the protocol.

3.5 Independent Review

The study was reviewed by two bodies independent of the sponsor. The study protocol was authorized by ANSM on June 26, 2015, and approved by the Brest regional Ethics Committee, France, on July 3, 2015. According to Bial, the study was approved in accordance with the guidelines of Good Clinical Practices with the Declaration of Helsinki and according to the laws inherent for clinical trials (under section “*18. Ethics and Regulatory Aspects*”, page 92). As this standard declaration is invariably written in most clinical study protocols, the ethical foundations of the study are never directly addressed in this study protocol. The typical lack of any explicit consideration of the ethical choices made in the design of a clinical trial makes it difficult for research ethics committees to discern whether and how the sponsor has effectively addressed relevant ethical questions [23]. In addition, no further information is obtainable for precisely how the independent review was conducted. It would be interesting to know whether there is declaration of conflicts of interest by members of the study review committee and whether there are measures to preclude compromise or bias professional judgment and objectivity.

3.6 Informed Consent

The procedure for obtaining informed consent was well described in the clinical study protocol. The protocol stipulated that participants must give written informed consent for participation in the study before any study-specific screening tests or evaluations are made.

3.7 Respecting Enrolled Participants

Affected volunteers were closely monitored and treated appropriately. Furthermore, 1/3 of the cohort who received lower doses of the drug have been followed up on since the accident, indicating that risk mitigation strategies were in place. However, the recent interim report from ANSM stated that the remaining volunteers were not given any information about the status of the first volunteers who did experience side effects before the second group were administered their daily dose, thus indicating a violation in terms of full respect for the participants [24].

4. CONCLUSION

This paper is a critical appraisal of the clinical study protocol BIA-102474-101 for the French “first-in-man” trial. It surveys for several ethical questions and argues that the assessment of risk and benefits depends on very complex Phase 1 clinical variables that require a structured and transparent process. This analysis is based on two assumptions, the first being that the trial was conducted “in accordance with all the good international practices guidelines, with the completion of test and preclinical trials”, as stated by Bial. The second assumption is that there was no error in administration, contamination by any impurity in the drug, or any misunderstood data. The limitation of this paper is that the analysis was performed without access to the Investigator’s Brochure and Investigational Medicinal Product Dossier that contains all the preclinical results of the drug, as Bial has refused access to these documents, citing trade secret protection.

The outcome of investigation by the Temporary Specialist Scientific Committee (CSST) has been now published at the ANSM website.

Interestingly, it was reported that the animal studies have been re-examined in detail, including additional documents, but no new information has been uncovered, particularly on the mechanism of toxicity [25].

Despite positive assessments from both ANSM and the Ethics Committee, the current risk-benefit assessment methodology failed to safeguard the lives of the volunteers due to adverse effects of the tested drug. Policies to strengthen the existing risk-benefit assessment process are needed to increase the transparency of the review process and ultimately increase participant rights and safety. It is hoped that this unfortunate incident and those that happened before will be a wake-up call for the ethics community to move forward and institute greater disclosure practices to ensure transparency in the risk-benefit assessment of all early trials.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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