An analysis of specific Phase I safety issues

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Abstract

Deaths or severe adverse reactions directly associated with the investigational drug during Phase I studies are rare. The 2006 TeGenero incident raised the level of public awareness of early-phase clinical trials in the EU, and led to an increase in volunteer rates. The 2016 Bial incident threatens to have the opposite effect and was potentially avoidable. In both cases, nonclinical animal studies did not indicate any safety signals or undue risks to humans. Both clinical protocols were approved by the responsible regulatory agencies and ethics committees and followed applicable regulations. However, both cases involved operational practices that took greater risks than good practice and common sense would have dictated. Most of the commentary regarding the TeGenero incident came from academic and governmental sources, with much of it emanating from the US, where the clinical trials infrastructure is more fully developed, especially for Phase I trials. Yet the vast majority of Phase I clinical trials are undertaken by contract research organisations (CROs), and we believe it is important that commentary and insights from that source be publicly provided as well. In addition to an overview of these two incidents and the resulting investigations, insight and considerations are offered from the viewpoint of a Contract Research Organisation (CRO) and an Institutional Review Board (IRB). Although conduct of clinical trials is time- and cost-intensive, common sense and good medical practice should prevail. Additional operational planning and documentation included in the approval package may prevent future incidents.

Overview of Phase I safety events

Study drug-related severe adverse events are extremely rare. However, during a 2016 Phase I trial to investigate the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) profile of BIA 10-2474, one healthy volunteer died.[1,2] The study drug, a fatty acid amide hydrolase (FAAH) inhibitor targeted neurological and psychiatric pathologies, particularly pain, and blocked the hydrolysis of endocannabinoids. The trial progressed through the single ascending dose (SAD) and food interaction parts without safety signals. However, in the multiple ascending dose (MAD) part, severe adverse events, leading to hospitalisation and subsequent death of a subject, occurred at the second-highest dose tested. The remaining five subjects in the same cohort were also hospitalised with adverse events of various degrees, but were later discharged.[2]

In 2006, Parexel International Corp undertook a first-in-human (FIH) trial of the superagonist anti-CD28 monoclonal antibody TGN1412 developed by TeGenero Immuno Therapeutics for treatment of immunological diseases such as rheumatoid arthritis and leukaemia.[3,4,5] When designing the study, Parexel/TeGenero followed the US FDA guidance for Phase I studies, which cites the International Council for Harmonisation (ICH).

The TGN1412 trial was a placebo-controlled, SAD study to assess safety, pharmacodynamics and pharmacokinetics of intravenously administered TGN1412 initially at doses 500 times smaller than that determined safe in animal studies.[6,7] The first group of eight healthy subjects was dosed at intervals of ten minutes (six received a single infusion of antibody and two placebo). The first subject experienced adverse reactions within 30 minutes, which became severe after one hour. Dosing of other subjects in the cohort continued. Within 50 to 90 minutes, all six subjects who received TGN1412 experienced a severe cytokine release syndrome resulting in multiple-organ failure necessitating hospitalisation in intensive care units. Although all subjects survived, long-term effects on their immune systems, increased risks of cancer, and disabilities including loss of toes and fingers remain. The circumstances of this study and recommendations for future FIH studies have been widely publicised.[6–8]

Similar to the Bial case, animal testing and other CD28-specific monoclonal antibodies provided no indication of adverse events for the TeGenero study,6 although there may have been an indication of swollen glands in two monkeys potentially signalling a safety concern.[9] Despite careful consideration of molecular properties,[10] adverse reactions are difficult to predict, and this incident illustrates the need for caution when interpreting negative animal data to predict human response.[6]

The TGN1412 trial investigation involved the UK's Medicines and

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Healthcare products Regulatory Agency (MHRA),[11] an Expert Scientific Group,[12,13] and the Royal Statistical Society.[14,15] Review of available information led to the conclusion that the event was not due to a drug quality issue and that nonclinical studies did not predict a safe dose for humans.[11,12]

The Joint Early Stage Clinical Trial Task Force recommended introducing an alternative initial dose-setting method (using the minimum anticipated biologic effect level [MABEL] instead of the no observed adverse event level [NOAEL]), as well as dosing only one subject on the first day, and staggering subsequent dosing.[16,17]

Phase I trial guidelines

Before the TeGenero trial, legal requirements for conduct of clinical trials in the EU were codified in Directive 2001/20/EC (to be replaced by Regulation EU No 536/2014), and concretised in European Commission Directive 2005/28/EC, detailing the implementation and principles of good clinical practice (GCP) and authorisation requirements. Except for ICH E6 (GCP), no clinical trial guidance has been codified into law. The requirements and recommended international standards for nonclinical studies supporting the conduct of clinical trials are largely addressed in ICH M3, which also describes approaches for determining adequacy of nonclinical data and estimating the FIH dose.

The TeGenero incident influenced guidance for the conduct of EU Phase I trials. The European Medicines Agency (EMA) released a concept paper on the development of a guideline for the nonclinical requirements to support early Phase I (EMEA/CHMP/SWP/91850/2006) within days of the incident that advocated the expedited start of Phase I studies, similar to the FDA Phase I guidance.[18] Subsequently, the EMA revised the considerations in its earlier concept paper and released guidance on requirements for FIH studies for potential high-risk medicinal products in March 2007. Uncertainties regarding mechanism of action, nature of the target and relevance of animal models create the potentially high risk of severe adverse events in FIH studies. This guidance recognised that higher risk warranted additional precautions including: determining the FIH dose using MABEL in addition to NOAEL; sequential initial dose administrations within each cohort; justification of non-sequential dosing and stopping rules for individual subjects, the cohort and the entire trial. Later in 2007, the EMA released a second guideline on identification and mitigation of risk in FIH trials.[18]

Current standards protecting study subjects

Ethics committees (ECs) and institutional review boards (IRBs) play an essential role in assessing measures to protect subjects in clinical research. They must determine whether risks to subjects are minimised and reasonable in relation to the anticipated benefits relying on nonclinical data and, if available, comparative drug intelligence from the sponsor or in the public domain (21 CFR 56.111). Assessing the risks in a Phase I study in which the risk profile is not well-established can be challenging.

Reviews of Phase I research should consider study design, starting dose, rate of dose escalation, time interval between dose escalations, data assessable before dose escalation decisions, number of subjects dosed simultaneously, standard assessments of subject eligibility criteria, and monitoring provisions. Informing subjects of potential risks is as important as informing them of the unknown and unforeseeable risks according to FDA guidance for IRBs, investigators and sponsors on informed consent.

The EMA guidance indicates that FIH trials should be conducted at facilities with appropriately trained investigators and access to emergency equipment. These facilities should also have well-documented and tested emergency management plans that include communicated expectations across the study team, the local hospitals and subjects, should an incident such as this occur. Timely and accurate transmittal of information to subjects is vital in these situations for them to be given the opportunity to determine if they wish to continue in the study. Therefore, IRBs and ECs need to assess the investigator and ensure sites are equipped with – or are reasonably close to – a hospital with appropriate emergency care trained staff, crash carts with rescue medications, 24-hour monitoring and up-to-date tested protocols for managing emergencies (eg, see FDA guidance for IRBs, investigators and sponsors on IRB responsibilities for reviewing qualification of investigators, adequacy of research site and of whether an IND/IDE [Investigational New Drug/Investigations Device Exemption] is needed).

Protocol evaluation

The Bial protocol and trial conduct were approved prior to initiation by the French regulatory agency, ANSM,[1] in June 2015, followed by the CPP Quest VI ethics committee (EC) in July 2015, with the first subjects enrolled the same month. Post-incident, a temporary specialist scientific committee (TSSC) formed by ANSM and the Inspectorate General for Social Affairs (IGAS) further reviewed the protocol and available data to better understand the mechanism of action and potential toxicity of BIA 10-2474. The TSSC concluded that nonclinical results supported proceeding with human testing.[19] The Bial protocol[1] was a standard Phase I study comprising multiple parts (SAD, MAD and food effect). The SAD part included a sentinel dose plan (24-hour assessment period after dosing two subjects before dosing the remainder of the cohort) only for the lowest dose; EMA guidance recommends sequential dose administration within each cohort with justification for non-sequential dose administration. The Bial protocol permitted staggered dosing in case of drug safety concerns. However, the eight subjects (six receiving test drug and two placebo) were given treatment doses at ten-minute intervals between subjects without staggering.[1]

Both EMA and FDA guidance recommend selecting the starting dose for Phase I trials by dividing the NOAEL by a safety factor, which was used for dose determination in the French study with no mention

of MABEL. The Bial protocol specified a fivefold increase between the first two doses, doubling for further cohorts until the dose exceeded 100 mg (human equivalent dose corresponding to the NOAEL in the rat).

Subjects were observed for five days for the SAD part and 14 days for the MAD part, based on the drug excretion times in animal studies. Inclusion criteria included normal neurological, cognitive and routine laboratory assessments and the absence of a history of clinically relevant neurological diseases and disorders. However, IGAS criticised the lack of specific neuropsychological and drug-abuse screening, and respective strict selection criteria.[20, 21]

The EMA guidance also specifies that the protocol should define stopping rules for individual subjects, a cohort and the trial. Bial's protocol included specific criteria for dose progression based on a review of safety and tolerability data through 48 hours after the last dose for six of eight subjects per cohort. The investigator, medical director, and medical monitor or representative of the sponsor would make a joint decision on progression to the next dose. The MAD group dose levels were determined after evaluation of available data from SAD and preceding MAD dose groups. The rules for not proceeding to the next dose required a frequency of adverse experiences on the greater end of the spectrum seen in most Phase I research: dosing was to be halted if drug-related severe adverse events (SAEs) were observed in at least four subjects or if clinically significant drug-related abnormalities were observed in six or more subjects.[1]

Ethical standards require that new information potentially influencing a subject's decision to continue participation must be provided to subjects in a timely manner. On 10 January 2016, the first subject in the second highest planned MAD dose was hospitalised after complaints of headaches. Other subjects in the cohort were dosed the next day. While it would have been impracticable to revise the written informed consent document, there is no evidence suggesting that the subjects were verbally notified of these events or given an opportunity to re-consent before dosing.[21,22]

Study-specific investigations

The TSSC released its reports in 2016[23,24] and concluded that BIA 10-2474 is an irreversible inhibitor with indication of off-target effects.[23–26] Bial's FAAH inhibitor had relatively weak, but long-acting activity (FAAH activity not recovered within 72 hours after almost complete product elimination from plasma) and little progressive effect – going from absence to almost total inhibition.

Appropriate animal toxicity studies conducted by Bial in four different species did not indicate any safety signals (EMA guidance requires use of two appropriate species, one being a rodent). However, on re-evaluation, the microscopic cerebral damage in mice, rats and primates was more extensive than previously thought, particularly at higher doses. Several higher dose group primates were euthanised for unspecified ethical reasons (the human equivalent dose was approximately 100 times that used in the trial). There were some pulmonary changes in beagles. Overall, the TSSC concluded that the nonclinical studies conducted were of good quality and the data did not preclude starting human trials.[24] However, the TSSC also raised questions regarding missing data and interpretation of results.

Although no aspects of the Phase I protocol prevented approval, the TSSC noted that: the trial was not immediately suspended; selection criteria did not require a neuropsychological assessment

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despite the molecule targeting the central nervous system; the dose increases between arms were inconsistent and too abrupt at high doses, and dosing continued beyond complete FAAH inhibition. The stereotypical profile and progression of neurological symptoms suggest a causal connection to the tested drug. Strikingly, toxicity was only observed in the MAD part at a high dose.[24]

The TSSC excluded drug administration or procedural errors, an infectious contamination, interaction with other products and common genetic/metabolic characteristics as causes for the severe adverse reactions, favouring the theory that the accumulation of BIA 10-2474 led to inhibition of other cerebral enzymes. The TSSC saw little likelihood of the toxic effect being due to endocannabinoid system stimulation by FAAH inhibition, anandamide or a metabolite. Instead, TSSC suspected toxicity was due to the test molecule binding to other brain cell structures facilitated by low specificity, multiple dose administration and gradual accumulation. Likely targets are the inhibition of other serine hydrolases or a harmful effect from the imidazole-pyridine "leaving group". It appears that BIA 10-2474 is ten times more active in humans than animals, which may in part explain the lack of toxicity in animals.[24]

The TSSC suggested that BIA 10-2474 would not fall under the EMA guidance for high-risk products. Data in the Investigators Brochure, which contained some errors, did not indicate a toxicity issue. The TSSC stressed that common sense and scientific logic must prevail when planning and executing clinical studies to protect human subjects, and recommended implementing the following into international Phase I requirements:[24]

- Demonstration of pharmacological activity, comparative if possible, reasonably predictive of real-life therapeutic efficacy before FIH studies
- Neuropsychological assessment during subject screening for test articles with central nervous system tropism
- Detailed, evidence-driven argument regarding the maximum dose proposed considering pharmacokinetics and pharmacodynamics
- Human subject safety should take priority over practical, economic and regulatory issues. Dose staggering is one aspect. Pharmacokinetic/pharmacodynamic data should be available for one cohort prior to commencing the next one
- Dose administration should occur in a staggered manner with smaller dose-increases at the higher level. Larger jumps between doses become problematic with non-proportionality of pharmacokinetics
- Open access to data (except company confidential information) from Phase I trials to increase human subject protection by

In July 2016, the EMA released a concept paper on the revision of the 2007 risk mitigation Phase I guideline, recognising that clinical trials have evolved to include a variety of other study parts such as SAD, MAD, food interaction, different age groups and early proof-of-concept or early proof-of-principle parts within a single trial protocol

enabling comparison of protocols, toxicity and clinical safety data to better inform regulatory agencies and ECs/IRBs when assessing applications.

The IGAS investigation commented on the continued dosing following the SAE, and the lack of confirming continued subject consent, and identified a miscommunication between the hospital treating the affected subject and the contract research organisation (CRO). Seemingly, the investigators in the trial were not informed of the worsening condition of the hospitalised subject. IGAS' final report[21] describes an oversight in reporting responsibility. Under French Law Article L.1123-10 CSP, new facts critically important for safety require immediate reporting to ANSM.

Consequential guidance updates

The EMA and ANSM are in the process of reviewing national and European practices for Phase I trials to increase subject safety including formation of a special unit at ANSM to address Phase I and II trials.[27–29] IGAS issued 19 recommendations including revision of the SAE reporting system and better organisation of alert management.[21]

The trial incident, considerations for trial subject safety and the lack of Phase I unit standards were also discussed by a panel at the DIA Annual Meeting in Philadelphia, suggesting uniform accreditation of all Phase I units (note that accreditation is already needed in Europe) and treating each adverse event as drug-related.[30]

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In August, the FDA announced that the toxicity observed in the BIA 10-2474 trial is unique to that compound and does not extend to other drugs in that class based on information available. Therefore, the FDA will be working with sponsors investigating FAAH inhibitors to determine the regulatory path forward.

Concluding thoughts

Subject safety is paramount for every clinical trial. Good medical practice is expected from all investigators and team members involved. Particularly when toxicity and severity of adverse reactions cannot be predicted from available data, good medical practice dictates a conservative approach to ensure subject safety.

A staggered dosing approach should be considered at least throughout the MAD trial segment, taking into account anticipated test article accumulation. It permits longer observation and improved communication regarding the health of subjects already dosed. In the Bial trial, the remaining subjects conceivably may not have been dosed, thus limiting the harm to only one subject.

Headaches are one of the most common adverse events in clinical trials, particularly in Phase I, because of the controlled environment, stress of artificial living arrangements and changes to daily routine and diet. However, if headaches are followed by more severe symptoms then all headaches in other subjects should be treated as warning signals and closely monitored, even if not identified as a signal by signalling tools. Currently, no information is available on the magnitude of the observed side-effects and monitoring.

TSSC offered guidance on dose range, dose escalation and dose skipping, and suggested using pharmacokinetic variability and extremes in addition to mean values when determining the next dose.[24] In addition, TSSC recommended Phase I studies to estimate the effect in humans and staggered dosing to permit signal detection. The final report advocated a particularly careful and sensible approach for higher doses (eg, dose staggering and reducing the increment between cohorts). Improved access to data of FIH trials would greatly support planning and assessment of future Phase I studies. In light of the FDA's comment regarding unique product-specific toxicity, it is sobering to reflect that, in both the Bial and TeGenero trials, had the SAEs not been so extreme, and made known to the public, different ECs/IRBs reviewing applications for other agents with the same mechanisms would not have been aware of earlier problems.

An additional consideration might be for sponsors to submit an operational plan with the trial application package to provide detailed information on the processes for possible eventualities and risks. Once approved, investigators would follow the operational plan. A deviation would be reportable to the EC/IRB, thereby providing some accountability for trial conduct.

Although the BIA 10-2474 trial met all regulatory and ethical requirements for approval and was conducted in an appropriately certified Phase I facility, it resulted in the death of one subject and left four others with potentially permanent disabilities. Phase I studies, particularly first-in-human, always have a risk of unforeseen adverse events even with a conservative plan and appropriate monitoring. We look to maximise human subject protection via implementation of current policies and recommendations to improve study design.

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