HOW TO ENSURE THE SUCCESSFUL DESIGN OF FIRST IN HUMAN (FIH) CLINICAL TRIALS

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FIH clinical trials are part of the exploratory early phase of drug development and represent a significant milestone in the clinical development of new medicines. Since only preclinical data are available to guide study design, including dose-selection, population, safety monitoring, appropriate expertise is critical to guarantee the safety of study participants as well as the quality of the data.

INTRODUCTION AND REGULATORY SUPPORT

There has been intense focus on the risks of FIH clinical trials by the regulatory authorities as a reaction to two serious incidents that occurred during the past ten years (e.g., Parexel in 2006, Biotrial in 2016). The European Medicines Agency's (EMA) "Guideline on strategies to identify and mitigate risks for first in human clinical trials with Investigational Medicinal Products" (2007) provides an overview of points to consider and is currently under review to further improve the safety of trial participants.
FDA guidance for industry, Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" (2005), outlines a process (algorithm) and vocabulary for deriving the maximum recommended starting dose (MRSD) for FIH clinical trials of new molecular entities with the purpose to ensure the safety of the human volunteers.

Another FDA guidance for industry 'M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals' (2010) recommends international standards for, and promotes harmonization of, the nonclinical safety studies recommended to support human clinical trials.

In 2005, the FDA recognized a new category of phase I studies called the 'Exploratory Investigational New Drug (IND) Studies'. This type of study is conducted at the beginning of Phase I to determine whether further human trials are worth pursuing. Exploratory IND studies are smaller and shorter than the usual Phase I study, typically involving no more than 10 subjects and lasting a week or less. The EMA also has guidelines on exploratory human studies as a 'Note for Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals' (2008).

Although many recommendations regarding the design, conduct and data analysis of FIH trials are available in the guidelines, we should not forget that "guidelines only describe the Agency's current thinking on a topic and should be viewed as mere recommendations". Because the objectives, uncertainties, and risks vary among different FIH trials, each FIH proposal must be evaluated individually.

The purpose of this article is to discuss some practical considerations for the design of FIH clinical trials, considering the current pharmaceutical and biotech drug discovery approach.

"ARE WE READY TO GO TO FIH?"

Drugs entering Phase I trials have approximately a 10% chance of getting to the market. As a result, the question to ask before thinking about a FIH is "How robust and complete are our pre-clinical study results to support a FIH administration?"

Reasons of drug development failure in Early Phase vary. Whereas in the 1990s one of the main reasons for attrition of drug candidates was a poor pharmacokinetic (PK) profile, currently more comprehensive knowledge, e.g, on PK and pharmacodynamic (PD) properties, is being gained at early development stage, leading to additional reason to halt further development [1, 2].

A continual reason of early drug failure is unexpected toxicity, which is closely related to PK properties of the drug, a fact often ignored. So, a more reliable assessment of how likely a project is to

fail at each stage would be helpful for companies when preparing their early clinical development plan.

In this context, pharmaceutical companies start to acknowledge the inadequacy of their animal models in guiding their drug development process, and write about this openly in scientific literature. In the beginning of this century, nine out of ten experimental lead compounds fail when entering the clinical phase because companies cannot accurately predict how the products will behave in human based on laboratory and animal studies. Thus, a serious challenge one faces in pharmaceutical research is the lack of translational ability of preclinical models to human clinical trials in terms of efficacy and safety, leading to a large attrition rate of INDs[1, 3].

Guidelines on pre-clinical development clearly explain different types of pre-clinical studies (in vitro and animal) required for testing products in human and for marketing approval of a pharmaceutical or biological IND. However, these should be viewed as a mere guidance, and nonclinical studies should be designed to represent an approach that is scientifically appropriate for the therapeutic indication and pharmacological properties of the IND.

CASE STUDY

To illustrate the importance of adopting a drug development program that tries foreseeing and countering attrition reason we refer to a recent case study. A drug under development for a central nervous system indication was stopped temporarily by the authorities because of unexpected non-linearity in PK during a FIH, requiring an explanation of the observation and an adequate investigational plan.

In this case, there was a solid package of in vitro and animal studies to motivate and allow the company to start a FIH trial. However, when looking in depth at the animal toxicokinetic data, the human non-linearity in PK could have been predicted. Additionally, despite the many preclinical experiments performed, some critical information was missing. This included:

- The high protein binding of the parent compound, while not investigated for the major pharmacologically active metabolite
- The high volume of distribution and tissue affinity which was not explained
- The enzyme inhibition/induction was studied but not the drug as substrate of enzymes nor for the metabolite

Finally, if animal data had been correctly analyzed and linked to each other, the non-linearity would have been concluded from these studies. Hence, the reason of this non-linear PK profile could have been deduced.

So in summary, the preclinical data set was neither complete nor adequate. As a consequence, the FIH trial was not correctly designed. Fortunately, when the PK issue was observed, the FIH was stopped. More serious safety issues could have occurred, such as unexpected toxicity, since the toxicity of major active metabolite had not been investigated sufficiently. Also, the therapeutic index was suspected to be narrow based on preclinical data analysis.

In this case project, in order to explain the problem first and, if justified, work on a further clinical development plan, the complete list of in vitro and animal studies needed was provided and modeling and simulation (M&S) services advised as support.

WHAT WILL BE THE BEST FIH DESIGN FOR OUR DRUG?

When choosing a design for FIH clinical trials, it is important to consider compound characteristics, such as level of risk, PK, PD, number of dose levels to investigate. It is also important to consider factors linked to timelines and logistics, such as:

- Number of doses per subject
- Number of subjects to be dosed per day
- Capacity of the clinical research unit to handle unexpected adverse events (AEs)
- Risk of dropouts with multi-period study
- Flexibility to changes in the study design as clinical data are generated

Some key design questions should be discussed well in advance with key staff from the research site (e.g. principal investigator, medical and pharmacology experts)[4, 5, 6, 7]:

What is the subject population?
A first choice to be made is on the subject population, which are usually healthy volunteers. This approach has the advantage of speed of recruitment, ease of scheduling cohorts, absence of potential confounding factors such as concomitant medications (CM) and high tolerability. Historically, the use of patients has been commonplace for oncology agents and agents with a narrow therapeutic index (NTI). The decision whether to conduct a FIH trial in healthy volunteers or patients should be carefully considered and fully justified on a case-by-case basis.

What is the starting dose for FIH?
The most critical decision will be to determine the starting dose for FIH. Obviously, the dose needs to be low enough to avoid toxicity at initial dose and high enough to allow reasonably rapid attainment of Phase I trial objectives. There are different methods to estimate the maximum recommended starting dose (MRSD):

- No observed adverse effect level (NOAEL), also called FDA approach
- Minimal anticipated biological effect level (MABEL) approach
- Using M&S
- Similar drug approach
- Microdosing or other alternative approaches

Determination of starting dose for FIH studies is not easy, and a case-by-case approach may be more appropriate. In any case, a conservative and consistent approach is required because safety is the most important factor.

What is the dose escalation/increase?
The following question will be on dose escalation/increase, where the common approach used is to apply a safe multiplying factor, i.e. factor 3 for the first 2 or 3 steps, then factor 2 for subsequent 2 steps and factor 1.5 at the end. However, review of safety PK and PD data should be done throughout the ongoing clinical trial, and the decision

to escalate to a next dose or to stop escalation should be made according to predefined criteria.

Will sentinel subjects be included?
Once the development team has agreed the compound's level of risk, they should consider whether the FIH design will include use of sentinel subjects or not. Dosing a limited number of subjects (often only one with an active compound) before the remainder of the cohort minimizes overall risk and is recommended by EMA and FDA for high risk compounds.

Will there be randomization, blinding and a placebo control?
Even if there is no regulatory need, randomization, blinding and a placebo control will minimize the potential bias in reporting adverse events and assessment of laboratory abnormalities during the course of this study.

What design option will be used?
The choice of design option should be tailored to the needs of the specific compound and development program: parallel, cross-over, sequential cohorts or interlocking cohorts. The main factors to consider when choosing the design, concern the compound and the logistics aspects.

What protocol approaches will be chosen?
Different protocol approaches may be chosen: conventional, umbrella, adaptive or adaptive umbrella. In all cases, the advice will be to be flexible within limits, cut away the unnecessary and focus on what is needed. The objective should be to get better information in less time and at lower research cost.

Are FIH based in experimental and scientific rationale?
Some authors mention that "FIH dose escalation trials are still conservative and seem to be based more on habit and preferences than experimental and scientific rationale" and they encouraged the scientific community to optimize these trials in healthy volunteers with statistical methodologies. For example, the Bayesian adaptive method combines a flexible number of cohorts and a flexible number of subjects per cohort with simple empirical stopping rules to increase performance and facilitate implementation [7].

A FIH STUDY EXAMPLE

As an example, a new tyrosine kinase inhibitor with favorable pre-clinical results was ready to go for a FIH. A FIH exploratory study design with primary objectives of safety/tolerability and PK needed to be developed.

The population of healthy volunteers (HV) was chosen since the biomarker (tyrosine kinase inhibition) can be obtained, no target related safety testing is needed and no high doses required.

The MRSD was calculated using the NOAEL method and compared to the value obtained by alternative MABEL method.

A conservative dose escalation schedule was chosen, since a narrow therapeutic range is suspected based on pre-clinical toxicology studies.

Sentinel groups were suggested in the high single ascending dose (SAD) and all multiple ascending dose (MAD) dose groups.

A long enough in-house stay period was planned based on plasma half-life and, because of delayed toxicities, observed in preclinical studies.

Sequential cohorts within an adaptive umbrella design were chosen, including the additional assessment of two different oral formulations in a cross-over way in one of the SAD cohorts.

CONCLUSIONS

One of the most important steps in drug development is the FIH trial. Safety is paramount but in addition all valuable information on drug properties needs to be collected. Therefore, all the required expertise should be brought together to analyze available preclinical data, use the existing scientific literature, consult information on similar drugs, and implement medical/clinical aspects, without forgetting the possibility of advanced PK/PD Modeling & Simulation support.

SOURCES (except FDA and EMA Guidances):

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