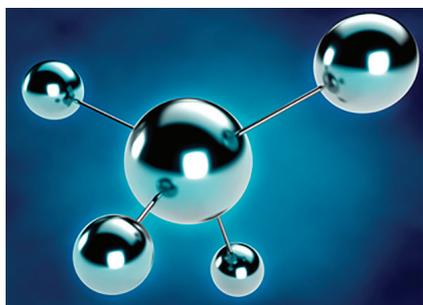


ANALYZE THOROUGHLY ALL PRE-CLINICAL DATA AND OPTIMIZE THE STUDY DESIGN

EARLY PHASE CLINICAL TRIAL **MAXIM #1**



When planning a first in human (FIH) trial, a carefully tailored design is mandatory for safety and further decision making. The design should not be based on the minimum regulatory requirements, or even just “good habits,” but on bespoke scientific rationale. Depending on the pharmacological and safety profile of the drug, broader pre-clinical data may be needed than those required by regulators to ensure not only safety, but also to increase the potential success

of the development. Most FIH trials are randomized, double-blind and placebo controlled, but many other protocol aspects need to be decided, based on in pre-clinical data only:

- Should the compound be tested in healthy volunteers or patients?
- How many dose groups and subjects are needed?
- Will these be run sequentially, or in cross-over?
- What is a safe starting dose and dose escalation scheme?
- Safety is a first objective, but what else is important from a pharmacokinetic (PK) and pharmacodynamic (PD) point of view?
- To maintain safety, what assessments and precautions are needed? Sentinel dosing is often recommended and stopping rules should be defined.
- Which schema of PK/PD sampling should be chosen?
- How long should the follow-up be?
- When should an interim analysis be done, and what should be included?
- Is there added value in using an integrated protocol testing a food effect, drug interaction or special populations?



CASE STUDY 1

The importance of pre-clinical data when designing a FIH study.

A drug under development by a small biotech company for the treatment of neurodegenerative diseases was stopped temporarily because of unexpected non-linearity in PK during the FIH trial.

SGS was contacted by the biotech company to support the finding of a scientific explanation, and to assist in developing an adequate investigational plan.

There was a solid package of in vitro and animal studies to allow the start of 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 pre-clinical experiments that had been performed, some critical information was missing, including:

- High protein binding of the parent compound was seen but not assessed for the major pharmacologically active metabolite

- Despite a high volume of distribution, tissue affinity was not investigated
- The capacity of the drug to inhibit or induce hepatic enzymes was studied, but not the drug as a substrate, or the metabolite
- Interaction of the drug and its metabolite with intestinal and other transporters was not assessed

If animal data had been correctly analyzed and linked, the non-linearity in PK could have been deduced.

At SGS, we concluded that the pre-clinical data set was neither complete, nor adequate, hence the FIH trial was not correctly designed. Fortunately, once the PK issue was

observed, the FIH trial was stopped. Serious safety issues could have occurred since the toxicity of the major active metabolite had not been investigated sufficiently. Additionally, based on the pre-clinical data analysis, the therapeutic index was suspected to be narrow.

To explain the problem and to work on a potential clinical development plan, a comprehensive list of additional in vitro and animal studies needed was provided. Furthermore, SGS-ExpriMo modeling and simulation (M&S) services were involved to assist in improved design development for a new FIH study.



CASE STUDY 2

How a complex but correctly developed design leads to a successful FIH trial.

A small biotech company wanted to start a FIH study with its new compound, indicated for the treatment of different age-related orphan diseases.

The company worked with SGS to perform an adaptive umbrella FIH study. All pre-clinical work was completed and analyzed before initiating the study design. The objectives were to determine safety, PK, and possible PD, as well as to evaluate the influence of food and age on product PK (and safety) profiles.

The FIH study was divided into two parts performed exclusively in healthy volunteers. Part 1 was a single ascending dose (SAD) study including the evaluation of both food and age effects. Three different alternating cohorts were included. Estimation of the starting dose was based on a no observed

adverse effect level (NOAEL) and a sentinel dosing approach was used. Wash-out period, dose escalation and timing of all samplings and assessments were calculated based on all available pre-clinical information.

Analysis of the Part 1 interim results enabled the determination of the doses and dosing regimen to be tested in the Part 2 multiple ascending dose (MAD) study. Since the data showed no difference between fed and fasting administration, just one of these could be selected for MAD. Additionally, no influence of age in terms of PK and safety was observed in SAD part, therefore, the MAD part was undertaken only on elderly

healthy volunteers, these being the age group of one of the targeted therapeutic indications. Dose escalations in Part 2 were calculated using the PK and safety data generated at every precedent step.

This adaptive umbrella protocol offered time savings and improved cost benefits. A clear protocol is an absolute requirement for approval and success of such approach. In addition, the choice of an experienced site is mandatory to successfully conduct such complex multistep FIH studies.

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