



Maxims for Early Phase Trials

E-BOOK

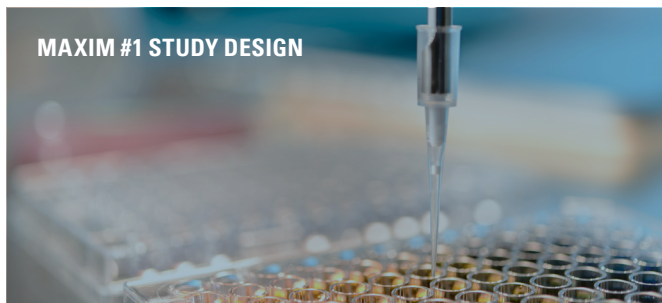
SGS

Early phase clinical trials Maxims

Over the last 40 years and thousands of early phase trials execution, SGS has acquired a unique expertise in complex early phase clinical trials.

From drug development consultancy, preclinical data analysis, formulation and manufacturing, study design and first in human (FIH), to exploratory trials and proof of concept (POC) studies, we are pleased to share, through the following Maxims, the early phase clinical trial drug development fundamentals.

MAXIM #1 STUDY DESIGN



MAXIM #2 REGULATORY PROOFED



MAXIM #3 SGS PACE



MAXIM #4 RISK ASSESSMENT



MAXIM #5 PATIENT RECRUITMENT



MAXIM #6 INNOVATIVE TECHNIQUES



MAXIM #7 PROTOCOL COMPLIANCE



MAXIM #8 INSPECTION READINESS



MAXIM #9 MEANINGFUL DATA



MAXIM #10 BUILDING BRIDGES



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 with 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, we optimized the design 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.



Regulator-proof your study

Early phase clinical trial Maxim #2



Working closely with regulators is a key strategy for successful drug development, not a barrier to be sidestepped or overcome. Early and frequent consultation with regulators helps to avoid surprises during all phases of product development, particularly in the earlier phases.

Building regulatory advice into a trial program is an effective strategy to mitigate the regulatory risk inherent in product development and improve the likelihood of early product approval.

Regulators in Europe, the United Kingdom and the United States have created tools to help developers to tailor research and development programs to meet regulatory needs:

“the request for scientific advice”.

Requesting scientific advice from the right regulatory body at the right time has become an essential tool to guide product development and to have answer on many aspects of the development program:

- Have I chosen the correct and most appropriate animal model? And if there is no pre-defined animal model, is my proposal appropriate?
- Is the manufacturing process well defined and appropriate?
- Have I well classified my IMP? Chemical, biologic, vaccine, ATMP, herbal?
- Is my FIH starting dose well calculated and are the escalation steps adequately chosen?

- Have I selected the appropriate comparator for my patient studies? Placebo/other treatment?
- Are my trials sufficiently statistically powered?
- Do I have sufficient data to start pediatric trials?
- Am I able to replace certain trials (TQT, Drug Drug Interaction) and include this in an integrated first in human protocol?

Requests for advice – and responses – can be multidisciplinary and focus on a broad range of questions from product quality to acceptance of novel study designs, pharmacokinetic/ pharmacodynamic considerations, biomarkers, hard versus surrogate endpoints or any other scientific question. Advice is also available on quality, nonclinical and clinical issues as well as pediatric issues in parallel with FDA, the World Health Organization (WHO), payers, patients and academic stakeholders.

The European Medicines Agency (EMA) provides financial incentives for micro, small and medium-sized enterprises (SMEs) to seek scientific advice early and often. SMEs can expect fee reductions of up to 100%, as can larger companies seeking advice on products with orphan designation or products intended for pediatric-only use.

With regard the US Food and Drug Administration (FDA), the agency is committed to multiple iterative meetings with sponsors during the preclinical and clinical phases of development.

CASE STUDY 1

The Importance of discussing non-clinical and manufacturing strategy before initiating a phase I trial Scientific Advice for phase I trial for a diabetes product

A US Biotech company contacted SGS to advise them on their non-clinical and manufacturing plan, as well as their FIH study outline, and to assist them in a Scientific Advice meeting with a European National Authority, for their innovative diabetes product.

SGS reviewed the available in vitro and in vivo non-clinical data as well as the proposed GMP manufacturing plan. A number of questions for the agency were prepared and the briefing book developed. An innovative study design based on an approach usually used in oncology was also prepared.

During the Scientific Advice process the following was discussed:

- Validation of testing strategy and analysis steps in the manufacturing program, particularly the adventitious agent testing
- Approval for the GLP non-clinical program, in particular for the choice of animal model, as there was no ‘standard’ animal model available for this type of compound
- Design of phase I trial, where the ‘oncology based’ design was validated by the regulator
- Agreement by the regulator the FIH study can be performed in patients

The successful advice allowed the company to start its non-clinical program quickly and assured a smooth approval of the FIH trial.



CASE STUDY 2

Agreeing with regulators on a 'late phase' regulatory strategy for a European biotech company with a compound in phase IIa in women's health

SGS worked with a European biotech company with a women's health compound in phase II, to design the phase IIb/III regulatory strategy and to have it validated by both the FDA and the EMA. The regulatory strategy was designed and worked out together with the sponsor and their license partner.

An agency meeting with both the FDA and EMA was organized to discuss:

- Set-up of the further clinical program
- Assessments to be conducted in the phase IIb study
- Further non-clinical testing, in particular carcinogenicity testing
- Development plan for specific sub-indication

The Agency meeting with both the FDA and the EMA gave a favorable result, as a clear outcome for phase IIb program was received and a more limited number of assessments for phase III was obtained.

The clear message from regulators in both Europe and the United States is that it is never too early to seek scientific advice. Whether the questions deal with broad issues of study design and appropriate indication/study population or more focused issues of chemistry, manufacturing and controls for a new product class, earlier agency consultation is better. Seeking and incorporating scientific advice into the product development program is an effective tool to reduce the regulatory risk inherent in product development and maximize the likelihood of product approval.



Navigating drug development: streamlining efficiency with SGS PACE

Early phase clinical trial Maxim #3



In the intricate landscape of drug development, the progression through clinical trials holds paramount significance. Navigating this terrain requires the establishment of robust strategic partnerships with specialized entities, including Contract Development and Manufacturing Organizations (CDMOs), Contract Research Organizations (CROs), and regulatory consultants. This challenge is particularly pronounced for smaller biotech firms contending with limited resources and the intricacies of pipeline management.

In the pursuit of expeditiously delivering innovative products to patients, especially those requiring accelerated FDA approval, the hurdles can be extremely tough. Overcoming these challenges entails streamlining the supply chain and engaging partners with specific expertise, ranging from CDMOs for formulation and manufacturing, to CROs equipped with Clinical Pharmacology Units for pivotal First-In-Human (FIH) and Proof-of-Concept (POC) studies and bioanalysis labs to develop new methods and to analyse the samples.

Coordinating multiple partners, reconciling conflicting timelines, and ensuring effective communication present significant challenges. These hurdles necessitate an agile and resilient approach for a seamless journey from the discovery phase to commercialization.

To address these intricate needs and challenges, innovative solutions have emerged. Beyond conventional services, biotech and pharmaceutical

companies are seeking comprehensive consultancy from the initial contact, leveraging the expertise of formulation, bioanalysis, regulatory and clinical professionals. This integrated approach ensures that companies receive multidisciplinary advice and support throughout the entire development process.

One such innovative model is SGS PACE (Product Accelerated Clinically Enabled). This model provides companies with a single point of contact, a dedicated program manager, and therefore a streamlined communication, offering seamless assistance from early preclinical stages to Proof-of-Concept. The collaboration between client teams and SGS experts results in custom strategies, efficient timelines, and cost-effective solutions tailored to specific needs and budgets.

The true value of SGS PACE lies in its ability to simplify complex project coordination. The consultancy service establishes a clear roadmap at the project's onset, outlining strategies for formulation, bioanalysis method development, manufacturing, and clinical development. This comprehensive plan, enriched with different scenarios, estimated timelines, and budgets, empowers clients to make well-informed decisions throughout their drug development journey. By tapping into SGS's considerable expertise, SGS PACE ensures successful project execution without the intricacies of managing multiple partners, providing clients with confidence as they embark on their drug development endeavors.



Managing time & risk – remember Murphy and Hofstadter

Early phase clinical trials – Maxim #4



Early phase clinical trial protocols tend to become more and more complex, focusing on gaining as much scientific insight as possible. Multiple objectives are embedded into one single design. Today, in addition to safety assessments and pharmacokinetic (PK) sampling, pharmacodynamic (PD) read-outs are nowadays implemented as standard in phase 1 protocols. These PD assessments can come in different forms: blood or other body fluid samples followed by special assays, imaging or specific functional testing.

As a result, time critical PK and PD sampling and PD testing need to be integrated at specific post-dose timings. Also, some of the PD tests require the inclusion of specific populations related to the targeted disease. As a consequence, operational execution of early phase trials has become even more challenging.

Although a “perfect” protocol may have been created on paper, many study aspects need to be evaluated from a practical point of view. These include:

- The recruitability of the exact study population
- Investigational Medicinal Product (IMP) preparation steps
- The use of sentinel dosing groups
- Sample-handling processes
- The frequency and types of assessments

Despite timeline pressures, clear communication on content and operational feasibility is key to avoid issues. During a feasibility review and subsequent trial preparation, all worst-case scenarios need to be considered – as the laws of Murphy and Hofstadter also apply to clinical research. With some complex assessment schedules, it is often best to organize a mock test run.

CASE STUDY 1

The importance of a thorough feasibility review

SGS reviewed a multiple dosing study designed to assess safety, pharmacokinetics and age effect.

The draft protocol of this multiple dosing study contained three different age groups: 18-50y, 65-75y, and >75y. After careful review, the team defined following criteria as not feasible:

- Subjects among different age groups needed to be weight-matched
- Some of the normal ranges for vital signs and laboratory values were too strict for the oldest age group
- Concomitant medication taken by elderly subjects needed to be taken into account.

- The study required many ambulatory visits, creating extra burden for those in the oldest age group >75y
After an open discussion with the client, important compromises were implemented, without jeopardizing the scientific value of the data nor the recruitment and retention of the older population. In summary:
- The weight matching was phrased more flexibly allowing a slightly bigger deviation
- Normal ranges were changed, where possible, for safety and some concomitant medication were allowed
- Importantly, the revised protocol contained flexibility for the eldest group to choose between in-house stays or ambulatory visits



CASE STUDY 2

The importance of thorough risk assessment and study planning.

A US Biotech contacted SGS to perform a phase 1 study in healthy subjects with a seasonal allergy.

After a single ascending dose in healthy volunteers to assess safety and pharmacokinetics, the study included a second part to assess pharmacodynamic effects in healthy people with a seasonal allergy. The pharmacodynamic tests consisted in a nasal challenge to provoke rhinitis, a skin prick inducing a flare and a food challenge inducing oral allergy symptoms. After a nasal challenge, different read-outs for rhinitis severity were combined using a symptom score card, peak nasal inspiratory flow and nasal aspirate for inflammation analyses.

Careful review of the protocol identified some practical risks:

- As many allergic people have more than one allergy, the in- and exclusion criteria could not be too restrictive so as to exclude all co-allergies
- As people could not have rhinitis symptoms at baseline, the study needed to be conducted outside the allergy season, putting some time constraint on the study timelines

- People needed to respond to the nasal challenge to a certain extent to be able to measure an IMP effect, but putting the response criteria to severe would lead to a high screen failure rate
- The pharmacodynamic tests involved many assessments that were time critical, time consuming and needed to be performed in a standardized way

Following measures were taken:

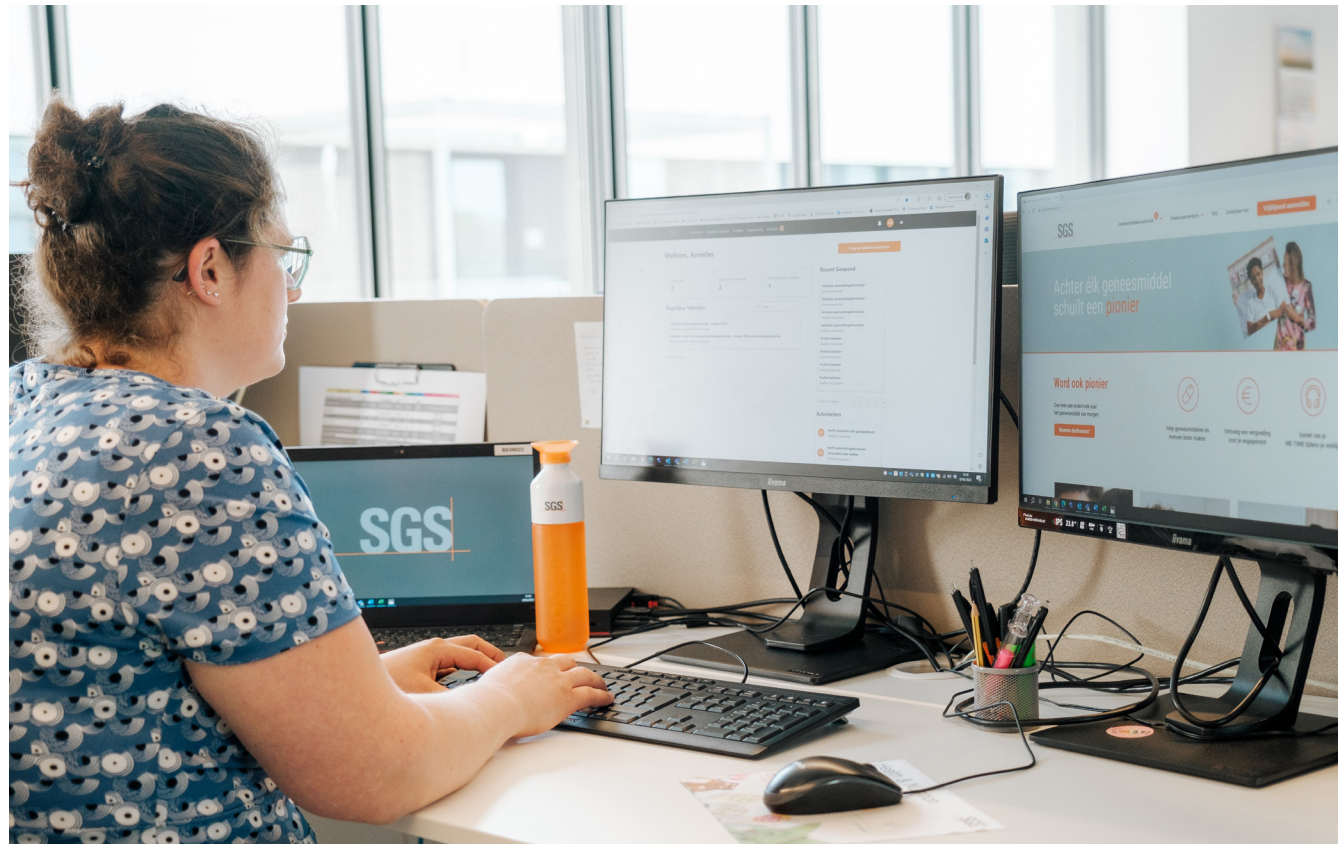
Careful review of the protocol identified some practical risks:

- A workable solution was found to describe eligibility criteria, allowing those allergies that would not cause rhinitis, or could be avoided during the study
- To reduce the risk of not finishing the trial before the allergy season due to unforeseen set-backs (remember the two laws!) the trial was conducted at 2 sites, recruiting in a competitive way
- The criteria for challenge responses were evaluated together with a local specialist to predict the screen failure rate
- Staff were trained to perform the pharmacodynamic tests by a specialist and a dummy run provided real-life estimates of the timings



Recruiting the studied population in a timely manner

Early phase clinical trials – Maxim #5



Recruitment and retention issues result in trial delays and costs and may potentially undermine trial results. Every clinical trial phase is facing its own specific hurdles. The fact that early phase trials do not offer therapeutic benefit for the subjects is a specific drawback. Phase 1 trials are typically performed in healthy volunteers, whereas from phase 2 onwards patient populations are needed. However, special populations and patient cohorts are increasingly included early on.

Subject enrollment is a key driver of clinical trial success but remains one of its biggest challenges. The exact challenges depend on the trial phase, the population specifics and study design details.

As phase 1 trials mainly involve healthy volunteers (HV), increasing general awareness, on safety for example, is paramount. Besides that, the incentive for HV to participate remains mainly a financial one.

For patients, the situation may slightly differ. Confronted with disease, they tend to be willing to help innovation. Nevertheless, fear of side effects and of getting a placebo (hence losing time to get treated) often deters them. As early phase studies typically contain frequent visits and assessments, the overall burden and time spent also becomes a decisive factor. Physicians play an important role in identifying and “convincing” eligible patients, but they are often dealing with similar constraints. In addition, eligibility

criteria are more restrictive in early phase. Hence, finding participants may be a little like looking for a needle in a haystack.

To assure recruitment in a timely manner it is important to tackle these hurdles at all stages of trial preparation and execution and respect the following measures:

- Simplify the protocol if possible to lower the burden for patients and physicians
- Evaluate eligibility criteria to identify overly restrictive components
- Identify factors that impact recruitment, both positively and negatively
- Foresee a realistic recruitment period, leave some flexibility
- Include experienced sites with demonstrated patient access and dedicated recruitment staff
- Foresee recruiting activities: advertising, social media, call centers
- Provide clear information to patients and physicians
- Keep close contact with sites in prescreening period
- Keep clinical trial investigators motivated by via frequent communication and assistance
- Ensure contingency measures that can be implemented quickly

CASE STUDY 1

How applying the right contingency measures can save patient recruitment

In a combined HV/patient study run by SGS, an experienced patient site was struggling with recruitment. By rapid implementation of a pre-study contingency plan, the study still met the initially agreed upon study timeline.

A European biotech company outsourced a combined single and multiple ascending dose study in HV and moderate-to-severe atopic dermatitis (AD) patients.

SGS Clinical Pharmacology Unit conducted the HV part as a single site. Two patient sites in Eastern Europe with experience in early AD trials, and reliable partners to SGS, estimated they could recruit the 24 patients in six months. As a pre-study contingency measure, SGS suggested to include their patient site in Hungary as a third site.

During the first patient cohort, one of the sites had unexpected recruitment difficulties, despite their proven track record in AD studies.

The project manager and operational team immediately undertook action:

- Follow-up with the site was intensified to investigate the patient pipeline and recruitment forecast
- The potential to increase the committed enrolment target was discussed with the other two patient sites
- The Hungarian site substantially increased their network through advertising in relevant patient groups and approaching additional collaborating specialists. Consequently, they could triple their initially committed enrolment
- The in-between cohort time was maximally compressed

As a result, the significant recruitment delay from the first cohort was entirely cleared. Having sites with dedicated recruitment staff proved to be an enormous added value to boost recruitment capability. The study ended within a week of the initially foreseen date.

We conclude that even experienced sites can encounter unexpected recruitment issues, especially in acute indications and indications with seasonal variations. Candid communication with all sites and implementation of contingency measures can be critical to rescue a trial.



CASE STUDY 2

Enrollment hurdles when looking for a “niche” population

SGS was contacted to assist in a phase 1b multicenter study in patients with Major Depressive Disorder (MDD).

The trial population consisted patients with early onset MDD that had to reach a certain level of symptom severity but were not allowed to take any antidepressant drugs.

While evaluating this request, the following challenges were identified:

- Many patients with early onset MDD would not yet have consulted a physician.
- Those seeking help are contacting their general practitioner, not a psychiatrist
- People are often reluctant to divulge their symptoms to others
- MDD represent a rather fragile population that might fear participation in a phase 1 trial
- Ethical considerations with the use of a placebo arm

- Availability of participants due to the need to two overnight stays of two consecutive nights

The following solutions were implemented:

- A public advertising campaign was set-up (social media, websites, newspapers) referring to a call center.
- An expert psychiatrist was involved from screening onwards to guide participants.
- Awareness was increased with accurate and accessible information
- The trial was executed at a first-rate medical facility
- Financial remuneration (for time spent and overnight stays) was provided to the “patient-volunteers”

Recruitment for this trial remained slow and difficult. The main reason being the required level of symptom severity (without any medication) which was often just not reached. Although 14% of the population faces depression, the patients needed in this trial represent only a very small niche.

This case study stresses the importance accessing “patient-volunteers” by making accurate, understandable information accessible.



Innovation powers research & development

Early phase clinical trials – Maxim #6



The development of new pharmacological compounds can be lengthy and very costly, with many failure risks even during later phase clinical trials. To estimate a drug's clinical potential, information on safety, pharmacokinetic and pharmacodynamic outcomes are all paramount. Via innovative techniques critical information on a compound's dose-response effect can be acquired in the early clinical phase.

Drug development programs are increasingly incorporating translational methodologies in early phase trials to gain more decisive information on a compound's pharmacodynamic potential alongside its safety and pharmacokinetic profile. These include the use of biomarker technologies and human challenge models.

Simply put, a biomarker (contracted from biological marker) is any objective measure that reflects a biological process. In relation to pharmacological responses, biomarkers aim to provide evidence of target engagement or signals suggestive of efficacy. Examples are: molecular assays for receptor occupancy or pathway activation, specialized imaging technologies and functional testing.

The implementation of a phase 1 clinical trial requires meticulous evaluation and planning in terms of the equipment needed, the expertise and training required of staff, and labor intensity.

Human challenge models are designed to generate symptoms and mimic a disease state in an otherwise controlled environment. Testing an investigational compound in such a setting generates the first evidence of efficacy. Examples are: ketamine challenge to mimic psychosis, LPS challenge for systemic inflammation and viral disease models.

In general, similar planning rules apply to all: safety, in-house expertise and needed equipment are crucial.

Viral challenge studies are extra demanding because of the potential contagious risk.

In summary, following items must be evaluated when considering a challenge study:

- The research question must be clearly justified and weighed to alternative methodologies
- The proposed methods must be appropriate and provide a meaningful, valid answer
- The method must be as safe as possible and appropriate management of possible risks in place
- Selection of study participants must be justified and safe
- Rigorous consent procedures must ensure full understanding
- Payments must not represent undue influence nor be based on possible risk
- The site needs to be adequately equipped
- The team needs to have the required expertise, experience and accountability
- In case of viral agents, harm to contacts and the environment must be minimized and managed. Given its controversial nature, public involvement and agreement might be needed
- The consequences of the challenge, the induced disease, should be taken care of and as such have been resolved or brought to a level of minimal sequelae (e.g. one can have built up immunity because of the challenge agent, but should not have any sign or symptoms of ongoing disease)

When confronted with more challenging and complex phase 1 trials it is necessary to carefully evaluate all safety, ethical and practical constraints.

An experienced and well-equipped unit is required to accommodate these trials.

CASE STUDY

Start-up of a malaria challenge modelling at the SGS clinical pharmacology unit (CPU) in Belgium



SGS was approached to perform a phase 1b trial assessing a potential chemoprotective agent in a validated controlled human malaria infection (CHMI) model using direct venous inoculation of *P. falciparum* sporozoites.

The SGS CPU is experienced in different challenge models including influenza inoculation, but the proposed malaria model had never been implemented before.

In close collaboration with the client, a thorough risk assessment was performed defining and managing potential issues:

- Expert opinion was obtained from study set-up onwards via the Global Health Institute of the University of Antwerp, to guide the overall study safety, specifically treatment and follow up
- of participants
- Risk of parasite transmission to staff and general population was assessed to be very limited to non-existing (transmission approx. 0%) because of:
 - The absence of sufficient numbers of the only known vector of malaria in Belgium (*Anopheles plumbeus*)
 - The average ambient temperature of the Belgian region being below the minimum temperature required to support *Plasmodium* spp. Therefore, complete isolation of inoculated participants was not deemed necessary

- The only risk for transmission would be needle stick injury. A clear treatment algorithm, dependent on time of inoculation with regards to life cycle and transmission of *plasmodium falciparum* was created to adequately protect staff in case such accident would occur
- Preventing or limiting any symptomatology as a result of *plasmodium* exposure:
 - Using golden standard testing techniques with high sensitivity to detect parasitemia at incredibly low counts could limit, or even prevent occurrence of symptomatology in subjects, due to quick initiation of standard of care treatment
- Theoretical possibility of certain lag time due to partial chemoprotectivity of IMP: importance of adjusting follow up period accordingly, including standard of care treatment
- Because the transmission risk was marginal, the participant could, in theory, leave the unit after inoculation and return for ambulatory assessment of safety, malaria signs parasitaemia. Upon confirmation of positive parasitaemia the subject would receive rescue therapy while being monitored daily at the clinical unit until treatment success. However, the SGS medical team decided in-house stay was warranted from inoculation onwards for a number of reasons:
 - Due to the uncertainty of when parasitaemia would develop and allowing for direct supervision of primary intake of rescue treatment
 - Being in the unit with medical supervision reassured the subjects of optimal safety precautions being taken, which proved to be important for their peace of mind (with regards to recruitment)
 - To eliminate the risk of inoculated subjects dropping out and losing them for further follow up
 - Safety monitoring in relation to the IMP taken was an extra reason to keep the participants in the unit

As during this risk evaluation, all concerns were addressed properly, with adequate contingency measures, the study was deemed feasible and successfully started.

In general, this example shows that although certain innovative models may appear risky or even not feasible at first sight, careful evaluation and planning may prove otherwise.

Respect the rules of the protocol

Early phase clinical trials – Maxim #7



The clinical trial protocol, as a detailed outline of a clinical study, must be rigorously followed by the clinical trial team, not only to be in line with regulations, but also to avoid harm to participants and erroneous conclusions. As early phase trials are becoming increasingly complex, the risk of protocol deviations, necessary amendments, incorrectly gathered data and even inaccurate conclusions may increase.

Per ICH-GCP, the protocol is “the document that describes the objective(s), design, methodology statistical considerations and organization of a trial”. Simply, it describes what you will do and how you will do it. It should be designed in such a way that it ensures participants’ safety and solid scientific answers at the same time. Flaws in the protocol will lead to deviations, violations, amendments and even to missing, invalid or uninterpretable data.

The development of a solid protocol is a stepwise process and involves various stakeholders. First, the outline of the study must be clear, defining the specific research question(s) and choosing an overall design. This step includes decision making on objectives, population (healthy volunteers or patients), and overall design (trial phase, number of cohorts, parallel or alternating, placebo-controlled).

STUDY PROTOCOL START DOCUMENT (PSD)

Once the scene is set, the study concept must be captured in a study PSD that must include the following elements:

- Objectives, to be defined as primary, secondary and exploratory.
- Endpoints for every objective, with corresponding measurements and statistical methods.

- Design aspect: randomization, use of placebo, blinding, cohorts and study parts.
- Population: number of participants and main selection criteria.
- Details on the test product: doses and route of administration.
- A time and event schedule capturing assessments for subject safety and data collection.

Thorough decision making during PSD development is paramount and requires input from clinical pharmacology, medical, regulatory, statistical and operational experts. Discussion points should be resolved at this stage to avoid issues at the stage of full protocol development, when the various required sections are further detailed in the official document, or even during study conduct.

COMPLEX STUDY DESIGNS

Early phase studies nowadays tend to formulate multiple objectives in one “umbrella” study. It is standard practice to combine cohorts for single ascending dosing (SAD) and multiple ascending dosing (MAD) in the same first-in-human (FIH) trial. Often a cohort to explore a food effect or to obtain a proof of pharmacology in a specific (patient) population is also included. As such, not only the dose escalation process but also the progression to the next study part(s) needs to be described. Decision making during the trial needs to be carefully determined: who will make the decision to proceed, when and based on which data?

In combined early phase protocols, some decisions can only be made after analysis of the collected data.

To avoid the need for protocol amendments after every decision, these aspects can be described in a flexible way. Examples of adaptive features are: the exact dose levels, the number of cohorts, the regimen for multiple dosing, assessments to be added or omitted, etc. As long as the changes follow what is written in the protocol, substantial amendments are not warranted. The advantage of combined, adaptive protocols lies in gaining efficiency, time and cost.

Following rules apply to make adaptive designs regulatory proof:

- Adaptations must be described in detail
- Clear boundaries must be set
- The decision-making process, including rules for stopping, must be clear

Examples of crucial decisions and possible pitfalls in a complex FIH synopsis are:

- The starting dose and maximum exposure need to be described and explained. Both the clinical pharmacology and medical expert must ensure that the dose range is safe and sufficient to make decisions on later dosing regimens.
- The exact dose escalation is to be decided, based on safety data, but collected pharmacokinetic (PK) and pharmacodynamic (PD) data may be needed as well. The compound's pharmacological profile will determine the exact data needed before going ahead. Dose levels can be left flexible in the protocol, but boundaries and decision making must be described. Importantly, enough time needs to be foreseen between cohorts and study parts to be able to obtain and analyze the required data.
- The exact population needs to be defined by in- and exclusion criteria. FIH trials often enroll healthy volunteers, but it is an emerging trend to also involve special populations (e.g. elderly) and patients. The design team needs to weigh the need for criteria, in terms of safety and data cleanliness, against the difficulty they may create for recruitment. For example, elderly people do not have normal kidney functions. One does not want to look for subjects who do not exist or are so rare that no one will be able to recruit them.
- The assessments needed to document safety and tolerability (as a primary objective of a FIH) as well as their exact timings, are to be determined by the preclinical safety data and comparison to similar drugs, if available. Medical experts need to choose accurate methods that can objectively demonstrate safety such as laboratory values, imaging techniques, or specific tests. Their correct timing in relation to the compound's predicted pharmacology (Tmax and half-life e.g.) is paramount for their validity.
- The correct time points for PK blood (and sometimes urine) sampling need to be defined



based on the product profile. Also, metabolites need to be considered. With a wrong sampling schedule, no accurate conclusions can be drawn regarding the product PK profile. The sampling schema may also be left flexible to adapt in function of obtained results from precedent groups.

- Biomarkers of PD effects, including receptor occupancy, activation of cells and pathways, can provide proof of pharmacology, indicative of a therapeutic dose range.
- All safety, PK and PD assessments need to be captured in a visit schedule. Although not always possible, the aim is to obtain a PK/PD/safety relationship for the new compound.
- In the whole synopsis development process, it is of the utmost importance that the operational team carefully review and finetune all aspects: the feasibility of enrolment criteria, all assessments in the given time frames, the impact on the participants and hence the recruitment, etc.

To conclude, designing a solid study PSD requires time and effort from a multi-disciplinary team. However, time spent and the investment to insource specific expertise at this important stage will pay off later. After all, what is written on paper needs to be doable in real life, and you shall respect the rules of the protocol!

Ensuring inspection readiness at clinical facilities

Early phase clinical trials – Maxim #8



The principles of Good Clinical Practice (GCP) serve to ensure the protection of trial participants and the integrity of the data recorded. Regulations require that all clinical trials be designed, conducted and reported in accordance with these GCP guidelines in order to be acceptable upon submission for marketing approval.

Any site involved in a clinical trial may be subject to GCP inspection by regulatory authorities, including the investigator sites, laboratories, the sponsor's premises, and the contract research organizations acting under arrangements with a sponsor. Clinical research is global, meaning it is increasingly important for sites to pass both FDA and EMA GCP inspections. These may be conducted on a routine basis or occur in response to a specific trigger, and can be related to ongoing or completed studies. Additionally, the inspections may or may not be announced.

The objectives of GCP inspections are to:

- Verify that quality assurance arrangements exist, in compliance with regulatory requirements and GCP
- Ensure the safety of human subjects is preserved and ethical standards are being applied

- Confirm that clinical trial data and results are scientifically valid and accurate

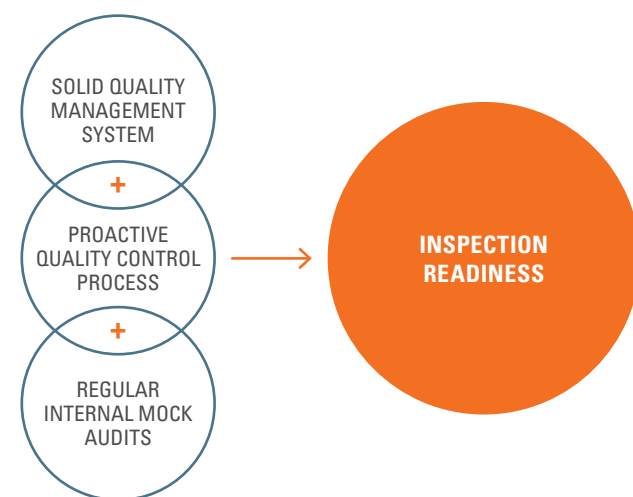
During an inspection, an inspector must be able to wholly reconstruct the clinical trial to confirm that all steps have been performed in accordance with the guidelines, that patients' rights and safety were protected at all times, and that all data is reliable.

For clinical teams undergoing inspection, the process brings with it the burden of administrative tasks and checklists. A common and recurring issue for a site is that getting ready for an inspection is regarded as a preparatory activity that starts only after notification of an upcoming inspection. This means that the team, headed by the Quality Assurance department, must ensure that all documentation is accessible, accurate and complete by the time the inspector visits the site, often leading to time pressure.

To overcome these last-minute activities leading up to an inspection, facilities can adopt a state of "inspection readiness" whereby the objective is to operate every day at a quality level ready for inspection and is achieved by developing a culture of compliance.



Inspection readiness entails the following activities:



1. Development of a solid Quality Management system, consisting of robust Standard Operating Procedures (SOPs) that cover the required measures to maintain high quality standards
2. Adopting a proactive Quality Control process, that not only checks activities but also aims for continuous improvement. The implementation of digital solutions for data, document and quality management supports this process
3. Carrying out regular, routine internal mock audits and inspections

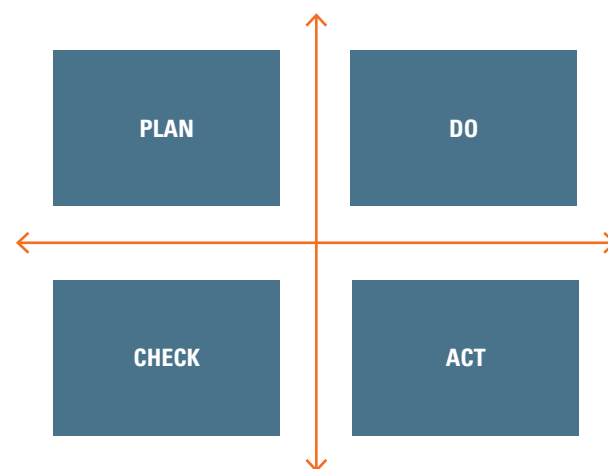
To foster a culture of compliance, the Quality Management process installs a set of procedures and policies which are monitored and evaluated to highlight where there may be room to improve. Trial activities and collected data are verified against protocol requirements, GCP and GDP regulations and internal procedures, and digitization of these data allows for much simpler review. The verification can be undertaken on all trial data which results in a 100% quality check, however, a more efficient approach may be to spot check only the crucial activities identified during an upfront risk analysis.

The checks need to be reported and interpreted, and whenever a flaw in a system or procedure is detected, its cause needs to be analysed (root cause analysis) to see if any action is needed to correct the fault or to prevent the situation happening again. This corrective and preventive actions (CAPA) process allows for improvement of the facility's overall quality, and its ability to be inspection ready at all times.

The cornerstone of a solid Quality Control approach is described by the Shewart Cycle (adapted by William E. Demming):

- Plan: look at the way of working, define how things can improve and set clear objectives
- Do: implement the planned improvements
- Check: measure results and evaluate if objectives were met
- Act: apply actions for improvement if needed

Internal mock audits and inspections are good tools to evaluate whether the quality system is working as intended, and if the team is indeed inspection ready. These types of self-compliance checks provide valuable opportunities for the identification of deficiencies in documentation or processes long before an inspector arrives, and additionally, help people to be clear, concise and confident when being interviewed.

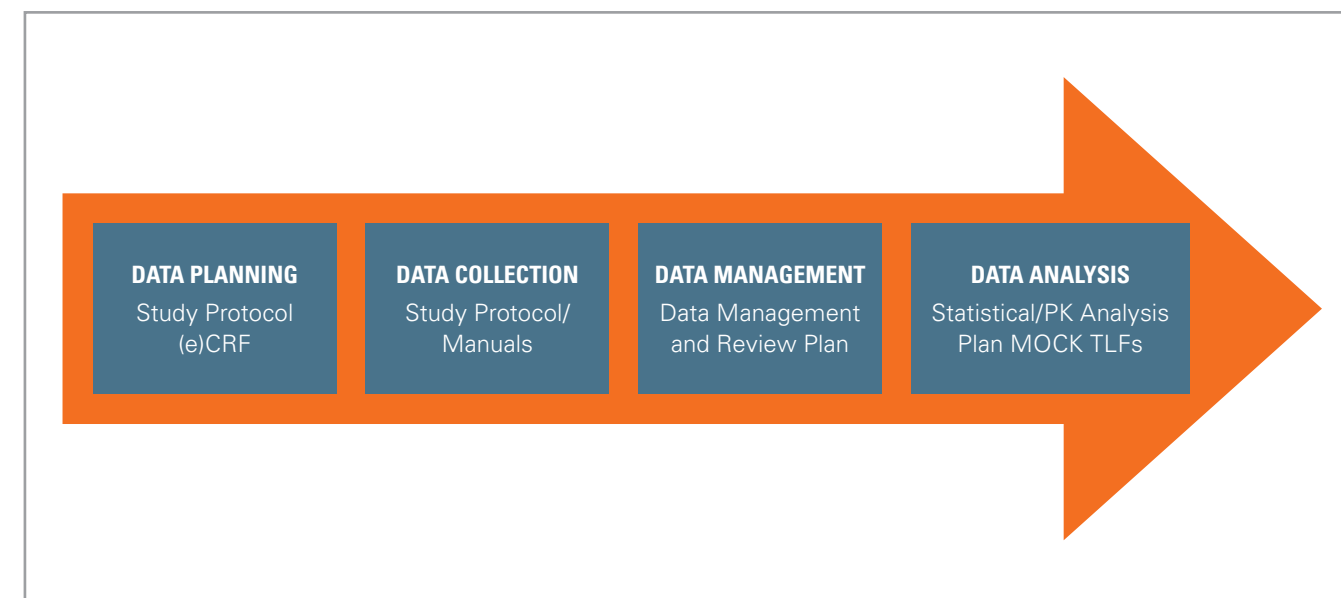


Appropriate and reliable data required for conclusive FIH/phase 1 trials

Early phase clinical trials – Maxim #9

Clinical trials are intended to find answers to a research question by generating data to prove or disprove a hypothesis. First-in-Human (FIH) and most Phase 1 trials by their very nature are exploratory, without a statistical hypothesis. They are aimed at obtaining reliable information on the safety, tolerability, pharmacokinetics and mechanism of action of a drug.

Various data is captured from FIH trials. Despite their exploratory character, this data needs to be relevant, accurate and appropriately analyzed to obtain meaningful results that are useful for future clinical development. We can highlight four main steps in clinical data processing:



DATA PLANNING

The first step is the planning of data at an early stage when developing the study design/protocol/ eCRF/ eSource: which measurements to foresee, when exactly, for how long and how frequently? These questions concern all the assessments in the FIH, i.e. safety, tolerability, PK and PD. Often, planning is not very targeted since the only supporting information available at this stage is preclinical data with human predictions and because there is no precise statistical endpoint.

DATA COLLECTION

Once the study starts, data is collected by the operational staff of the Research Unit on an ongoing basis. Any inappropriate methodology and non-adherence to protocol/manuals/eCRF/eSource may have a critical influence on data reliability and introduce bias. Thus, trained and punctual staff, aware of the importance of their work, are mandatory, without ignoring the training and preparation of the study subjects. The relatively high-risk nature of FIH studies and the absence of therapeutic benefit brings with it the ethical obligation to limit the number of exposed subjects, stressing even more the need for good quality data capture and handling.

DATA MANAGEMENT

Clinical Data Management (CDM) is the process of collecting, cleaning, coding and managing subject data in compliance with regulatory standards. The primary objective of CDM processes is to provide good quality data and gather the maximum data for analysis. To meet this objective, best practices (software, standard automatic process, eCRF/eSource, electronic data review) should be adopted.

DATA ANALYSIS

At the end of the trial, the data is analyzed to "become results". If appropriate methods of analysis are used with the appropriate data, it will be possible to interpret results and come to a conclusion. In the case of FIH studies, the conclusion should allow a decision to go, or not go, to the next phase of development and to give initial indications on how to design the next study.

In summary, 'high-quality' data is needed in all clinical studies including exploratory FIH. These should meet the protocol-specified parameters and comply with the protocol requirements.

CASE STUDY 1

Major role of appropriate PK data planning in FIH study

A substantial amendment was introduced, and study conduct changed because of inappropriate PK data planned in an initial version of the study protocol.

SGS was in charge of the conduct and analysis of a complex FIH study including SAD and MAD parts. In the SAD escalation part, the PK sampling until 24h needed to be analyzed before the next dosing.

This time point was based on a predicted human short half-life of the compound. Accordingly, the planning in the Clinical Pharmacology Unit at SGS was fixed to start next dosing 14 days after the preceding dose.

The starting dose being very low, in most subjects the plasma drug concentrations were very low or even non-quantifiable. Hence PK parameters (including half-life) were not relevant; therefore, the 14 day interval was sufficient but perhaps “not needed”.

Interestingly, with the third and fourth doses, the 24h PK sampling proved to be not long enough, and thus the half-life could not be estimated correctly (as it was longer than predicted in the protocol).

The protocol was amended after the fourth dose, and additional subjects were included to repeat the third and fourth doses with PK sampling up to 72h and 96h post-dose, respectively, before escalating to the fifth and final dose in the SAD part.

Take home message: FIH trials are exploratory, with PK as one of the primary objectives. It is obvious that SGS was in charge of the conduct and analysis of a complex FIH study including SAD and MAD parts.

In the SAD escalation part, the PK sampling until 24h needed to be analyzed before the next dosing. PK data/assessments cannot always be precisely planned in the initial protocol. Therefore, an adaptive approach can be used with careful and tailored PK data review steps.



CASE STUDY 2

Importance of rigorous safety data collection in a Phase 1 study

The safety data collection method, for a precise AE, was changed after two MAD groups to obtain the necessary information on drug/dose relationship, severity and actions to be taken during further clinical development.

During a Phase 1 MAD study conducted at the SGS Clinical Pharmacology Unit (CPU), frequent GI events were observed in the first two dose groups of subjects, increasing with the higher dose: in around 70% of subjects. As usually done, and as foreseen by the CRF, the date/time and severity of this AE was reported by the clinical site. However, since it was a frequent AE, related to dose and might occur multiple

times in the same subject, it became of interest to know if vomiting/diarrhea only occurred once in each subject or multiple consecutive times and if so, how often and within what time frame.

So far, the CPU medical team and sponsor suggested to start collecting details for these particular AEs, i.e. a separate record for each vomiting/diarrhea episode for each subject. No amendment to the CTP or other actions related to the CRF were needed, but only a modification to the way data was collected in the CPU.

Take home message: the more granular the safety information collected, the more useful the data. Clinical sites should be reactive and ready to adapt the data collection process in response to ongoing observations.



Bridging to patient clinical trials

Early phase clinical trials – Maxim #10



Early phase clinical trials, known as human pharmacology studies, start principally with the aim of collecting information on the safety and tolerability of the drug product. However, the ultimate objective of a drug development program is to provide a medicine that is safe and shows positive benefit-risk balance for treatment of the target patient population. As outlined in ICH E8(R1) guideline, the cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies. Scientifically sound bridges should therefore be established linking human pharmacology studies to initial exploratory studies and later confirmatory studies. This advancement through the late phase life cycle development of the drug product is performed by collecting precise data during the early phase clinical trials that are performed in majority of cases in healthy volunteers.

Investigation of possible biomarkers, or surrogate markers, is one of the measures that could help to better understand the mode of action and predict the efficacy in patients in the later stages. Modeling and simulation (M&S) can also be of tremendous support in some cases to extrapolate data from healthy volunteers and to predict efficacy and drug behavior in patients using different models such as disease-based, pharmacokinetics (PK)/ pharmacodynamics (PD) or complex mechanistic models. The best strategy in order to provide information on efficacy of the drug product remains to involve patients as soon as possible in clinical studies. Obviously, in some cases this approach is mandatory when administration of drug product is a serious risk to healthy individuals, such as genotoxic oncology drugs. In other cases, in follow-up of an early phase clinical trial in healthy volunteers, the drug product can be investigated in patients after a short duration of drug exposure to a limited number of patients with target indication, or

sub-population of patients, that could be investigated under the roof of a combined protocol in order to assess the preliminary efficacy of the drug product. This approach has further been endorsed in ICH E8(R1) guideline justifying involvement of patients early in human pharmacology studies depending on drug properties and objectives of drug development program.

The below scientific aspects should carefully be studied and addressed during development of the study design for various early phase studies in patients:

- To determine the safe dose range that could be used in early clinical studies in patients considering the dose to be well tolerated, but high enough to be effective;
- To discover and predict adverse events that could be foreseen, or possibly avoided, in patients, keeping in mind that patients are the target population for treatment;
- To establish and understand PK properties of the drug product (absorption, distribution, metabolism, and excretion; ADME), as early as possible in target patient population in order to use this knowledge to improve dosing regimen for a beneficial efficacy;
- To collect as much as possible PD and efficacy data in early patient trials to be more precisely prepared for late phase clinical development.

So far, exploratory proof-of-concept studies in the intended target patient population, should enable to define the safe and effective dose and regimen that will be used in subsequent confirmatory studies.

The below case studies shortly discuss the input that was provided by SGS to two clients to start clinical trials in patients and moreover, in management and conduct of the studies.

CASE STUDY 1

A small-to-medium-sized enterprise (SME) contacted SGS to support them in their first-in-human (FIH) study with an investigational medicinal product for pain due to osteoarthritis, to be administered via intra-articular injection.

The goal of the first study was to have an idea on the maximum tolerated dose. The maximum tolerated dose could possibly vary in patients with knee pain compared to healthy volunteers. Moreover, seeing the mode of administration, it was considered not ethical to conduct the FIH study in healthy volunteers without osteoarthritis.

Outcome: The FIH study was conducted in 20 patients with knee pain due to osteoarthritis with a pain score of at least 4 on the visual analogue scale. It allowed the client to not only assess the tolerability of multiple doses of the product in patients, but also have a first signal on the analgesic effect of the compound at several doses in the actual target population and to assess directly the potential therapeutic benefit allowing easy bridging to a larger dose-confirmation and proof of efficacy phase-2 trial. Seeing the prevalence of the condition, recruitment was fast involving only 2 sites in a single country.



CASE STUDY 2

SGS was consulted by an SME involved in development of innovative products in women's health to support study design and conduct of a FIH single ascending dose (SAD)/multiple ascending dose (MAD) study in healthy volunteers and a proof-of-concept phase-2 study in the target patient population in postmenopausal women with vasomotor symptoms.

Two studies in healthy volunteers were designed, conducted and managed at the SGS phase-1 unit enrolling 65 and 40 individuals, including several female-only cohorts. The objective of these studies were safety and tolerability of different dosages,

as well as collecting information on PK/PD defined as effects on sex hormones and LH/FSH levels. These data were considered as the scientific basis for the design of the later proof-of-concept study in patients and justifications for dose selections.

Outcome: In the phase-2 study, about 90 postmenopausal women with vasomotor symptoms were enrolled at 8 European sites in around 12 months. Thanks to the PK/PD response data in the healthy volunteer studies, in combination with the available safety data of each dose level, a correct dose selection was decided upon in the phase-2 trial with a clear first proof-of-efficacy result and leading to the most appropriate dose selection for the first pivotal phase-3 study.



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SGS

When you need to be sure