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) draft guideline, the cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of subsequent 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) draft 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.

The goal of the first study was to have

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.

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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