

Shaping Research for the Future Proof-of-Concept Approach for Early Answers

▷ **Aernout van Haarst PhD** Director, Scientific Affairs

Today, industry is focusing on getting quicker answers to important questions, not only aiming to speed up development of their candidate drug, but also to enable early, informed go/no-go decision making and sound investments.

So what has changed for early clinical drug development over the past 2-3 decades? In the exploratory stage of drug development, patient involvement is increasingly required. The purpose of this paper is to illustrate how Celerion, a leader in early phase clinical research, has adapted to the consequent needs of the sponsors.

THE TREND TOWARDS INCREASED INVOLVEMENT OF PATIENTS IN EARLY STAGE DEVELOPMENT HAS EMPHASIZED THE NEED TO INVOLVE CLINICAL EXPERTS FOR EARLY PHASE CLINICAL STUDIES.

Proof-of-Concept and Early Involvement Patients

The need for earlier access to patients in drug development goes back to a shift in paradigm, from a traditional phased approach to a Proof-of-Concept (PoC) approach. PoC is pursued in the early, exploratory stage prior to confirmation in late stage trials. This is prompted by an increased demand for informed decisions, for instance driven by novel mechanisms of action (MoAs), the need for target validation and a desire to shift attrition to avoid the costly expenditure of later stage studies. At the same time, this is facilitated by the expanded options to demonstrate early signs of drug action in humans, e.g. by innovations in bioanalysis of blood biomarkers and in imaging technologies.

One could state that the main clinical go/no go decision gate in early drug development often is the proof of the drug's concept, asking: "Does the drug work in humans the way it was designed?" As there is no regulatory requirement, other types of "proof" may be pursued depending on drug characteristics and sponsor preferences; examples are Proof-of-Presence (does the drug get to its target) and Proof-of-Mechanism (does the drug engage with its target). All these proofs create added value and are important for decisions on whether or not to invest more money and effort in further clinical studies and help develop real value of the drug for the sponsor.

Yet, PoC goes beyond target engagement and typically involves biomarkers reflecting impact on disease. Obtaining clinical PoC generally requires a small number of patients - preferably with stable disease. In addition to that, one needs investigators to ensure scientific and medical robustness and, of critical importance, is a controlled study setting that meets all the requirements for early phase trials.

It is exactly this combination of prerequisites that is the heart of the matter. Clinicians and academic scientists have expert knowledge on standard treatments, comorbidities, disease state variability, and have access to the patients as well as recent patient data – aspects that CROs often struggle with. However, the need for confinement and frequent PK sampling in the exploratory phase is too often a challenge for academia and routine hospitals. They may lack sufficient operational support to adequately take care of practicalities around patient recruitment and study conduct aside routine patient care.

Partnering with Clinical Experts – the Queen's University Belfast Example

Clearly, collaborations between CROs and academia involving specialized clinical pharmacology units are ideal for running good PoC studies. Celerion's preferred model employs a partnership with academia that balances industry-sponsored versus investigator-initiated research.

We have had a key partnership with Queen's University Belfast, collaborating on respiratory disorders for over 15 years. Such collaboration has provided Celerion with access to clinical and scientific expertise, which is essential for the judgment of study feasibility, rational design of studies, clinical monitoring of patients, and (occasionally) access to specific patient populations. The support of the clinical experts has also enabled Celerion's research facility to conduct and implement specialized procedures (e.g. broncho-alveolar lavage and body plethysmography). For the purpose of PoC studies, such procedures also required validated equipment, training and SOPs to reduce inter- and intra-observer variabilities.

The evolved ability to perform a wide range of techniques and to contribute high quality to the conduct of clinical studies has placed the Belfast unit in an excellent position to run studies with complex and innovative designs. These multi-faceted studies include both healthy volunteers and patients up to phase II. The case study hereafter illustrates the advantages of our successful partnership model.

Case Study

A biotech client requested Celerion to run a First-in-Patient study in cystic fibrosis patients in a multicenter setting. The purpose of the study was to assess safety and tolerability of their novel drug and to explore the compound's pharmacodynamics.

In practice, there are a number of typical challenges for such studies in cystic fibrosis patients. First, recruitment of cystic fibrosis patients, a rare disease, may be cumbersome – not only for the limited number of patients, but also due to the

often tight inclusion/exclusion criteria. Moreover, an adequate selection of endpoints may require complex methodologies to assess respiratory function, which in turn may negatively affect the willingness of patients to participate. Finally, management of cystic fibrosis patients is difficult due to the high risk of cross-infection and the variability in their health status.

With a focused review and consideration of protocol design, the university helped Celerion design the eligibility criteria for this study in such a way that we would be optimally able to recruit the patient population, while still ensuring the scientific validity of the study. Similarly, the university experts provided advice on the selection of endpoints – balancing a maximal anticipated yield and minimal burden to the patients. The study design that finally emerged was a MAD, parallel, randomized, placebo-controlled study with treatment up to 15 days.

From a practical perspective, the clinic was organized in such a way that we could minimize the risk of cross-infections between patients. For instance, measures were taken to create separate rooms, modify the cleaning policy, increase stringency of access control, and prevent more than two patients being dosed at a time. These measures were all laid down in specific SOPs. During study conduct, we were also able to adapt to the fluctuating levels of health of the cystic fibrosis patients by being flexible in our scheduling to accommodate the patients. Finally, the expertise to run specialized pulmonary procedures, gained through our partnership, completed the clinic's capabilities to run the study.

The synergy between Queen's University and Celerion resulted in the successful inclusion of 17 cystic fibrosis patients. A fast turn-around of results following each dose level allowed a rapid dose-escalation. Altogether, the interval between first patient in and last patient out was only 14 months. This would sound slow for healthy volunteer studies, but such a time span is very short for this type of study involving cystic fibrosis patients.

Most importantly, the observed changes in sputum and blood biomarkers corresponded to the drug's mechanism of action in cystic fibrosis, which helped the sponsor to secure investment for further development of the drug. The results also provided useful data for the design of subsequent trials.

Conclusion

PoC studies provide a popular and excellent means to add value in the early stage of drug development, however, such studies can be challenging for the need to combine operational skills, specialist procedures and access to clinical expertise and patients. Our Belfast clinic exemplifies how lasting, synergistic relationships with clinical experts and academia are critical to staying at the forefront of the changing early phase clinical landscape and the conduct of good PoC studies.