Exploratory Studies in Cystic Fibrosis

Early stage, exploratory clinical trials involving cystic fibrosis patients are typically marred by a number of challenges. First, recruitment of cystic fibrosis patients may be cumbersome – due to the low prevalence of the disease, and to the often restrictive inclusion/exclusion criteria. An adequate selection of endpoints may require complex methodologies to assess respiratory function, which may negatively affect the willingness of patients to participate. Even as early stage studies, these trials will often require a multi-centre approach. Overnight stays and frequent blood draws are general operational challenges that add to the complexity of conducting exploratory studies involving patients. Finally, management of cystic fibrosis patients is difficult due to the high risk of cross-infection and the variability in their health status.

The key to Celerion's success (Figure 1) in conducting early stage studies on respiratory disorders within its Phase I clinic, in particular involving cystic fibrosis patients, is a strong partnership with Queen's University Belfast. With a focused review and consideration of protocol designs, cystic fibrosis experts at Queens University have worked with Celerion to design the eligibility criteria for early stage patient studies to optimally recruit the patient populations, while ensuring the scientific validity of exploratory studies. Similarly, academic experts and key opinion leaders also provide advice and insight into the selection of endpoints – thus balancing a maximal anticipated yield and minimal burden to the patients in each study.

Celerion has also extended its collaborations to sites with (respiratory) Phase I facilities, such as Medicines Evaluation Unit (MEU) in Manchester and the Royal Brompton Hospital in London, enabling study conduct at multiple centres.

Patient Focused

With our inherent focus on patient safety, Celerion has organized its Belfast clinic in such a way that we can minimize the risk of cross-infections between patients. Measures have been taken and laid down in specific SOPs to create separate rooms, modify the cleaning policy, increase stringency of access control, and prevent more than two patients from being dosed at a time. To accommodate the fluctuating levels of health of cystic fibrosis patients during study conduct, we provide flexible scheduling. Celerion's expertise to run specialized pulmonary procedures, along with that of our partnerships, completes the clinic's capabilities to run respiratory studies.

The effectiveness of Celerion's capabilities was illustrated in a multi-centre Phase Ib trial, managed by Celerion. Our Belfast clinic, together with our partnering sites, successfully enrolled a total of 17 cystic fibrosis patients. The interval between first patient in and last patient out was only 14 months, a very short time span for this type of study.

Value of Exploratory Patient Studies

An example of the value a well-designed, early stage patient study can bring is illustrated through a First-in-Patient study that was conducted in cystic fibrosis patients in a multi-center setting (Elborn et al., Clin Transl Sci 2017). The purpose of that study was to assess safety and tolerability of a novel drug and to explore the compound's pharmacodynamics. The study was designed as a MAD (multiple ascending dose), parallel, randomized, placebo-controlled study in cystic fibrosis patients with treatment up to 15 days.

During this study, a selection of inflammation markers was assessed in sputum and blood samples. After 2 weeks of treatment, changes from baseline were found in all sputum biomarkers, in particular reductions in sputum neutrophils and elastase in comparison with placebo. Importantly, the observed changes corresponded to the drug's mechanism of action in cystic fibrosis, and the effects on WBC (white blood cell count) and neutrophil counts in sputum were suggestive of a positive effect on lung inflammation status.

These preliminary biomarker results helped the sponsor secure investment for further development of the drug.

For more information on Celerion's experience see Figure 2.

Figure 1. Challenges & Celerion Capabilities

Challenge	Celerion Capabilities
Design exploratory study including cystic fibrosis patient panel	Celerion has a long-standing relationship with cystic fibrosis experts, ensuring a study design that balances a maximal yield and minimal patient burden
Respiratory studies often require complex methodologies and delicate sample handling	Celerion is fully equipped to run respiratory assessments and handle specific samples
Even in the early stage, cystic fibrosis studies tend to require multiple sites	Celerion collaborates with experienced partners with Phase I facilities Celerion has one of the industry's most experienced project management and monitoring teams
Cystic fibrosis patients have fluctuating health status, complicating scheduling of visits	Celerion is able to flexibly schedule study visits
High risk of cross infection	Celerion clinics operationally set up to accommodate patients and prevent cross infection

Figure 2. Track Record of CF Trials (<5 Years)

Study Type	Study population	# CF Patients	Year	# Sites	Route of Administration
MAD (Safety & Tolerability)	Healthy	NA	2018	1	Oral
MAD (Safety & Tolerability)	CF	32	2017	2	Oral
MAD (Safety & Tolerability)	CF	34	2017	2	Oral
SAD (FIH)	Healthy/CF	9	2017	3	Inhalation
MAD (Safety & Tolerability)	CF	3 (24)	2017	1(3)	Inhalation
Bioavailability	Healthy/CF	6	2016	1	Oral
SAD (FIH)	CF	6 (64)	2015	1 (10)	Inhalation
DDI	Healthy	NA	2014	1	Oral
SAD/MAD (FIH)	Healthy	NA	2015	1	Inhalation
MAD (Safety & Tolerability)	CF	17	2013	3	Oral
SAD	CF	10	2013	1	Inhalation

CF = Cystic fibrosis; SAD = Single ascending dose; MAD = Multiple ascending dose