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Translating Science to Medicine

Challenges and Solutions for NAFLD/NASH Phase I-IIa Clinical Studies

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Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are complex, chronic disorders associated with obesity, diabetes and metabolic syndrome. NASH is a more severe form of the disease, defined as excess fat infiltration within the liver combined with inflammation and injury. If left untreated, NASH can lead to cirrhosis, end-stage liver disease and liver cancer. With no FDA-approved drug for NASH, this creates a large unmet medical need. As a relatively new indication, clinical drug development for NASH also has its challenges such as high screen fail rates, determining appropriate biomarkers as well as access to biopsy-proven NASH and hepatic impaired patients. Celerion, a world-class, full service clinical research organization and leader in NASH drug development, has solutions to progress your compound from first-in-human through Phase IIa, in addition to NDA submission support with labeling studies.

CHALLENGE: REDUCING SCREEN FAIL RATES

CELERION SOLUTION: PRE-SCREENING PARTICIPANTS WITH FIBROSCAN® TECHNOLOGY

Celerion has curated a robust NAFLD database of study participants pre-screened with FibroScan to reduce screen failures and expedite study enrollment. FibroScan is an ultrasound-like device that measures liver fat and stiffness (a marker of fibrosis). This noninvasive test helps pre-select candidates to undergo more expensive imaging measurements such as magnetic resonance imaging with proton density fat fraction (MRI-PDFF) or elastography (MRE) as part of study inclusion criteria. In addition, each subject in the database has a complete set of clinical laboratory blood work-up. Our NAFLD database can accommodate inclusion criteria pertaining to elevated TG, ALT or other clinical labs.

- Over 350 pre-screened subjects are in Celerion's NAFLD database. More than 80% have fatty liver and 30% have liver stiffness. Additionally, we have a large database (>7,000 participants) of otherwise healthy obese (BMI >30 kg/m2) subjects.

CHALLENGE: CHOOSING AN APPROPRIATE SOLUBLE BIOMARKER

CELERION SOLUTION: ANALYTICALLY AND CLINICALLY VALIDATED SOLUBLE BIOMARKERS

Both U.S. and EU regulatory authorities recommend incorporation of soluble biomarkers in NASH drug trials. However, it seems like almost every other day a new NASH biomarker comes out, adding complexity in choosing appropriate soluble biomarkers. Celerion offers a breadth of platforms for biomarkers, from ELISA, ELISPOT, flow cytometry to RT-PCR and more. Our scientific team is comprised of NASH experts, able to provide advice on soluble biomarkers acting within your drug's signaling pathway, to maximizing pharmacodynamic data from your study. Moreover, we understand the regulatory implications regarding the utility of your biomarker and offer various stages

of analytical validation depending on the context of use. For example, exploratory biomarkers do not require the same degree of testing as does a secondary endpoint. In addition, we have a rich library of validated NASH biomarkers, designed to save you time and money.

- Analytically validated soluble NASH biomarkers of inflammation, injury and fibrosis:
- CRP, CK18, Fibrinogen, FGF-21, IL1b, IL6, IL8, MCP-1, MIP-1b, TNF-a.

CHALLENGE: IDENTIFYING EARLY SIGNALS OF TARGET ENGAGEMENT

CELERION SOLUTION: DETERMINING PROOF-OF-MECHANISM

Confirming target engagement and proof-of-concept as early as possible is an important milestone in drug development. Celerion has experience with a number of "challenge assays" typically performed in healthy volunteers, which push physiological processes into a pathophysiological range, useful to demonstrate target engagement, proof-of-mechanism and efficacy, in a safe and controlled environment. For the NASH indication, Celerion's experience includes upregulating de novo lipogenesis via continuous fructose administration, monitoring FXR target engagement with bile acid derivatives such as C4 (7α-Hydroxy-4-cholesten-3-one levels), and enzyme phosphorylation in PBMCs.

CHALLENGE: ACCESS TO BIOPSY-PROVEN NASH PATIENTS

CELERION SOLUTION: NETWORK OF EXTERNAL SITES WITH ACCESS TO BIOPSY-PROVEN NASH PATIENTS

Carrying your investigational product through from first-in-human to proof-of-concept with Celerion is a seamless transition. Our three clinics located in Lincoln, NE; Phoenix, AZ; and Belfast, Ireland, all specialize in single ascending and multiple ascending dose escalation studies, providing adaptive study designs, cardiodynamic monitoring and a vast database of health volunteers as well as subjects with metabolic syndrome and NAFLD. Celerion then partners with patient sites for access to biopsy-proven NASH patients as your compound progresses to efficacy studies. Our Global Clinical Development team ensures there is consistency in data quality, project management, as well as clinical & medical monitoring.