The FibroScan® Advantage in Early NASH Clinical Studies

Nonalcoholic fatty liver disease (NAFLD) is a chronic metabolic disorder characterized by an excess of fat within the liver, termed steatosis. Nonalcoholic steatohepatitis (NASH) is a more severe form of the disease in which hepatic steatosis is accompanied by inflammation and injury to liver cells. This can lead to fibrosis, cirrhosis, end-stage liver disease and even hepatocellular carcinoma.

Cutting out the liver biopsy

Currently, NASH is diagnosed with a liver biopsy and histological tissue assessment. The liver biopsy is an invasive procedure that can be painful, resulting in complications and tends to have low patient acceptance rates. Moreover, the liver biopsy sample only represents 0.002% of the entire liver and the analysis can be afflicted by inter-operator variability (reviewed in [1]). In addition, due to the invasiveness of this procedure it is not appropriate for short-term interventions or frequent serial measurements. Therefore, alternative, non-invasive approaches to diagnose and monitor disease progression are needed, especially for early clinical phase studies.

NASH drug development

Over 80 investigational drugs are currently in clinical development for NASH. Metabolic disturbances, lipogenesis, inflammation, apoptosis, oxidative stress, and fibrogenesis all play a major role in the pathogenesis and progression of the disease [2]. Therefore, drug targets under investigation for the treatment of NASH are just as diverse as they are numerous. Detecting early signals of efficacy in a clinical trial is an essential step in a NASH drug development program, and FibroScan® (Echosens, Paris) is the *essential tool* (Figure 1).

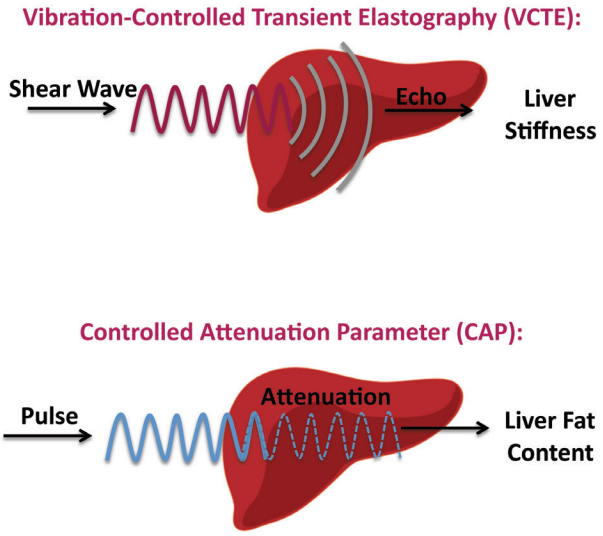
Figure 1. The FibroScan® Advantage:

Non-invasive procedure
Exam area is 100x larger than the traditional liver biopsy approach
Reproducible results
The procedure is painless and takes about 10 minutes
FDA cleared
Over 2,000 scientific publications

Measuring liver stiffness and steatosis with FibroScan®

FibroScan® is an ultrasound-like instrument able to simultaneously measure liver stiffness and steatosis through Vibration-Controlled Transient Elastography (VCTE) and Controlled Attenuation Parameter (CAP), respectively. Propagation of a mechanical shear wave through the skin and liver tissue is measured using low energy ultrasound. Liver fibrosis is estimated as a function of liver stiffness, and the attenuation of the signal is proportional to hepatic steatosis (Figure 2).

Figure 2. Illustrations of FibroScan® liver stiffness and fat content mechanics.



Implementing FibroScan® in Early Clinical Studies

FibroScan® is often included as a primary or secondary endpoint in clinical studies, especially with drug targeting steatosis or fibrosis pathways (Table 1).

In addition, the Liver Forum, a consortium of regulators, academics and industry, recommends FibroScan® as part of study inclusion criteria [3]. Subjects in Phase I and IIa NASH studies should demonstrate evidence of steatosis by FibroScan® CAP or magnetic resonance imaging (MRI) and evidence of fibrosis by either FibroScan® VCTE (>7.0 kPa) or magnetic resonance elastography (MRE). More recently, the FDA issued draft guidance for NASH drug development. This document indicates the use of imaging techniques for early clinical study enrollment [4]. Therefore, FibroScan® offers value to NASH drug development programs as part of inclusion criteria and/or a pre-screening measure to identify suitable candidates for costly imaging measures such as MRI and MRE.

Table 1. FibroScan® Application in NASH Clinical Studies.

Trial Phase	Drug Name	Mechanism of Action	FibeScan® Application	Trial Status
Phase II	GS-9674	FXR Agonist	Secondary Endpoint	Completed
Phase II	GRMD-02	Galectin 1 & 3 Inhibitor	Primary Endpoint	Completed
Phase II	Solithromycin	23S rRNA Inhibitor	Secondary Endpoint	Completed
Phase II	GRMD-02	Galectin 1 & 3 Inhibitor	Secondary Endpoint	Completed
Phase II	GS-0976	ACC Inhibitor	Secondary Endpoint	Completed
Phase II	Emricasan	pan-Caspase Inhibitor	Secondary Endpoint	Ongoing, not recruiting
Phase II	GS-0976; GS-9674; Selonsertib	ACC Inhibitor; FXR agonist; ASK1 Inhibitor	Inclusion Criteria	Ongoing, not recruiting
Phase II	Tropifexor	FXR Agonist	Secondary Endpoint	Ongoing, recruiting
Phase II	Namodenoson	ADORA3 Agonist	Secondary Endpoint	Ongoing, recruiting
Phase II	BI-1467335	AOC3 Inhibitor	Inclusion Criteria	Ongoing, recruiting
Phase II	PF-05221304	ACC Inhibitor	Inclusion Criteria	Ongoing, recruiting
Phase II	GS-0976; Selonsertib	ACC Inhibitor; ASK1 Inhibitor	Inclusion Criteria	Ongoing, recruiting
Phase II	Insulin	Insulin Receptor Agonist	Secondary Endpoint	Planned
Phase II	PXL-770	AMPK Activator	Primary Endpoint	Planned
Phase II	Aramchol	SCD1 Inhibitor	Secondary Endpoint	Planned
Phase II	Foralumab	ATP4A Inhibitor	Inclusion Criteria	Planned
Phase I	DUR-928	Epigenetic regulator	Inclusion Criteria	Completed

Source: GlobalData, NASH and FibroScan search 01-May-2018

Two sites, One mission

Celerion strives to deliver high-quality clinical trial results faster. Incorporating FibroScan® into participant pre-screening efforts, and using FibroScan® for early signals of drug efficacy is how we can expedite your NASH program. That's why FibroScan® is available at both of our US clinics (Table 2).

Table 2. Celerion's NASH service offerings

Essential early NASH study requirements	Lincoln, NE	Phoenix, AZ
FibroScan®	✓	✓
Soluble NASH biomarkers	✓	✓
Diverse participant population	✓	✓
Access to MRI/MRE	✓	✓
Bed capacity	224	300
Pharmacokinetic analysis	✓	✓
Data management services	✓	✓
Regulatory services	✓	✓

Summary

The global prevalence of NAFLD has reached epidemic proportions as it affects an estimated 25% of the general population [5]. Meanwhile, the need for effective therapy is dire. Signals of early efficacy in drug development are critical to advance potential treatments up the pipeline, and in this regard FibroScan® can serve as a valuable tool.

References

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