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FACT SHEET

Non-Invasive Methods for the Assessment of Hepatic Steatosis in NAFLD/NASH Trials

Defining Nonalcoholic Fatty Liver Disease

NAFLD is an umbrella term that comprises a continuum of liver conditions that is not attributable to alcohol consumption and is broadly classified into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH):

- **NAFL** is defined as hepatic steatosis with no evidence of hepatocellular injury and is associated with a low risk of adverse outcomes. An estimated 30-40% of adults in the US have NAFLD (1).
- **NASH** is defined as the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis and is associated with an increased risk of progression to cirrhosis and liver transplants. An estimated 3-12% of adults in the US have NASH (1).

Clinical Drug Development in NASH is Evolving and is Faced with Significant Challenges

There are no FDA approved treatments of NASH, and most therapies in the pipeline are in early- or mid-stage development with late-stage studies still years away from potential approval. NASH clinical development, therefore, qualifies for accelerated regulatory approval (Subpart H) and the use of a surrogate endpoint (histopathology obtained from liver biopsy) with confirmatory post-marketing trials. The need for paired liver biopsies in phase 2b and phase 3 trials to demonstrate treatment response, however, creates significant obstacles (including slow subject enrollment, delayed timelines and significant costs) for biopharma companies due to its limitations in accuracy, patient participation and observer reliability and an urgent need exists for more accurate non-invasive biomarkers for all stages of the drug development process.

The Assessment of Hepatic Steatosis in Early Phase Clinical Trials

The use of paired liver biopsies in phase 1 and phase 2a trials is not realistic due to the short nature of these studies. Instead, a wide range of non-validated surrogate biomarkers of metabolic, inflammatory and fibrosis outcomes are currently used to demonstrate target engagement of the investigational compound. Deciding which of the broad range of surrogate biomarkers is optimal for a clinical trial should be based on the compound's mechanism-of-action. For example, magnetic resonance imaging (MRI) proton density fat fraction (PDFF) has been shown to be a useful biomarker for compounds (e.g. GS-0976, PF-05221304, NGM282, BMS986036) targeting hepatic steatosis (2,3).

Non-invasive Imaging Assessment of Hepatic Steatosis.

Non-invasive imaging methods, such as ultrasound, controlled attenuation parameter (CAP) and PDFF, using either MRI or magnetic resonance spectroscopy (MRS), are currently used to measure liver fat in NASH clinical trials.

- **CAP** methods are easy to use and relatively inexpensive screening tools to pre-identify subjects with NAFLD but have limited utility as an endpoint to assess treatment response due to the inaccurate nature to distinguish different grades of steatosis.

- **MRS** is considered the most robust and quantitative of the non-invasive imagining methods, but its use is limited by technical demands and availability and has only been used in relatively small studies in specialized centers.
- **MRI-PDFF** is emerging as the surrogate biomarker of consensus for quantifying treatment effects on hepatic steatosis in early phase clinical NASH trials due to its precise, accurate and quantitative nature. MRI-PDFF is reproducible across scanner manufacturer and field strength which facilitates its use in multi-center clinical trials and has been shown to be responsive to treatment effects (2,3).

Figure 1. Proton density fat fraction (PDFF) map from a subject with 'normal' liver fat levels (PDFF ~ 1.5%) (4)

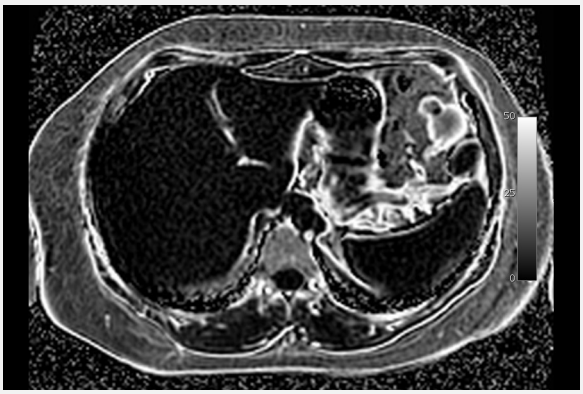
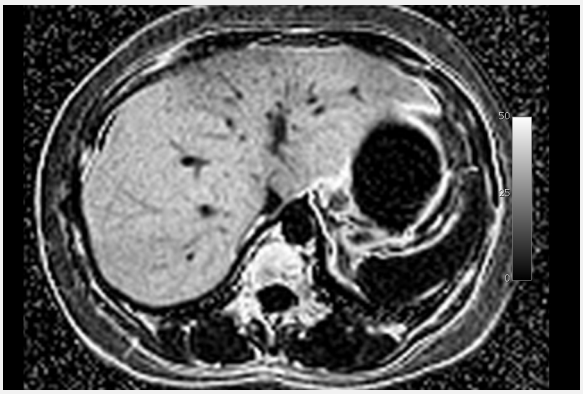


Figure 2. Proton density fat fraction (PDFF) map from a subject with elevated liver fat levels (PDFF ~39%) (4)



To speak to a member of ProScientо's scientific services team about clinical study design, protocol development, or customized biomarker selection and utilization, please contact us at bd@prosciento.com.

References

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