

NASH: KEY CONSIDERATIONS FOR DRUG DEVELOPMENT

Non-alcoholic steatohepatitis (NASH) is predicted to become the leading cause of liver transplantation in the United States within the next five years, but there are no approved therapies. This unmet medical need has generated substantial interest from pharmaceutical companies, regulatory agencies, patients and physicians in the development of an effective therapy to treat this complex disease. No clearly defined pathway for regulatory approval exists, but the emerging pathway suggests that an accelerated or conditional marketing authorization can be obtained using surrogate endpoints, with later studies required to confirm clinical benefit and liver outcomes.

NASH drug development presents distinct challenges, including the following key issues:

- ▶ Primary and many secondary endpoints still require an invasive biopsy, and patients often are reluctant to have multiple liver biopsies.
- ▶ Scientific research is advancing so rapidly that new, noninvasive endpoints may become available partway through trials.
- ▶ NASH progresses very slowly. The natural history is often heterogeneous, and it is difficult to predict which patients will progress.
- ▶ Spontaneous remission can occur. Enrolling the right target population can mitigate this risk.
- ▶ Reaching a conclusive answer about outcomes takes several years
- ▶ The complexity of the disease adds to the complexity of clinical studies. It is important to select clinical sites that not only offer strong support for liver biopsies but also incorporate state-of-the-art diagnostic techniques. Informatics tools can aid the decision-making process by providing metrics on NASH investigator performance, such as enrollment rates.

Keeping the above considerations in mind will smooth the clinical development path for a NASH treatment.

Choosing a Preclinical Pharmacological Model

NASH is difficult to replicate in animal models. Although a number of models are available, none entirely recapitulates the human disease¹. However, animal models are valuable for answering specific questions about disease etiology and pathology, as well as for testing therapeutic approaches that cannot safely be applied to patients. Current data using noninvasive biomarkers and detailed histopathology suggest that these findings are highly relevant and can be translated to the clinic.

Many potential pharmacological targets can be evaluated to treat NASH, and animal models are highly specific to particular studies. Therefore, drug developers must carefully choose the appropriate model and induction diet for their experiments, based on the compound's mode of action and the hypothesis to be tested. Regardless of the model chosen, it is important to evaluate fibrotic features and/or biomarkers for fibrosis.

Many of the biomarkers employed in clinical trials — such as liver enzymes, cytokeratin-18, the European liver fibrosis (ELF) panel and other panels — also can be used preclinically. Hepatic triglyceride measurements provide valuable information about fat accumulation in the liver. Portal hypertension, one of the major complications that occur in nonalcoholic fatty liver disease (NAFLD) patients and in animal models of NAFLD, can be measured in rodents at the terminal stage of the experiment. Finally, imaging in preclinical studies is under development. Lipid spectroscopy with magnetic resonance imaging (MRI) can show accumulation of lipids in living animals, but this technique is highly specialized and not widely available.

Early Clinical and Market Access Considerations

Clinical pharmacology considerations in Phase I NASH trials are similar to those for other drugs. However, it is possible to generate some initial data in parallel with Phase I studies. A subgroup of NASH patients could continue for at least four to six weeks so that initial biomarker results can be obtained. Although this preliminary data provides no guarantee of success in later studies, it does generate a degree of confidence to move forward.

Early in the development process, companies also need to consider issues related to reimbursement. Key questions include what the final label will look like, how clinicians will decide which patients to treat and the criteria payers will use to determine eligibility for treatment. To increase the chances of successful reimbursement after marketing approval, sponsors should seek advice from health technology assessment groups early in the process, when it is still possible to modify clinical protocols.

Options for Proof of Concept Trials

Two main options should be considered for the design of proof of concept (PoC) trials. In the first scenario, studies can enroll patients who are highly likely to have NASH but have not undergone a liver biopsy for confirmation. In this case, patients with fatty liver and other risk factors for NASH (i.e. presence of type 2 diabetes, metabolic syndrome or high transaminase levels) are recruited. Enrollment for these studies can be faster and easier compared to trials that require biopsy-confirmed NASH patients. However, the limitation is that the target population is not exactly the one that will be explored in the Phase IIb and Phase III trials. Imaging can be used to enrich the population. For example, transient elastography, a methodology based on ultrasound, can provide information about liver stiffness, a signal of fibrosis. A new technology, multiparametric MRI, can indicate not only fat levels but also signs of inflammation and/or fibrosis.

Early short-term trials present a challenge because changes in liver histology will not be evident in such a brief period, and most patients are unwilling to have a second liver biopsy after only six months. Because resolution by histology is not possible, studies must essentially demonstrate a surrogate of a surrogate endpoint. Changes in liver fat, as well as liver enzyme levels and other biomarkers of liver inflammation and fibrosis can provide information and facilitate the decision to move forward to Phase IIb trials. Once in Phase IIb, changes in histology can be assessed in patients with biopsy-confirmed NASH with the NAFLD activity score (NAS), which quantifies steatosis, ballooning and inflammation.

An alternative scenario is an adaptive design trial, in which biopsy-confirmed NASH patients are recruited and an interim analysis (IA) is conducted after a six-month intervention period. In addition to safety and tolerability, changes in liver fat and noninvasive biomarkers can be evaluated and support decision-making. Only patients on the most promising doses are rolled over for a second six-month period until a new liver biopsy can confirm the compound's efficacy in improving histological features of NASH.

Selecting Clinical Endpoints in Phase IIb and Phase III

Pivotal Trials

Although liver biopsy has multiple limitations, it remains the best method for tracking the progression of NASH. The primary objective of a NASH treatment is to prevent liver-related morbidity and mortality, which occur mainly due to development of cirrhosis. While prevention of progression to cirrhosis by histology is a reasonable surrogate endpoint, it can take approximately 6 to 7 years to see a 1-point progression in fibrosis in NASH patients. Therefore, other surrogate endpoints such as improvement in resolution of NASH and improvement in liver fibrosis by histology are valid surrogate endpoints for Phase IIb or Phase III trials.

The NAS offers a relatively objective way to evaluate severity of the liver injury and is useful for assessing changes in clinical trials. This score ranges from 0 to 8, and a NAS of 5 or more is associated with a greater likelihood of NASH; however, it does not confirm NASH. The diagnosis of NASH is defined by the presence and pattern of specific histologic abnormalities.

A validated method for the staging of NASH should be used to assess changes in disease stage in clinical trials. The NASH Clinical Research Network (CRN) fibrosis staging system is the most validated system currently available. Total scores range from no fibrosis to cirrhosis (0 to 4).

The Need for Clinical Outcomes

At present, an accelerated or conditional approval is possible based on surrogate endpoints — in this case, resolution of NASH with no worsening of fibrosis and a co-primary endpoint of improvement in fibrosis with no worsening of NASH. However, a clinical benefit study to show that the drug improves liver outcomes must be in progress at the time of the marketing approval application.

While accelerated or conditional approval is an important milestone to reach, it also raises some challenges in the post-marketing phase. Patients in the clinical benefit study may drop out and ask their physicians to prescribe the drug, in order to avoid running the risk of being on placebo for more than a year. Strategies to retain patients in these studies will need to be developed.

The Future of NASH

Many NASH patients are undiagnosed, and the real prevalence is unknown. There is an urgent need to identify and validate noninvasive biomarkers for this disease. Since the pathogenesis of NASH is multifactorial, it is reasonable to assume that a combination of products will likely be the best treatment option for patients. Bringing a safe and effective NASH drug to market presents a significant challenge, but with substantial resources being directed toward this condition, it seems inevitable that a therapy will be available in the not-too-distant future.

Table: Target Populations and Endpoints throughout the Development Path

Phase	Target Population	Potential Endpoints
Proof of concept	Patients with biopsy-confirmed NASH or patients at high risk for NASH	<ul style="list-style-type: none"> ▶ Changes in liver fat ▶ Changes in ALT and/or other markers of cell injury/death <ul style="list-style-type: none"> - Inflammation, oxidative stress and fibrosis
Phase IIb	Biopsy-confirmed NASH patients; include patients with liver fibrosis, to inform Phase III	<ul style="list-style-type: none"> ▶ Changes in NAFLD activity score (NAS) without worsening of fibrosis ▶ Resolution of NASH without worsening of fibrosis
Pivotal	Patients with NASH and moderate to severe fibrosis	<ul style="list-style-type: none"> ▶ Resolution of NASH without worsening of fibrosis ▶ Improvement in liver fibrosis with no worsening of NASH ▶ Clinical benefits underway at time of approval: progression to cirrhosis, overall death, compensated cirrhosis, decompensation events

Note: NASH is an evolving therapeutic space. It is likely that as our understanding of the disease matures and clinical trials progress, we will see changes to these development scenarios.

References:

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- ⁴ Filozof C *et al*. Non-Alcoholic Steatohepatitis: Limited Available Treatment Options but Promising Drugs in Development and Recent Progress Towards A Regulatory Approval Pathway. *Drugs* 2015. 75 (12) 1373-92.

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