

Leveraging Clinical Pharmacology to Optimize Drug Development for Nonalcoholic Steatohepatitis (NASH) and Cholestatic Liver Diseases

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Discussion Guide

Introduction

Nonalcoholic fatty liver disease (NAFLD) and cholestatic liver diseases are frequent indications for liver transplant^{1,2} and represent major areas of unmet need in therapeutic development. The progression of nonalcoholic steatohepatitis (NASH), a significant histologic subtype of NAFLD, is incompletely characterized; while the pathogenesis of common cholestatic liver diseases, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), also remains elusive.³ New drugs in development for the treatment of these non-viral chronic liver diseases target different steps in the pathogenesis of chronic liver injury, many of which are shared between NASH and cholestatic diseases.⁴ While some drugs have been assessed in both conditions, and are increasingly assessed as part of combination therapies for an individual indication, there are currently no drugs approved for the treatment of NASH, no FDA-approved therapies for PSC, and limited therapeutic options approved for the treatment of PBC.⁵

Several instances of late-stage attrition in clinical trials for NASH-indicated therapies underscore the significant scientific barriers impeding drug development for NASH and related liver diseases.⁴ Researchers and trialists face persistent challenges in NASH diagnosis and staging as well as patient identification and selection. The identification and validation of non-invasive biomarkers for NASH that accurately measure disease severity and that can reliably correlate with a clinical benefit of treatment remains elusive. Consequently, dose-finding and dose-optimization for patients with varying degrees of liver disease remains an important goal of drug development. Clinical pharmacology may provide tools to address these challenges, including those associated with the assessment of disease progression, and may support the development of models for predicting the impact of hepatic impairment (HI) on dose-response relationships.

To advance therapeutic development, the Duke-Margolis Center for Health Policy and the U.S. Food & Drug Administration are convening this public meeting to discuss how clinical pharmacology tools and methods can support the optimization of drug safety and efficacy. Stakeholder discussion will explore disease pathophysiology and the impact of hepatic impairment on pharmacokinetics and pharmacodynamics. Additional discussion will provide an opportunity to gather stakeholder input on aspects of clinical trial design for NASH and cholestatic liver disease, including the utility of emerging biomarkers for liver function and clinical pharmacology approaches to effective dose-finding.

Session 1: Liver Disease Pathophysiology and the Impact of Liver Dysfunction on Pharmacokinetics, Pharmacodynamics, Drug Safety and Efficacy

The ability of the liver to metabolize a drug is influenced by hepatic blood flow, passive and facilitated diffusion, active transport, and liver enzyme activity, all of which can be affected by liver disease.⁶ NASH in particular lacks reliable translational models⁷, further impacting the characterization and prediction of drug absorption, distribution, metabolism, and excretion (ADME). In addition to its complex effects on

pharmacokinetics (PK), liver disease alters pharmacodynamics (PD).⁶ Furthermore, the molecular mechanisms driving fat accumulation and liver inflammation in NASH are not well understood, but may also affect hepatic drug disposition.⁷

While hepatic impairment can affect the drug disposition and pharmacodynamics in plasma as well as in the liver, the availability of data from clinical trials in patients with HI is generally limited. Additionally, the degree of HI is not well correlated with the type of liver injury, its severity, or liver function test results, and the efficacy and safety of a drug in patients with HI is difficult to predict.⁸ This discussion will focus, in part, on approaches to better understanding disease pathophysiology and how to measure liver function in patients with NASH and cholestatic liver disease, as well as how to use this information to inform trial design in studies for these indications, including in the identification of promising therapeutic targets. Discussion in this session will also address the complexities of disease diagnosis and staging and their implications for clinical trial design and drug development. Trends in clinical trials and major clinical pharmacology questions that may arise during drug development for NASH and cholestatic liver diseases will also be discussed.

Discussion Questions:

1. What are the key knowledge gaps with respect to the pathophysiology of NASH and cholestatic liver disease and how can basic research in this area address these gaps in a way that better facilitates the design and conduct of clinical trials?
2. What are the best understood molecular pathways for disease pathogenesis and progression in NASH, PSC, and PBC?

Session 2: Early Discovery and Development—Treatment Mechanisms, Molecular Targets, and Biomarkers in Early Development of Therapies for NASH and Cholestatic Liver Diseases

The complex pathophysiology associated with NASH or chronic cholestatic liver diseases can be attributed to the interaction of numerous molecular pathways involved in inflammation, fibrosis, and steatosis (in the case of NASH).⁹ Disease pathogenesis has implications for the identification of plausible therapeutic targets and new approaches in molecular targeting may be necessary given recent negative clinical trial results for investigational therapies for NASH.⁹

Clinical trials are further complicated by difficulties ensuring reliable diagnosis and disease staging, critical steps that currently require liver biopsy.^{10,11} Use of the liver biopsy poses clinical and logistical challenges due to its invasiveness, which is associated with increased risk for patients and increased cost for investigators. Less invasive biomarkers are needed to decrease reliance on the liver biopsy and to aid in identification and assessment of disease severity. New, less-invasive biomarkers may better characterize disease by ascertaining information about a larger sampling of liver than what is available with liver biopsy and reducing the variance introduced when biopsies are performed at different clinical sites and interpreted by different pathologists.

Discussion in this session will cover the utility of pharmacodynamic markers measured in healthy subjects for proof-of-mechanism as well as PK/PD for NASH and cholestatic liver disease. Discussion in this session will also cover approaches to the development of less invasive biomarkers that predict or assess disease progression, liver function, histologic changes, pharmacokinetic and pharmacodynamic impacts, and target engagement.

Discussion Questions:

1. In previous clinical trials, what barriers to understanding target engagement have manifested and how can these barriers be addressed?
2. Do current candidate biomarkers have the potential to sufficiently address challenges associated with the diagnosis and measurement of disease severity in NASH and cholestatic liver disease?
 - a. Do genomic associations with NASH have the potential to guide biomarker development and inform treatment decisions in the near-term?
3. How can novel biomarkers be more reliably validated considering limitations inherent in comparison with liver biopsies (e.g., limited sampling, inter-observer variability, etc.)?
4. How can composite biomarkers be used in early phase proof-of-concept studies to streamline development for NASH and cholestatic liver disease indications?
5. How useful are emerging functional biomarkers for predicting changes in PK?

Session 3: Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases

Dose-response and dose-exposure relationships for drugs indicated for NASH and chronic cholestatic liver disease are complicated by impaired liver function and associated impacts on drug metabolism. Early-phase proof-of-concept (POC) dose-finding trials can be conducted as stand-alone studies or integrated as part of adaptive phase 2a/2b studies designed to capture information about exposure-response and exposure-efficacy and, with interim analysis, roll patients over to the most promising doses as clinical study continues.¹²

There are also several opportunities for clinical pharmacology-driven approaches to support the design of phase 2 dose-finding studies. For example, the MCP-Mod framework for dose-ranging studies can be used to support POC of initial dose efficacy in addition to dose-response modeling and the selection of a target dose.¹³ This and other model informed drug development strategies can be used to support the collection of information in early phase drug development and can also be leveraged to support dosing regimen justification as part of regulatory submissions. This discussion will focus on the role of clinical pharmacology and quantitative modeling for dose optimization in patients with impaired hepatic function.

Discussion Questions:

1. What advantages might innovative designs (e.g., combined or seamless phase 2 and phase 3 studies) for dose-finding studies have on trial conduct and how can clinical pharmacology support adaptive trial designs?
2. How can investigators successfully leverage modeling and simulation approaches in dose-ranging studies and what implications do these approaches have for clinical trial design?
3. What considerations factor into dose selection for combination therapies targeting different pathogenic pathways in NASH and in cholestatic liver disease?

Session 4: Clinical Trial Design and Endpoint Selection—Clinical Pharmacology Approaches to Optimizing the Safety and Efficacy of Therapies for NASH and Cholestatic Liver Diseases

Technical and methodological challenges continue to limit the efficient identification of potential patients for enrollment in clinical trials for NASH and chronic cholestatic liver disease. Enrollment is impacted by screening failures, when potential participants undergo biopsies following initial non-invasive screening and ultimately fail to meet histological inclusion criteria for enrollment. Enrollment is additionally complicated given that NASH is frequently asymptomatic and its pathogenesis is complex.

Furthermore, the progression from non-cirrhotic NASH to cirrhotic NASH is also relatively asymptomatic and it is not until patients with NASH develop decompensated cirrhosis that symptoms of chronic liver failure become evident.¹⁴ While patients with chronic cholestatic liver disease can be identified by symptoms occurring before they progress to cirrhosis, many patients are not identified until they develop decompensated cirrhosis.

Trials conducted to demonstrate improvements in steatohepatitis or fibrosis differ in design and duration. While changes in steatohepatitis may occur across relatively shorter durations, significant changes in fibrosis more commonly manifest over several years.¹⁵ Because fibrosis is strongly associated with clinical outcomes in NASH, pharmacological measures of fibrosis that adequately predict change in disease are desired and may represent novel surrogate endpoints in future trials.^{16,17} In the case of cholestatic liver disease, fibrosis is not as strongly associated with clinically meaningful outcomes.¹⁸ While markers of fibrosis and histological assessments may indicate disease progression in some patients, identifying appropriate biochemical markers remains critical.¹⁸ Discussion in this session will focus on clinical pharmacology approaches to support trial design for NASH and cholestatic liver disease, including tools to facilitate patient screening and enrollment and the bridging of endpoints to clinically meaningful outcomes.

Discussion Questions:

1. What biomarkers are most promising in terms of identifying patients with liver fibrosis, or cirrhosis that can be confirmed by histology, and the achievement of trial enrollment targets?
2. What are the advantages and challenges to the conduct of hepatic impairment studies and what other clinically useful measures of hepatic function to predict changes in PK and PD are available?
 - a. Should hepatic impairment studies consider the etiology of cirrhosis?
3. How can clinical pharmacology programs be optimized to facilitate the timely collection of ADME data and to inform patient selection and other aspects of trial design?
4. How can clinical pharmacology tools and methods be leveraged to enable the identification of endpoints that are linked to clinically meaningful outcomes and avoid late-stage attrition in clinical trials?

Session 5: Synthesis Discussion and Next Steps

The use of clinical pharmacology-driven approaches to understand disease progression and drug properties can streamline and accelerate drug development for progressive liver disease. This final session will cover key takeaways from the day as well as a synthesis discussion on the identification of promising molecular pathways, dose-finding strategies, and trial design approaches to the optimization of patient safety and drug efficacy.

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