

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

Sheraton Silver Spring Hotel | Magnolia Ballroom  
8777 Georgia Avenue | Silver Spring, MD  
December 9, 2019

### Agenda

There is significant unmet medical need in the prevention and treatment of NASH, primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC). Despite the increasing prevalence of NASH and its potential to cause severe liver-related morbidity and mortality, there are currently no drugs approved for its treatment. There are also no FDA-approved therapies for PSC and limited therapeutic options approved for the treatment of PBC. Recognizing that the variability in etiologies, natural histories, and pathophysiologies of NASH and cholestatic liver diseases are major impediments to ongoing drug development, the U.S. Food and Drug Administration (FDA) released two draft guidances to assist industry in the clinical development of drugs for the treatment of NASH with liver fibrosis and with compensated cirrhosis.

To further assist in drug development for NASH and cholestatic liver disease, Duke-Margolis and the FDA are convening this public meeting to discuss clinical pharmacology-driven considerations and promising approaches to optimizing drug safety and efficacy. Discussion will encompass (1) the impact of liver dysfunction on pharmacokinetics, pharmacodynamics, patient safety, and patient outcomes; (2) emerging biomarkers, including non-invasive biomarkers, and their utility in the early-phase development of drugs for NASH and cholestatic liver disease; (3) challenges associated with optimizing clinical trial design, including the adequate characterization of pharmacologic effect, selection of study population, and bridging of trial endpoints to clinically meaningful outcomes and; (4) clinical pharmacology approaches to optimizing the safety and efficacy of new drugs.

**8:30 a.m. Morning Refreshments**

**9:00 a.m. Welcome and Introductions**

- Mark McClellan, Duke-Margolis Center for Health Policy

**9:10 a.m. Opening Remarks from FDA**

- Patrizia Cavazzoni, U.S. Food & Drug Administration

*Presentation:*

Clinical Development of Drugs for the Treatment of NASH: General Considerations, Challenges, and the Role of Clinical Pharmacology

- Shirley Seo, U.S. Food & Drug Administration

**9:35 a.m. Session 1: Liver Disease Pathophysiology and the Impact of Liver Dysfunction on Pharmacokinetics, Pharmacodynamics, Drug Safety and Efficacy**

*Moderator:* Mark McClellan

*Objectives:*

- Hear from academic healthcare professionals regarding the pathophysiological changes that occur in patients with liver disease, focusing on therapeutic targets and pathways amenable to identifying relevant biomarkers
- Hear about staging and diagnosis, as well as trial endpoints, as they are presented in FDA guidance
- Discuss how liver disease and dysfunction may adversely impact pharmacokinetics (PK) and pharmacodynamics (PD) as well as patient safety and outcomes
- Discuss the evolving need for dose selection and adjustments or clinical management of drug interactions in patients with liver diseases

*Presentations:*

- Manal Abdelmalek, Duke University
- Kim Brouwer, University of North Carolina
- Insook Kim, U.S. Food & Drug Administration

*Audience Discussion*

**10:35 a.m. Break**

**10:50 a.m. Session 2: Early Discovery and Development—Treatment Mechanisms, Molecular Targets, and Biomarkers in Early Development of Therapies for NASH and Cholestatic Liver Diseases**

*Moderator:* Mark McClellan

*Objectives:*

- Discuss proposed molecular targets and mechanisms for the treatment of NASH and cholestatic liver diseases (e.g., anti-steatosis, anti-fibrosis)
- Discuss biomarkers in early-phase development for NASH and cholestatic liver diseases. Specifically,—
  - Emerging biomarkers for liver function and potential utility to predict PK and histologic changes as well as other diagnostic and prognostic biomarkers
  - Biomarkers for exposure/response, target engagement, and pharmacodynamics in healthy subjects and patients with NASH and cholestatic liver diseases
  - PK/PD for biomarkers representing disease progression including histology and imaging biomarkers
  - The use of non-invasive biomarkers in early proof-of-concept studies
  - Quantitative approaches to understanding and enhancing the utility of translational biomarkers
- Present a NASH biomarker case example

*(Session 2 continues on page 3)*

*Presentations:*

- Naga Chalasani, Indiana University
- Jeffrey Edwards, Intercept Pharmaceuticals, Inc.

*Case Study Presentation:*

- Saurabh Gupta, Takeda Pharmaceuticals Co., Ltd.

*Panel & Audience Discussion*

- Roberto Calle, Pfizer Inc.
- Gregory Everson, HepQuant, LLC
- Anand Balakrishnan, U.S. Food & Drug Administration
- Abbas Bandukwala, U.S. Food & Drug Administration
- Robert Schuck, U.S. Food & Drug Administration

**12:15 p.m. Lunch**

**1:15 p.m. Session 3: Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases**  
*Moderator:* Mark McClellan

*Objectives:*

- Discuss general PK/PD approach to dose-finding and the impact of NASH and cholestatic liver diseases on dose-concentration and dose-response
- Discuss the use of biomarkers and their relationship with clinical outcomes to support dose-finding for clinical trials for NASH and cholestatic liver diseases
  - Discuss the potential utility of biomarkers and histologic endpoints in phase 2 as initial evidence of dose efficacy
- Discuss other challenges and opportunities for clinical pharmacology to support dose-finding and therapeutic development (e.g., combination therapy)

*Presentations:*

- Shen (Steven) Li, U.S. Food & Drug Administration
- Ruby Mehta, U.S. Food & Drug Administration
- Arthur Bergman, Pfizer Inc.

*Panel & Audience Discussion*

- Ajit Dash, Genentech, Inc.
- Claudia Filozof, Covance Inc.
- John Franc, Madrigal Pharmaceuticals, Inc.
- Yaning Wang, U.S. Food & Drug Administration

2:40 p.m.

**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**

*Moderator:* Mark McClellan

*Objectives:*

- Discuss how to optimize trial design through the generation of comprehensive quantitative machinery to understand disease progression, drug effects, and relevant trial aspects (e.g., dropouts)
- Discuss the design, timing, and utility of hepatic impairment studies to support the development of therapeutics for NASH and cholestatic liver diseases
  - Discuss how hepatic impairment studies help to ensure the safety of pediatric patients in clinical trials for liver diseases
- Discuss challenges associated with patient identification and selection in clinical trials for NASH and cholestatic liver diseases
- Discuss challenges associated with matching trial endpoints to clinically meaningful outcomes and potential clinical pharmacology approaches to addressing any challenges

*Presentations:*

- Carol Addy, GENFIT
- Michael Badman, Novartis AG

*Case Study Presentation:*

- Varun Aggarwal, Critical Path Institute

*Panel & Audience Discussion*

- Dilara Jappar, U.S. Food & Drug Administration
- Lara Dimick-Santos, U.S. Food & Drug Administration
- Scott Siler, DILsym Services Inc.

3:55 p.m.

**Break**

4:10 p.m.

**Session 5: Synthesis Discussion and Next Steps**

*Moderator:* John-Michael Sauer, Critical Path Institute

*Objective:*

- Discuss key takeaways from the meeting, opportunities to better understand how pathophysiological changes in patients with NASH and cholestatic liver diseases impact PK/PD and clinical trial design, and promising clinical pharmacology-driven approaches to support drug development

*Presentation:*

- *Real-time summary of information presented during the day*

*(Session 5 continues on page 5)*

*Panel & Audience Discussion*

- Manal Abdelmalek, Duke University
- Arthur Bergman, Pfizer Inc.
- Frank Anania, U.S. Food & Drug Administration
- Mark Avigan, U.S. Food & Drug Administration
- Insook Kim, U.S. Food & Drug Administration

**4:50 p.m.**

**Closing Remarks and Adjournment**

- Shirley Seo, U.S. Food & Drug Administration

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