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

December 9, 2019 • Silver Spring, MD

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**
Issam Zineh, 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, Duke-Margolis Center for Health Policy

Objectives:

- Hear from academic healthcare professionals regarding the pathophysiological changes that occur in patients with liver disease, focusing on drugable targets and amenable pathways to identify 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 drug pharmacokinetics (PK) and pharmacodynamics (PD) as well as patient safety and outcomes
- Discuss the evolving need for dose adjustments or clinical management of drug interactions in patients with impaired liver function

Presentations

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, Duke-Margolis Center for Health Policy

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. More specifically, discuss—
    - 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 noninvasive biomarkers in early proof-of-concept studies
    - Quantitative approaches to understanding and enhancing the utility of translational biomarkers
- Present a NASH biomarker case example

Presentations

Case Study Presentation

Panel & Audience Discussion

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, Duke-Margolis Center for Health Policy

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)

(Session 3 continues on next page)

Presentations

Panel & Audience Discussion

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, Duke-Margolis Center for Health Policy

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

Case Study Presentation

Panel & Audience Discussion

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

Presentation:

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

Panel & Audience Discussion

4:50 p.m. **Closing Remarks and Adjournment**

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