Non-Alcoholic Steatohepatitis Hepatitis (NASH)  
The FDA Perspective

Liver Forum 10  
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Yao-Yao Zhu, MD, PhD  
Division of Gastroenterology and Inborn Errors  
Products (DGIEP), CDER
Disclaimer

The views and opinions expressed here are my own and do not represent official guidance from the FDA.
Outline

• NASH/NAFLD submission trends
• NASH guidance comments
• Study Populations
• Baseline Assessments
• Endpoints and Biomarkers
• FDA-DGIEP Liver Team
Type of Submission

![Graph showing the number of submissions for NASH/NAFLD and Other Liver Dz from 2012 to 2019 (Q3)].

YEAR SUBMITTED

NUMBER SUBMITTED

- NASH/NAFLD
- Other Liver Dz

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Submission Trends

• **Development Program**
  – Commercial; phase 1 and 2; completed phase 3

• **Investigational Treatment**
  – Repurposing of previously approved/studied agents: e.g. T2DM agents, anti-hyperlipidemia, weight loss
  – Combination therapy

• **Failed Phase 3 Trials**
  – Variability of histological readings
  – Adequacy of the surrogates
  – Biomarkers

• **Potential efficacy endpoints**
NASH Guidance

• **Two Draft Guidance** (December 2018 & June 2019)
  – (1) “Noncirrhotic NASH With Liver Fibrosis” & (2) “NASH with Compensated Cirrhosis”
  – Phase 2 & Phase 3 programs
  – Eligibility criteria, study design, efficacy endpoints & safety monitoring

• **Comments to Draft Guidance**
  – Efficacy endpoints
  – Eligibility criteria
  – FDA internal discussions ongoing at this time
Accelerated Approval - Challenges

• A pattern throughout clinical trials for liver diseases
  – Phase 4 trials to verify and describe the clinical benefit of a drug
  – Serious challenges in completion and obtaining necessary efficacy data

• Difficult enrollment and retention
  – Once the product is approved for market

• Potential solution & path forward
  – Detailed natural history studies starting early in drug development
Compensated Cirrhosis NASH Population

• Subpopulations
  – Early cirrhosis without clinically significant portal HTN (i.e., mildly elevated HVPG)
  – Cirrhosis with clinically significant portal HTN (varices, thrombocytopenia)

• Enrichment of clinical trials
  – Advanced disease (portal HTN) more likely to achieve decompensation endpoint

• Clinical benefit endpoint
  – Development of varices requiring treatment in patients without varices at baseline
  – Based on appropriate definitions and agreed-upon methods of detection
Subpopulations in Compensated Cirrhosis

- **Early Cirrhosis without Clinically significant Portal HTN (no varices, utility of HVPG)**
  - Need to define cut-offs for HVPG measurements, platelet count, INR, TB, albumin

- **Compensated Cirrhosis with Clinically significant Portal HTN**
  - Clinical-based Definitions
    - Presence of varices
    - HVPG based on selected thresholds/cut-offs
    - Platelet count based on selected thresholds/cut-offs
    - Albumin
  - Child-Pugh-Turcotte (CPT)
    - TB <2
    - INR < 1.7
  - DILIN
    - TB 2
    - INR 1.5
Composite Clinical Endpoints

• Current composite clinical benefit endpoint in compensated NASH
  – Death, liver Tx, decompensation events (varices bleeding, HE, ascites), MELD score ≥15 in patients with MELD≤12 at baseline

• New composite with a component of varices?
  – Development of varices requiring treatment (banding or pharmacological)

• Prospective statistical planning for single component drivers of composite endpoints
  – Need ways to ensure that all aspects of the disease will be positively impacted by the drug
Pros/Cons of Baseline (BL) Assessments

• Are BL assessments needed to measure efficacy of an endpoint?
  – Is BL histology necessary?
• Generally, it is possible to assess treatment difference between randomized groups on an endpoint without baseline measurements
  – Not possible to assess and compare improvement (i.e. change from baseline) in biopsy based outcome measures/metrics
• No BL measurement may increase uncertainty regarding the enrolled population
  – Current NASH/liver fibrosis biomarkers not accurate in identifying/differentiating non-cirrhotic NASH fibrosis stages 2 or 3 or early cirrhosis
  – Variability in liver biopsy
  – May require large sample size to detect treatment effect
Alternative/Potential Endpoints

• Weight loss as a potential surrogate?
• ALT, ELF (Enhanced Liver Fibrosis), TE (transient elastography), and other Biomarkers
• Pediatric population considerations
  – Progression to diabetes (may be challenging to dissect the relationship to NASH given the prolonged delay to NASH outcomes and complex physiology interplay)
Liver Team - DGIEP

SUPERVISORS
• Dragos Roman, MD – Acting Director
• Bindi Nikhar, MD – Acting Deputy Director
• Lisa Soule, MD – Associate Director

TEAM LEADS
• Frank Anania, MD (Acting)
• Veronica Pei, MD (Acting)
• Stephanie O. Omokaro, MD (On Detail: Acting Deputy Director, Division of Medical Policy Development)

PROJECT MANAGERS
• CDR Cheronda Cherry-France, RN, BSN, MPH
• Evangelia Covert
• LCDR Navi Bhandari

STATISTICIANS
• George Kordzhakia
• Gregory Levin

CLINICAL REVIEWERS
• Mari Blackburn, MD
• Lara Dimick-Santos, MD
• Ruby Mehta, MD
• Yao-Yao Zhu, MD, PhD
THANK YOU!