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Non-Alcoholic Steatohepatitis Hepatitis (NASH) The FDA Perspective

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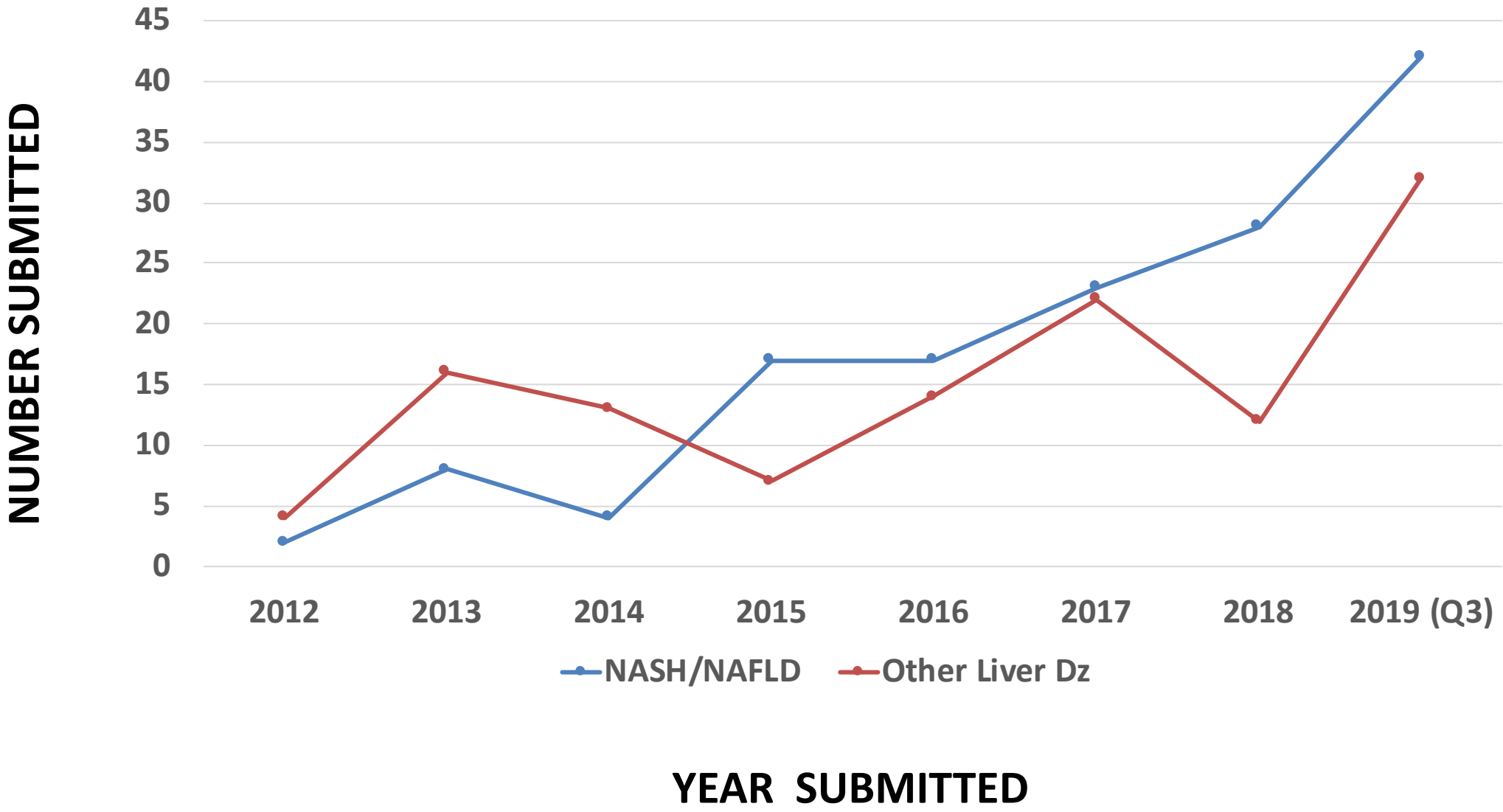
Disclaimer

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



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- **Two Draft Guidance** (December 2018 & June 2019)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- **Comments to Draft Guidance**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

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THANK YOU!


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