Drug Development for Nonalcoholic Steatohepatitis (NASH) with Fibrosis: A Regulatory Perspective

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Conflict of Interest and Disclaimer Statement

I have no financial disclosures regarding pharmaceutical drug products. I have no conflict of interest.

Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position.

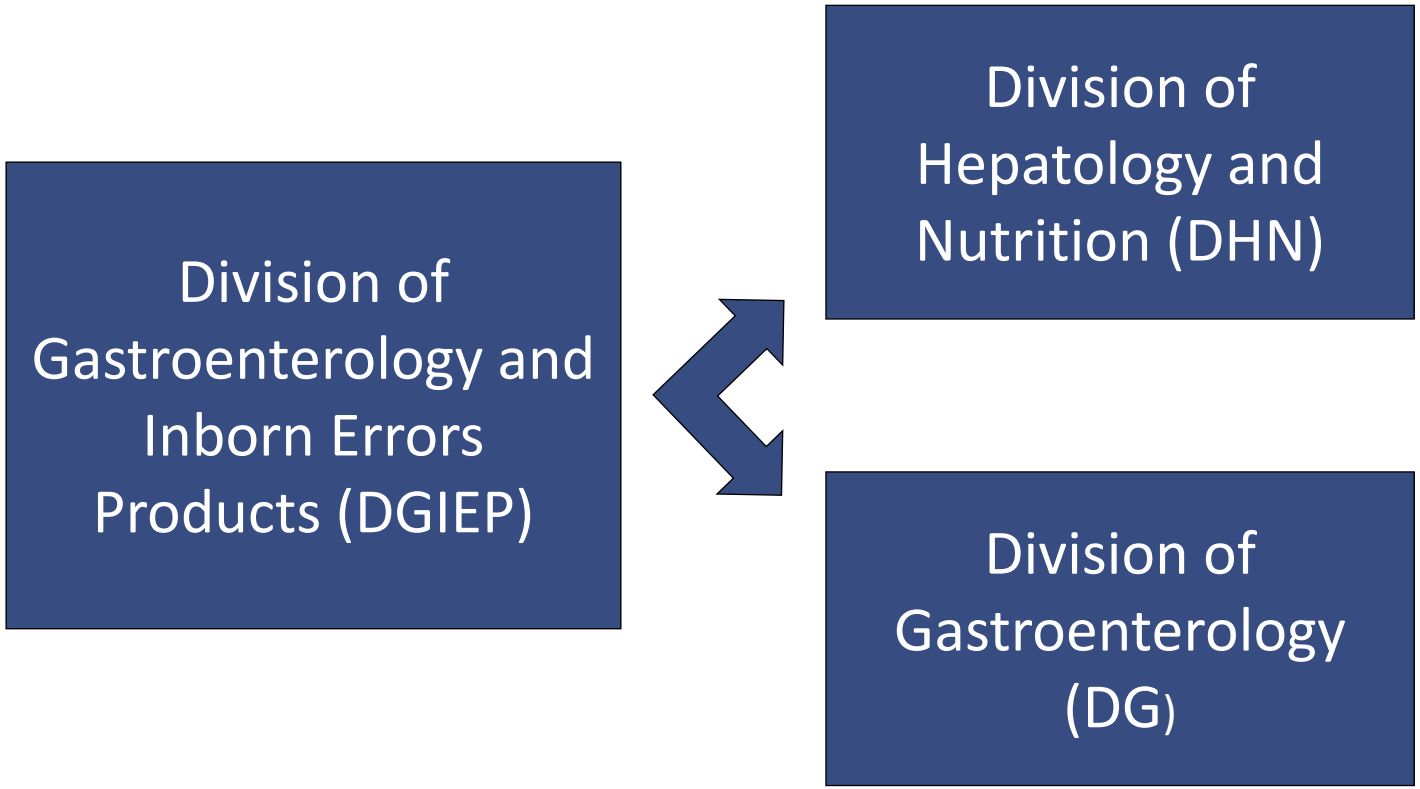
Learning Objectives

- Confirm the reasons why NASH is a serious condition as defined in 21 CFR
- Understand the importance of early clinical development and proof-of-concept trials
- Describe the rationale for the choice of the surrogate endpoint reasonably likely to predict clinical benefit
- Identify the endpoints used to characterize the confirmation of clinical benefit

Outline

- Mission of DHN (Division of Hepatology and Nutrition)
- Overview of NASH
- Early phase drug development for NASH
- Expedited Programs - Accelerated Approval Path
- Surrogate endpoints and liver biopsy
- Phase 3 program development, confirmatory clinical trials
- Trials for NASH-related compensated cirrhosis
- Summary

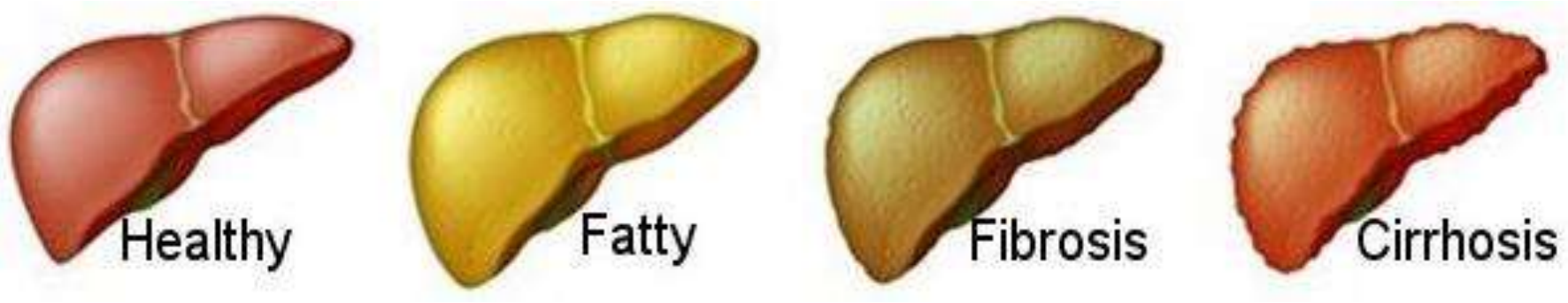
Division of Hepatology and Nutrition

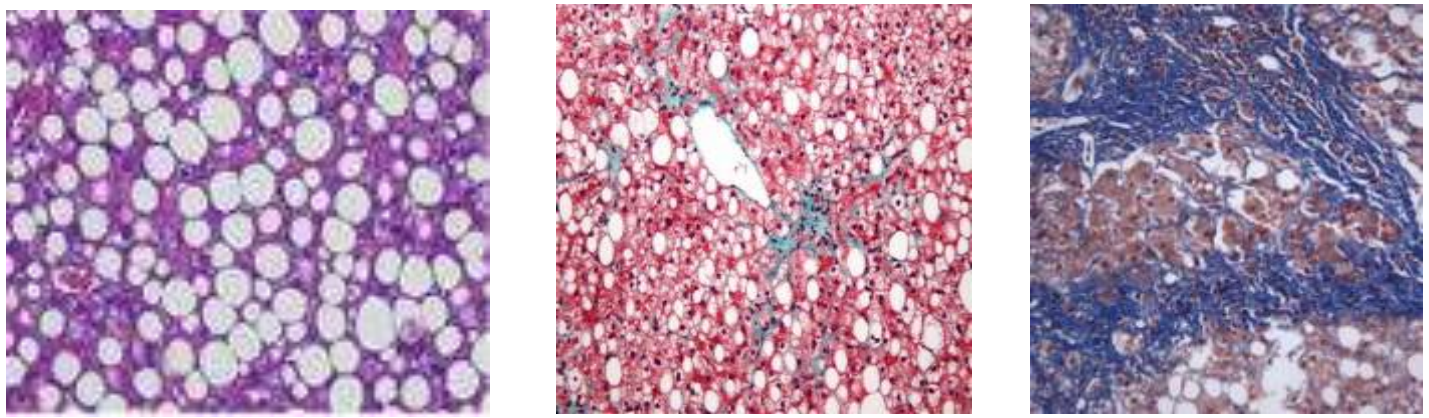


DHN's review activities:

- Development and review of drugs for
  - Treatment of specific diseases of the liver
  - Nutrition products
- Consultations from any FDA review divisions on drug-induced liver injury (DILI)

Progression of NAFLD to Cirrhosis





Nonalcoholic fatty liver (NAFL)

Nonalcoholic steatohepatitis (NASH)

Cirrhosis

Estimated prevalence in US (%) *30-40%* *3-8%* *(1.5-2%)*

- **Increased risk of HCC**
- **No approved drug for NASH**
- **Identification of patients likely to progress is not clear**

Source: http://www.txliver.com/patient-education/fatty-liver-2/
https://aasldpubs.onlinelibrary.wiley.com/doi/pdf/10.1002/cld.585

Challenges of Drug Development for NASH

1. Gradual and slow progression of chronic inflammatory changes in the liver
2. Potential lifelong treatment necessary
3. NASH patients vulnerable to comorbidities

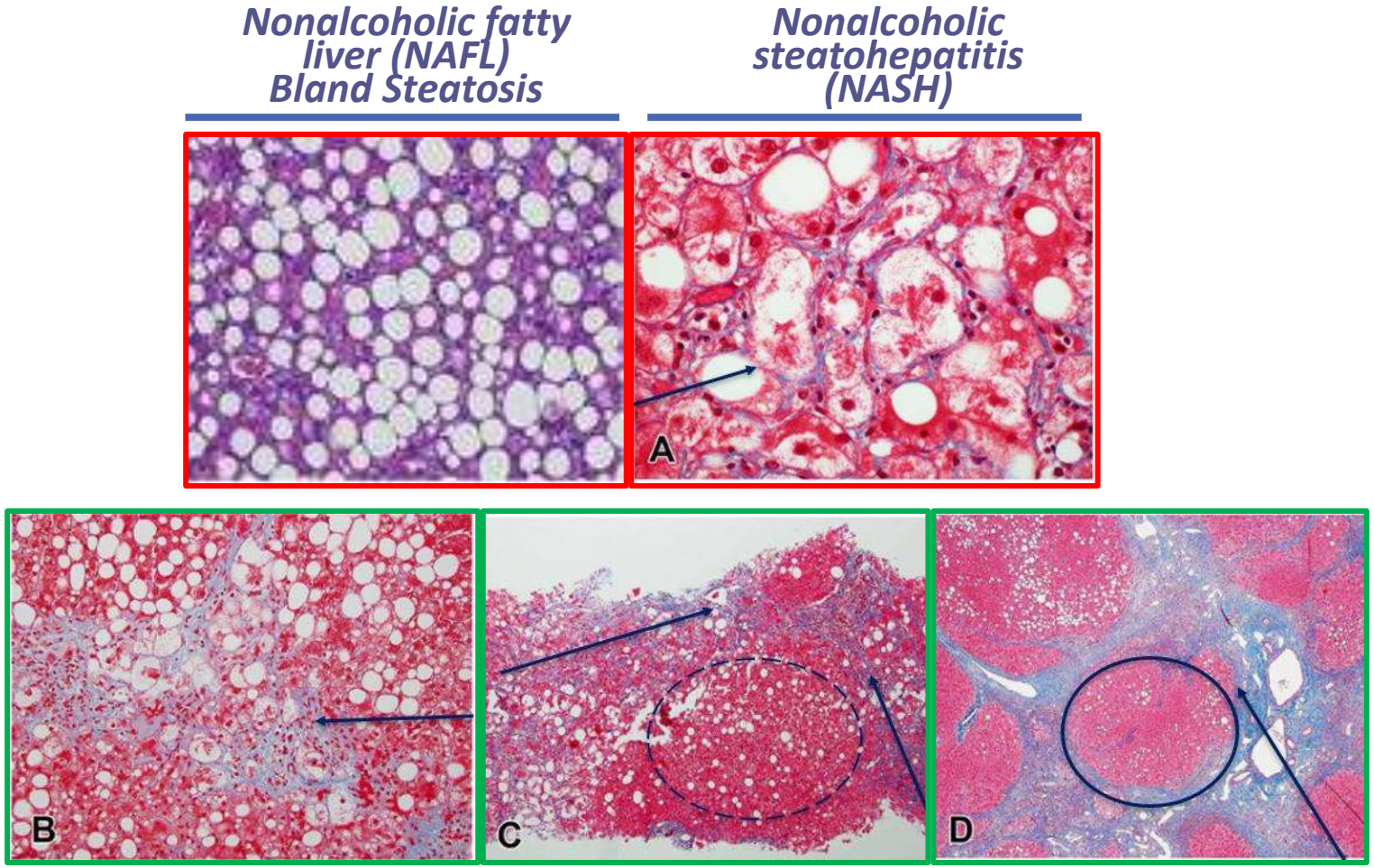
NAFL versus NASH in Drug Development

Studies of patients with NAFL (bland steatosis) and DHN's position

- Patients with NAFL can be enrolled in early phase trials (phase 1, POC)
- Diet, exercise and weight loss seem most important to address NAFL
- Weight loss management (e.g. surgical, pharmacological) not under DHN's domain
- DHN supports drug development for NASH with advanced fibrosis

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Progression from Fatty Liver to Inflammation and Fibrosis to Cirrhosis in NAFLD



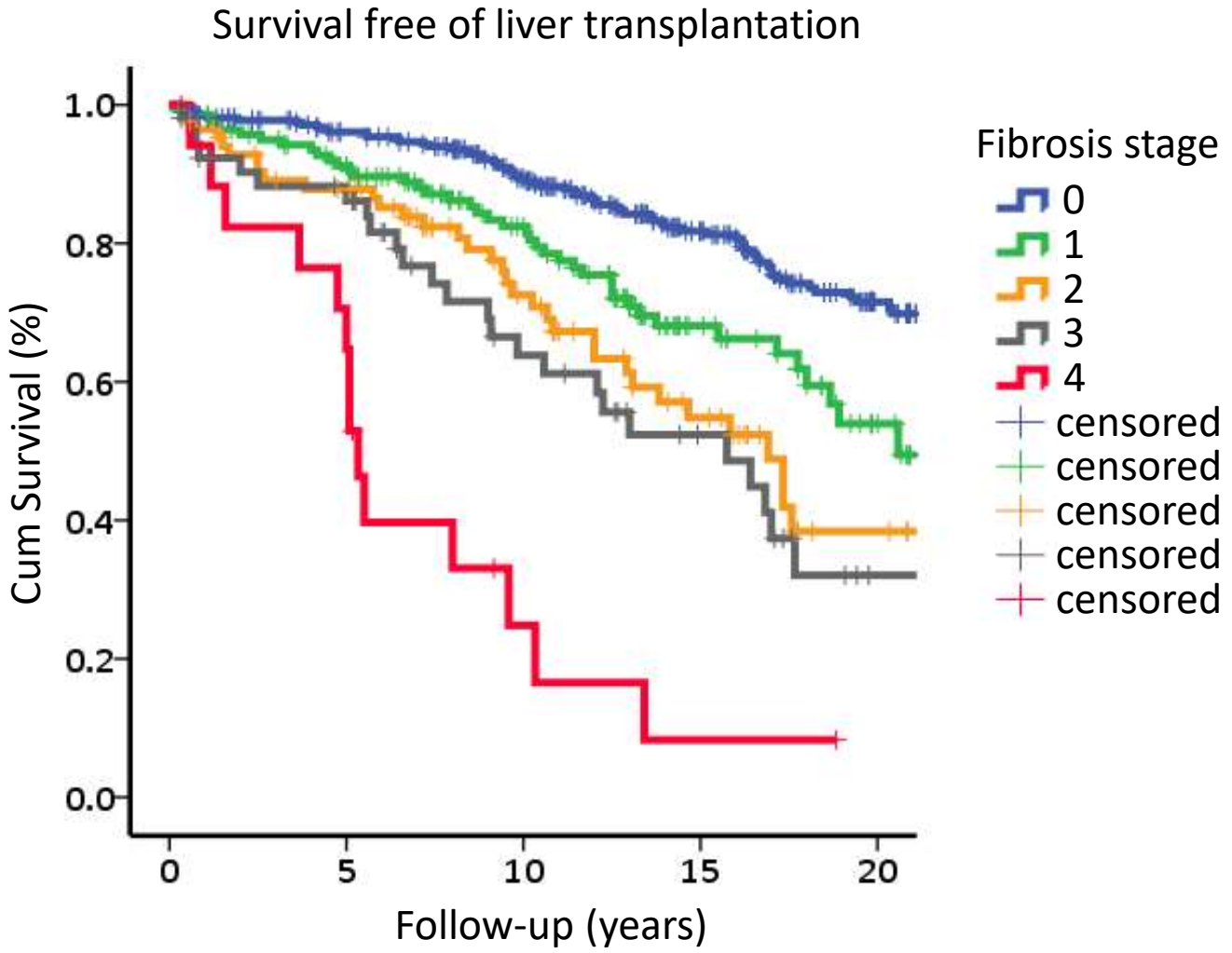
Stage 2 Fibrosis | **Stage 3 Fibrosis** | **Stage 4 Fibrosis** *NASH-related cirrhosis*

Source: Kleiner DE, Makhlouf HR, Clinical Liver Dis. 2016 May; 20(2): 293-312

Why is Histology Accepted as a Surrogate Endpoint?

Histopathology is a surrogate endpoint reasonably likely to predict clinical benefit

- Fibrosis stage, but no other histologic feature of steatohepatitis, has been associated independently with increased mortality, transplantation, and liver-related events



Angulo, P. et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015;149:389-397

Key Points for Early Phase Drug Development for NASH

Trial Design and Considerations

- Need adequate rationale and justification
- Use of noninvasive, disease-specific biomarkers (e.g., an aminotransferase), total bilirubin, and radiographic modalities (e.g., elastography, MRI-PDFF) to assess liver stiffness
- Evaluation of multiple dose levels

Enrollment Criteria

- Known NASH risk factors
- Histological diagnosis of NASH
- Biochemical and/or imaging evidence for steatosis, steatohepatitis, or fibrosis

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

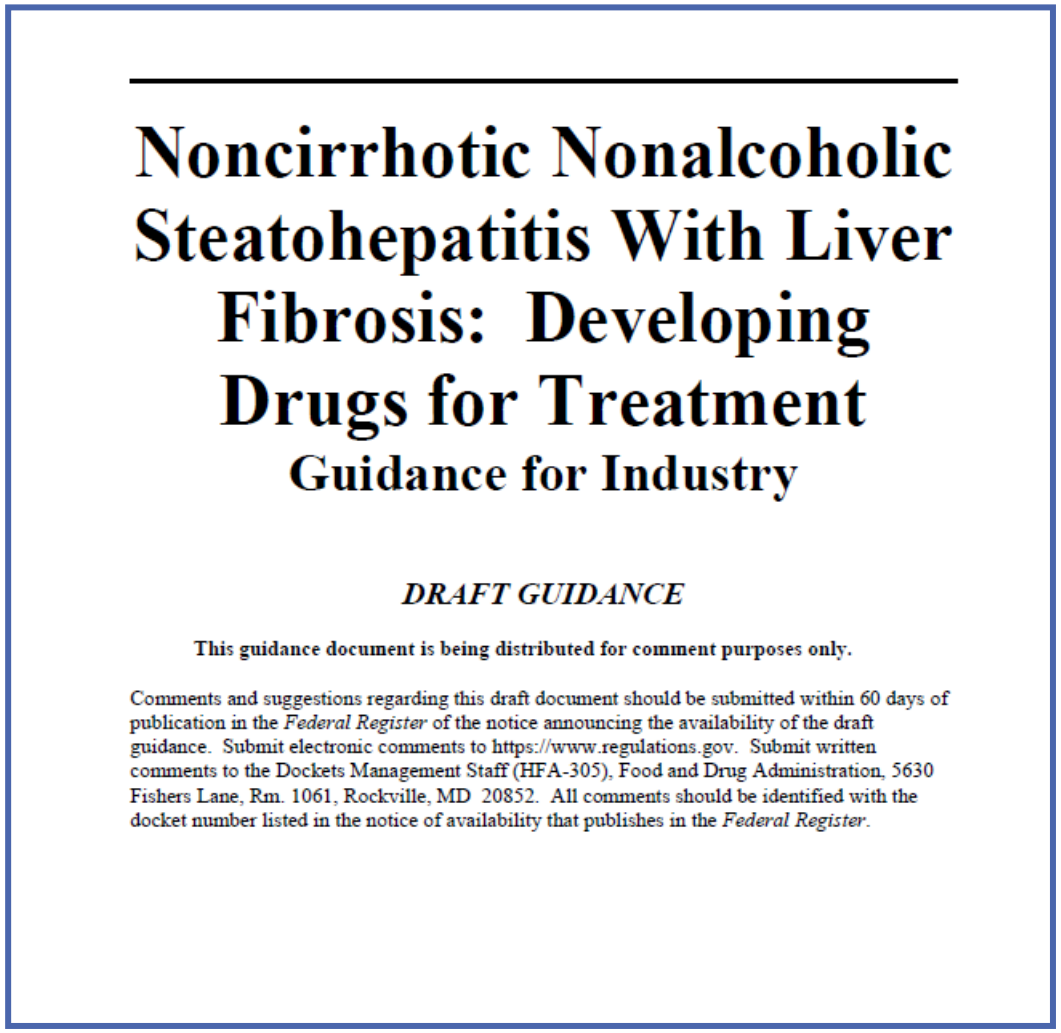
Late Phase 2 Clinical Trials for NASH

Goals of Late Phase 2 Clinical Trials

1. Preliminary evidence of efficacy
2. Characterize treatment effect size and variability to support planning of statistical analyses and powering for Phase 3 trials
3. Obtain adequate dose response to support Phase 3 trial dose selection
4. Assess time course of treatment response to inform Phase 3 trial duration (at least 12-18 months study recommended)
5. Inclusion of patients with comorbidities reflective of target population

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

FDA Guidance Documents Related to NASH



Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Guidance for Industry

Expedited Programs for Serious Conditions – Drugs and Biologics

- Serious condition
- Meaningful advantage over available therapy (Consider lack of alternative treatments, no approved drugs for NASH)
- Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit

- Liver histology as surrogate endpoint to support accelerated approval of noncirrhotic NASH

Source: https://www.fda.gov/media/119044/download, …/127738/download, and …/86377/download.

Expedited Programs for Serious Conditions

- **ACCELERATED APPROVAL**
- FAST TRACK DESIGNATION
- BREAKTHROUGH THERAPY DESIGNATION
- PRIORITY REVIEW

Source: https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf

The Accelerated Approval Pathway#

§ 21 CFR part 314, subpart H

§ CFR part 601, subpart E

506(c) of the FD&C Act, as amended by section 901 of the FDASIA

Requirements:

A drug that treats a serious condition AND generally provides a meaningful advantage over existing therapies

AND

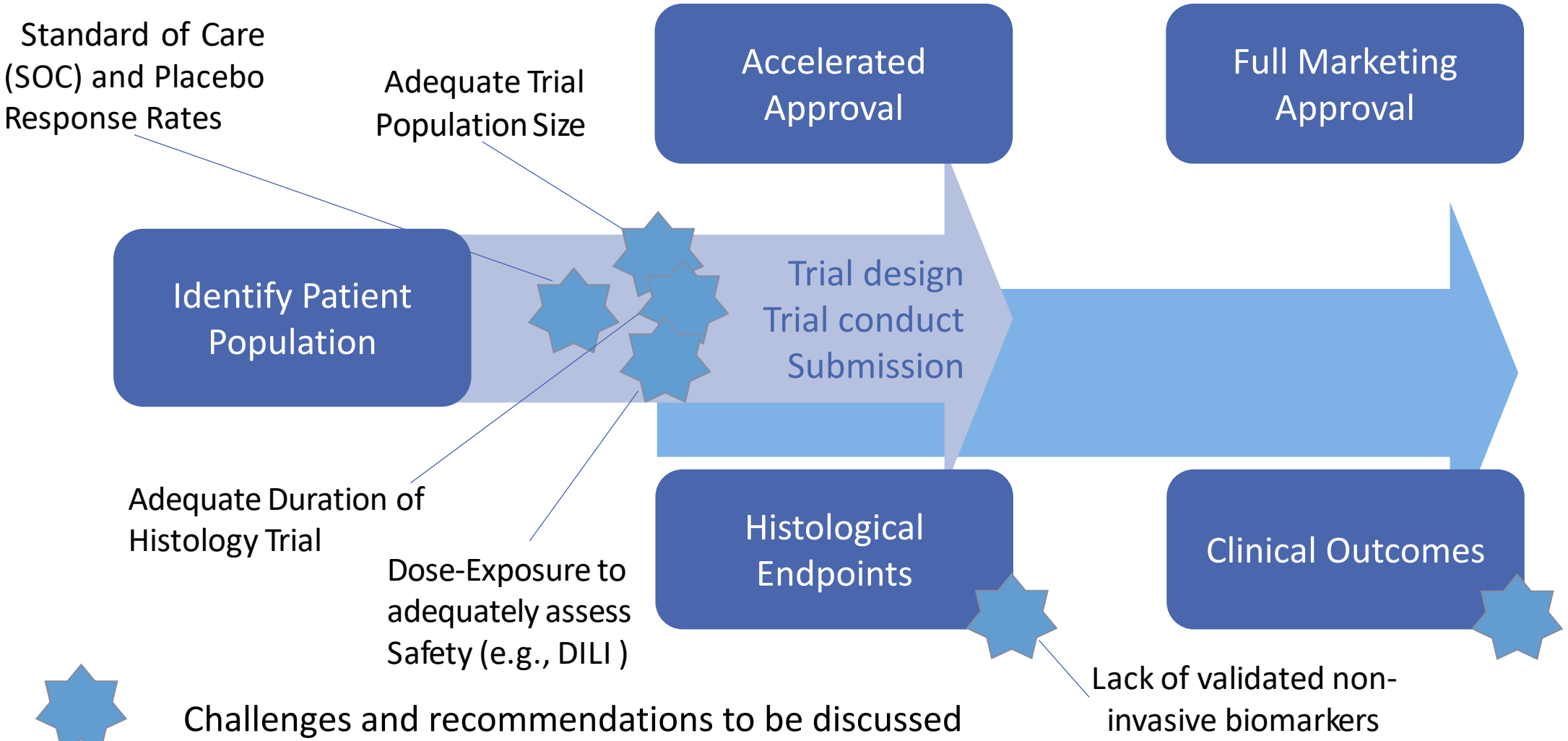
Demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality that is also reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (i.e. an intermediate clinical endpoint

→ In pre-cirrhotic NASH, the Agency will accept improvement in liver histology as defined in the guidance*. Liver biopsy is a surrogate based on research demonstrating that improvement in histology is likely predictive of an improved clinical outcome in NASH patients.

*Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

#Expedited Programs for Serious Conditions

Phase 3 Noncirrhotic NASH Trials Under Accelerated Approval



Key Criteria for Phase 3 Trials

Inclusion Criteria

- Histological diagnosis of ≤6 months before enrollment
- Baseline Model for End-stage Liver Disease (MELD) score ≤12
- Type 2 diabetes if well controlled for ≥3 months
- Stable background therapy ≥6 months with drugs that may affect efficacy assessments
- Standard of care, background therapy for other chronic conditions, and weight stable for ≥3 months
- Stable weight between biopsy and trial initiation

Exclusion Criteria

- Other causes of chronic liver disease
- Decompensated cirrhosis by pre-specified and agreed upon criteria including, but not limited to
  - Evidence of portal hypertension (e.g., varices)
  - Elevated total bilirubin (≥ 1.3 mg/dL)
  - Increased INR (> 1.3)
- ALT and/or AST >5X ULN (~250 U/L)
- ALP >2X ULN (~250-300 U/L)
- Significant weight loss between biopsy and enrollment

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Histology Based Surrogate Efficacy Endpoints to Support Accelerated Approval

- Resolution of steatohepatitis on overall histopathological reading AND no worsening of liver fibrosis on NASH CRN fibrosis score
  OR
- At least one stage improvement in liver fibrosis AND no worsening of steatohepatitis
  OR
- Both resolution of steatohepatitis and improvement in fibrosis

Liver Biopsies

- Fibrosis stage
- Inflammation
- Ballooning
- Steatosis
- Other histopathology endpoints

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Grading and Staging of Liver Tissue for Accelerated Approval Pathway for NASH

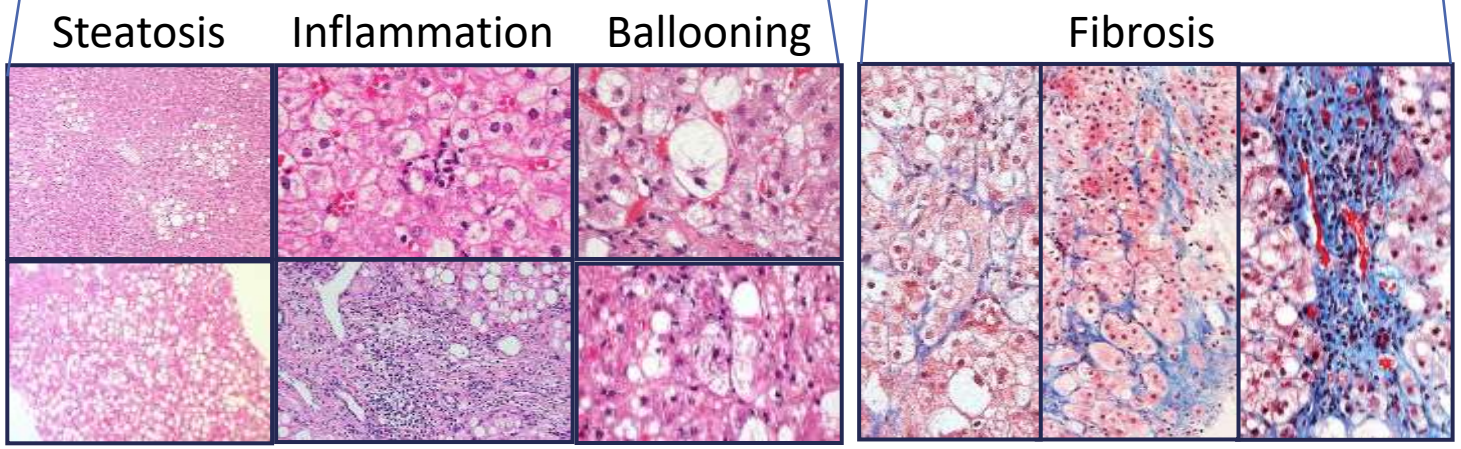
NAFLD Activity Score (NAS)

- Ballooning [0-2]
- Polymorphonuclear leukocyte inflammation [0-3]
- Steatosis [0-3]

+

Fibrosis

Stage 0 (none)
Stage 1
Stage 2
Stage 3
Stage 4 (cirrhosis)



Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA. Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology.* 2011;53(3):810-820.

Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, et.al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005; 41: 1313-1321.

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Histological Endpoints Based on Liver Biopsies

Used For	Challenges	Examples of Potential Solutions
• Eligibility criteria • Stratification • Efficacy	• Sampling issues • Pathologist reading discordance* : inadequate inter- and intra-reader concordance	• Standard procedure for processing slides • Training of pathologists before/during the trial • ≥2 pathologists: if discordant, 3rd pathologist • Same slide read by all pathologists • Central pathology reading • Histopathology adjudication committee • ***Sponsor should prespecify the details of liver biopsy interpretation***

*Source: Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials, Journal of Hepatology, Davison, B.A. et al, available online 28 June 2020.

NASH Recommended Endpoints

Accelerated Approval: Histology

Resolution of steatohepatitis AND no worsening of liver fibrosis

-OR-

Improvement in liver fibrosis AND no worsening of steatohepatitis

-OR-

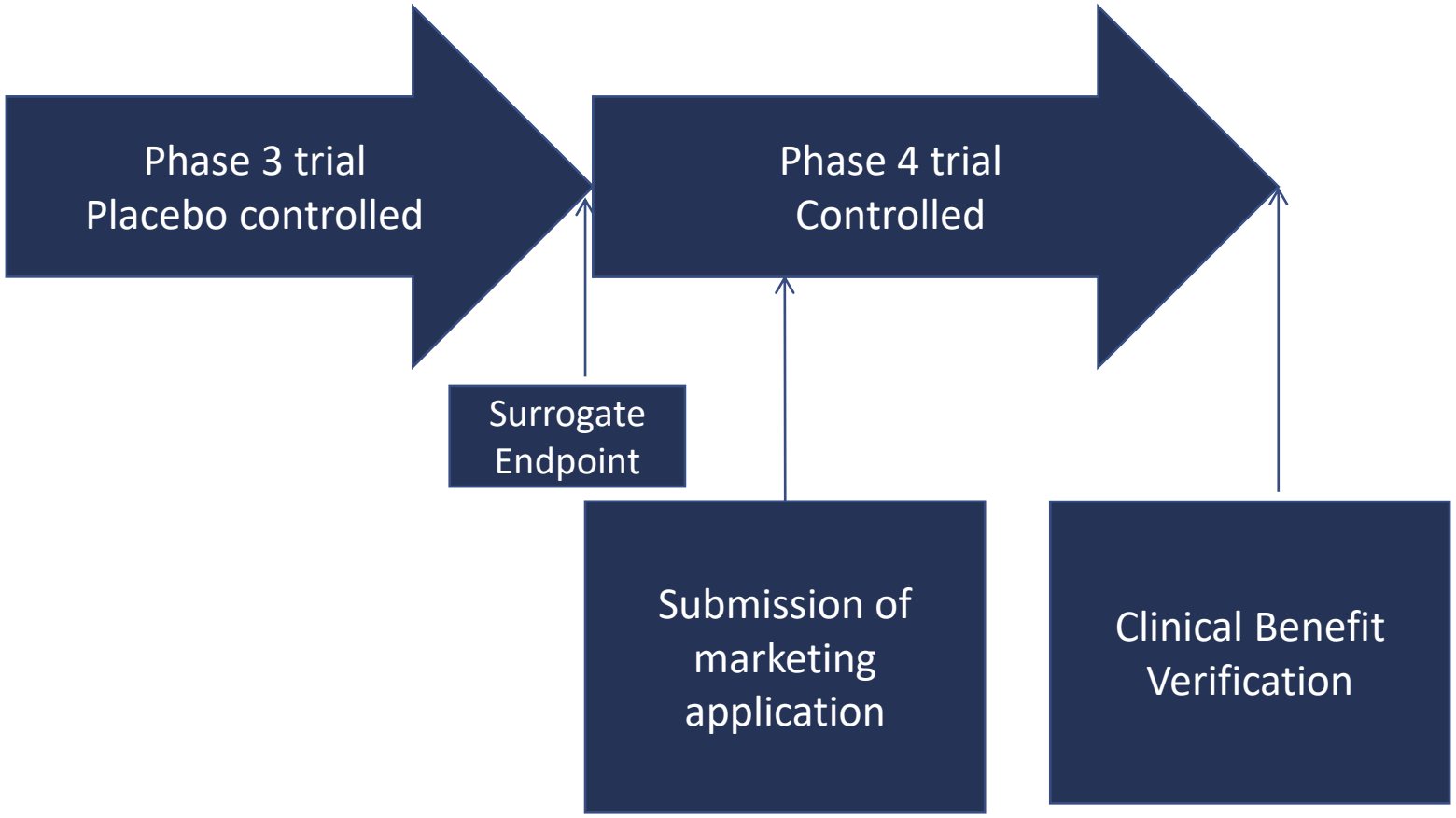
Both resolution of steatohepatitis and improvement in fibrosis

Full Clinical Approval: Clinical Outcomes

- Progression to cirrhosis
- Hepatic decompensation
- Change in MELD score from ≤12 to >15
- Liver transplant
- All-cause mortality

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Accelerated Approval for NASH with Fibrosis



Source: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

Final Thoughts on Phase 3 Clinical Trials for Pre-cirrhotic NASH - 1

Sample Size	Duration	Standard of Care
• Large enough to provide pre-approved safety database • Benefit-risk assessment may require more than one trial powered for efficacy	• At least 12 to 18 months, but 2 years or more may be necessary	• SOC needs to be prespecified • Ensure SOC is uniform across all treatment arms

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Final Thoughts on Phase 3 Clinical Trials for Pre-cirrhotic NASH - 2

- FDA does not recommend combining pre-cirrhotic and cirrhotic patients in the same analysis population given different:
  - eligibility criteria
  - endpoints
  - monitoring
  - management
- Dedicated Hepatic Impairment (HI) studies recommended early (e.g., after proof-of-concept)
- A Drug-Induced Liver Injury (DILI) algorithm should also be established in early phase development.

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

Enrollment of Patients in Phase 3 Trial with the Indication of NASH Cirrhosis - 1

Establish…

- A potential subject's compensated cirrhosis is secondary to NASH
  - Supported by histology or scientifically-backed non-histologic criteria
- Specific criteria to exclude patients with decompensated cirrhosis
  - Patient who decompensates between screening and enrollment should not be randomized
  - Safety criteria for decompensated cirrhotics in clinical trials have not been established

Enrollment of Patients in Phase 3 Trial with the Indication of NASH Cirrhosis - 2

Exclude…

- Patients listed for liver transplantation
- Patients with a baseline MELD score >12
- Patients with a past history of hepatocellular carcinoma (HCC) or HCC treatment

Special Considerations

Patients with compensated NASH cirrhosis taking vitamin E or pioglitazone can either discontinue the respective treatment or be on a stable dose for ≥ 6 months prior to trial enrollment with a constant dose during the trial

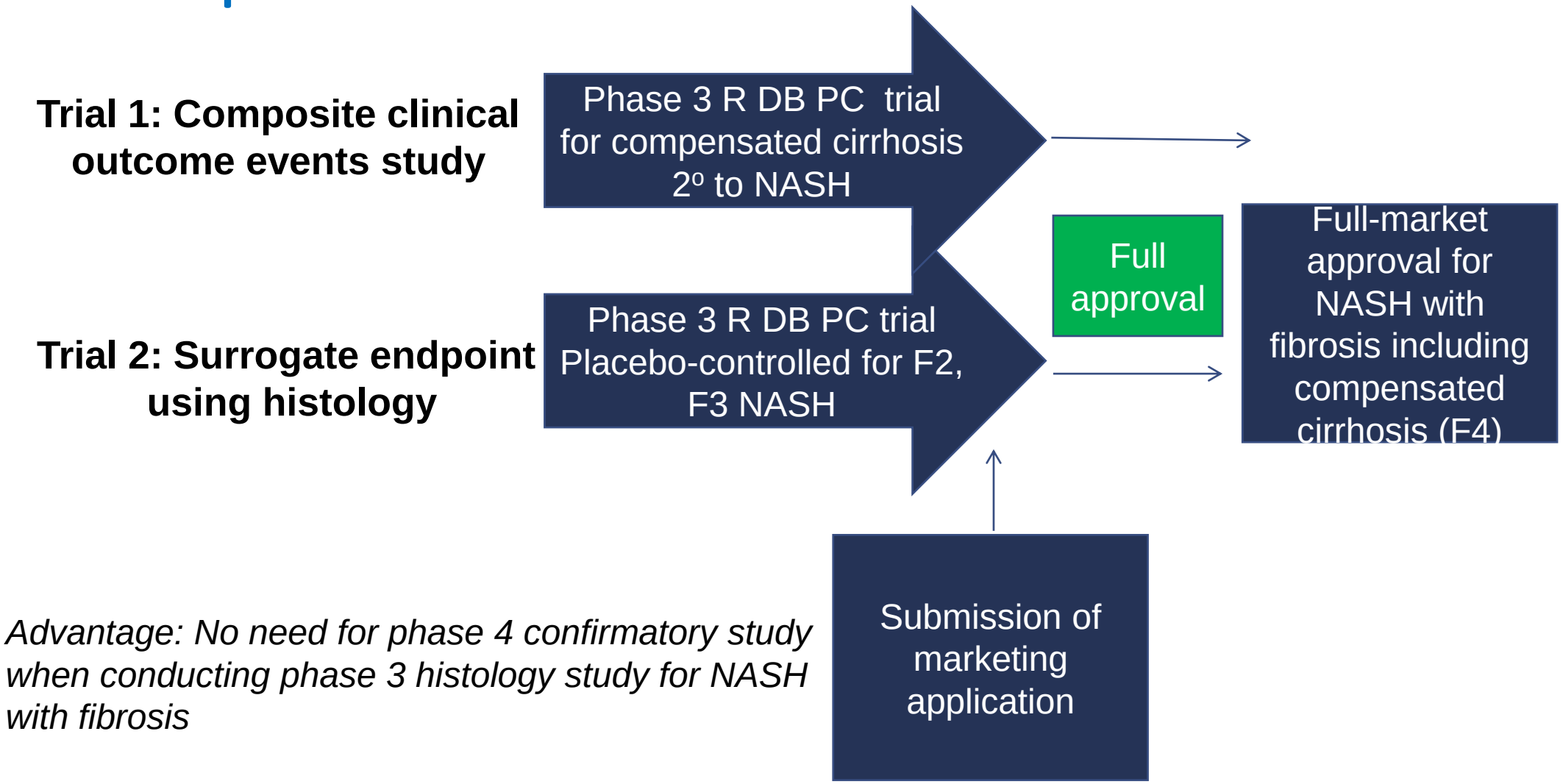
NASH Cirrhosis Trials: Efficacy Endpoints

Pre-specified clinical events (e.g. time-to-event analysis compared with placebo):

- Ascites requiring treatment (e.g. diuretic-resistant ascites, refractory ascites)
- Complication of ascites (e.g., spontaneous bacterial peritonitis)
- Variceal hemorrhage (esophageal or gastric)
- Hepatic encephalopathy (West Haven score ≥2) requiring hospitalization
- Worsening in the MELD score ≥15 (this endpoint approximates listing for liver transplant)
- Liver transplantation
- Death from any cause
- Others proposed by Sponsor?

Source: https://www.fda.gov/media/127738/download

An Alternative Approach for NASH Drug Development



Advantage: No need for phase 4 confirmatory study when conducting phase 3 histology study for NASH with fibrosis

Challenge Question #1

An accelerated approval for a drug to treat NASH may be based upon a surrogate clinical endpoint that is reasonably likely to predict clinical benefit.

A. True

B. False

Challenge Question #2

Which of the followings is an acceptable indication for the accelerated approval pathway?

A. Nonalcoholic fatty liver

B. NASH with compensated cirrhosis

C. NASH with F2/F3 fibrosis

Summary

This presentation reviewed the drug development for NASH with fibrosis from regulatory perspective:

- Highlighted the Agency's commitment to the accelerated approval pathway (Subpart H) using liver histology for developing therapies for NASH with liver fibrosis (F2 and F3)
- Reviewed the histologic and clinical endpoints required for both the histologic and confirmatory trials to achieve full-market approval
- Reviewed key components and common challenges of phase 2 and 3 clinical trials

Thank you!