

Statistical Considerations for Noncirrhotic NASH Trials

Weiya Zhang, Ph.D.

Mathematical Statistician, FDA

ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

September 23-25, 2020

Disclaimer

The views and opinions presented here represent those of the speaker and should not be considered to represent advice or guidance on behalf of the U.S. Food and Drug Administration.

Disease Background

- Nonalcoholic fatty liver disease (NAFLD) is the most common causes of chronic liver diseases in the U.S. Thirty to 40% adults in the U.S. have NAFLD. About 3% to 12% adults in the U.S. have nonalcoholic steatohepatitis (NASH).
- NASH can lead to complications such as cirrhosis, and cirrhosis may lead to chronic liver failure which would require liver transplant for survive.
- No approved drug for NASH
- Unmet medical need

Source: <https://www.niddk.nih.gov/health-information/liver-disease/naflid-nash>

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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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*.

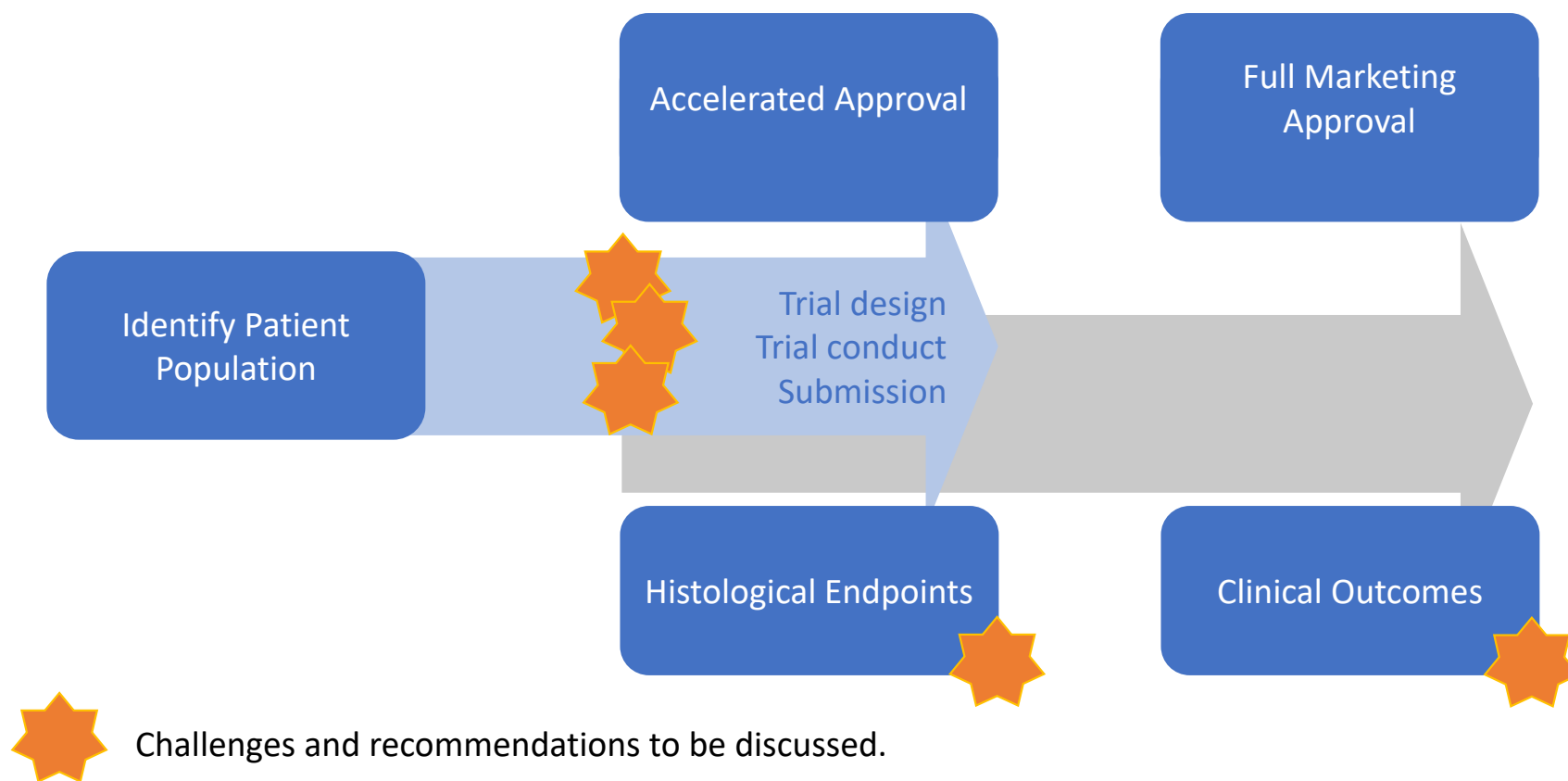
For questions regarding this draft document contact Evangela Covert 301-796-4075.

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 endpoints to support accelerate approval of noncirrhotic NASH

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

Phase 3 Noncirrhotic NASH Trials under Accelerated Approval



Histological 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: FDA guidance for industry - Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis

Histological Endpoints Based on Liver Biopsies

Used for	Challenges	Recommendations
<ul style="list-style-type: none">• Eligibility criteria• Stratification• Efficacy	<ul style="list-style-type: none">• Technical challenges• Pathologist reading discordance*<ul style="list-style-type: none">- % of agreement- Kappa, weighted kappa- Other	<ul style="list-style-type: none">• “Anchor” pathologists’ reading prior to read study slides• Pathology reading consensus• Independent reads and majority wins• Address reading concordance• Adjudication committee• Other suggestions?

* Reference: 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.

Clinical Outcomes for Noncirrhotic NASH

Clinical outcomes*

- Progression to cirrhosis
- Hepatic decompensation
- Change in MELD score from less than or equal to 12 to more than 15
- Liver transplant
- All-cause mortality

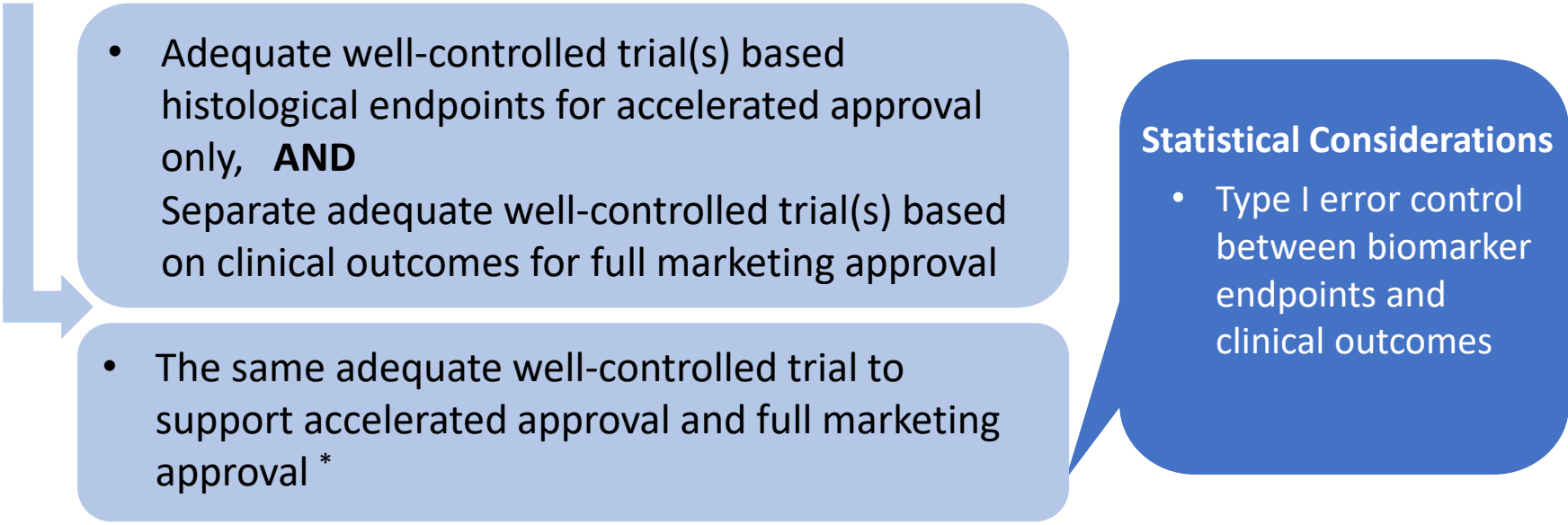
Recommendations

- Adjudication committee for clinical outcomes
- Report, collect, and adjudicate clinical outcomes in a timely manner

* Source: FDA guidance for industry - Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis

Trial Designs Supporting Accelerated Approval

- Confirmatory trial(s) should be underway at the time the marketing application for accelerated approval is submitted*.

- 
- Adequate well-controlled trial(s) based on histological endpoints for accelerated approval only, **AND**
Separate adequate well-controlled trial(s) based on clinical outcomes for full marketing approval

- The same adequate well-controlled trial to support accelerated approval and full marketing approval *

Statistical Considerations

- Type I error control between biomarker endpoints and clinical outcomes

Source: * FDA guidance documents for noncirrhotic NASH and Expedited Programs for Serious Conditions.

Trial Conduct

(General Considerations for Trials Supporting Accelerated Approval)

Recommendations

- Follow good clinical practice.
- Plan ahead for public dissemination of study results for biomarker endpoints and assess its impacts on the retention and conduct on the ongoing clinical outcome trial.
- Document clearly the data access levels of study results for biomarker endpoints.
- Maintain trial integrity.

Submissions Supporting Accelerated Approval (General Considerations)

Drugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval*.

Pre-NDA/BLA

- Communicate on the content format of the NDA package
- Integrated summary pooling strategies
- others

NDA/BLA Package

- Follow pre-NDA communication
- Clearly lay out drug efficacy and safety
- Be ready for information not submitted
- **Include evidence that a proposed surrogate endpoint is reasonably likely to predict the intended clinical benefit**

NDA/BLA Review

- Fully ready
- Be responsive

Source: * FDA guidance for industry - Expedited Programs for Serious Conditions

Take Home Messages

- In noncirrhotic NASH trials, assess pathologists' concordance before trial initiation and establish a process for the trial.
- Consider Type I error control between biomarker endpoints and clinical outcomes if a seamless design supports accelerated approval and full marketing approval.
- Drugs granted accelerated approval meet the same statutory standards for safety and effectiveness as those granted traditional approval.
- Provide evidence that a proposed surrogate endpoint is reasonably likely to predict the intended clinical benefit.

References

- FDA Draft Guidance for Industry: Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (<https://www.fda.gov/media/119044/download>)
- FDA Draft Guidance for Industry: Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment (<https://www.fda.gov/media/127738/download>)
- FDA Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics (<https://www.fda.gov/media/86377/download>)
- FDA Draft Guidance: Demonstrating Substantial Evidence of Effectiveness Human Drug and Biological Products (<https://www.fda.gov/media/133660/download>)
- FDA Draft Guidance: Biomarker Qualification: Evidentiary Framework Guidance for Industry and FDA Staff <https://www.fda.gov/media/122319/download>
- 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.