Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of noncirrhotic nonalcoholic steatohepatitis (NASH) with liver fibrosis. Specifically, this guidance describes the FDA's current thinking regarding the necessary components of a drug development program for noncirrhotic NASH with liver fibrosis and identifies knowledge gaps that represent important challenges in the development of drugs for the indication.

This guidance does not address the clinical development of drugs for the treatment of cirrhosis caused by NASH. This guidance also does not address the clinical development of in vitro diagnostic (IVD) devices that may assist in drug development for NASH.[2]

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Division of Gastroenterology and Inborn Error Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] This guidance does not address the regulatory issues related to commercial development of an IVD device to identify a specific biomarker, which may require FDA clearance or approval of the IVD. Manufacturers interested in pursuing the development of a specific assay for commercial use should consult the Office of In Vitro Diagnostics and Radiological Health in the Center for Devices and Radiological Health. For further information on the process for obtaining an investigational device exemption for an IVD, see the guidance for sponsors, clinical investigators, institutional review boards, and FDA staff *FDA Decisions for Investigational Device Exemption Clinical Investigations*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological changes that begin with simple fatty infiltration of the liver, also known as *simple or isolated steatosis* or nonalcoholic fatty liver (NAFL), which may gradually, sometimes over decades, progress to the development of chronic inflammation (*steatohepatitis* or NASH), fibrosis, and ultimately cirrhosis. Only a subgroup of patients with NAFL will progress to NASH and subsequent cirrhosis. Currently, there are no clear criteria to identify this group of patients.

NAFLD is the most common cause of chronic liver disease in North America.[3] Currently, there are no approved drugs for the treatment of NASH. Given the high prevalence of NASH, the associated morbidity, the growing burden of end-stage liver disease, and limited availability of livers for organ transplantation, FDA believes that identifying therapies that will slow the progress of, halt, or reverse NASH and NAFLD will address an unmet medical need.

III. GENERAL CONSIDERATIONS

Splitting NAFLD into three successive stages (NAFL, noncirrhotic NASH, and NASH with cirrhosis) can provide sponsors a convenient conceptual framework to identify areas of potential future drug development. At this time, because patients' NAFL can exist for many years and may not progress to NASH, it may be challenging to demonstrate a favorable benefit-risk profile of pharmacological treatment(s) in NAFL patients. Therefore, NAFL treatment may be better addressed by interventions such as diet and exercise.

Of the histologic features of NASH, fibrosis is considered the strongest predictor of adverse clinical outcomes, including liver-related death. Because of the significant prognostic differences between NAFL and NASH with fibrosis and the absence of clear clinical, biochemical, or histological criteria that can identify patients with NAFL who are at risk for progression to NASH, the FDA encourages sponsors to focus drug development on the area of greatest need and potential effect on health (i.e., noncirrhotic NASH with liver fibrosis).

At this time, reliable diagnosis and staging of NASH can only be made by histopathological examination of a liver biopsy specimen. Liver biopsy, however, is an invasive procedure that is associated with occasional morbidity and, in rare circumstances, mortality. The use of liver biopsies in clinical trials poses significant logistical challenges (e.g., cost, availability of pathologists with specific expertise in NASH); in addition, some patients are reluctant or unwilling to undergo biopsy. Therefore, noninvasive biomarkers are needed (including imaging biomarkers) to supplant liver biopsy and provide a comparable or superior ability to accurately diagnose and assess various grades of NASH and stages of liver fibrosis. Identification and validation of such biomarkers could significantly accelerate drug development in NAFLD. FDA encourages sponsors to consider biomarker development.

[3] Chalasani N et al., 2018, The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guidance From the American Association for the Study of Liver Diseases, Hepatology, 67(1):328–357.

IV. CONSIDERATIONS FOR DRUG DEVELOPMENT PROGRAMS

A. General Considerations

Sponsors should consider the following during drug development for treatment of noncirrhotic NASH with liver fibrosis:

- FDA encourages the sponsor to use animal models for NASH to screen and identify potential investigational drugs. The sponsor should select a specific animal model based on the mechanism of action of the investigational drug.

- If there is a potential for liver toxicity based on animal toxicology studies, the sponsor should institute an appropriate plan to monitor liver safety early in drug development. For such a plan, the sponsor should consider the challenges of effectively recognizing a liver signal in a chronic liver condition such as NASH.

- Until a sponsor can characterize a drug's initial tolerability, preliminary safety, and pharmacokinetics, patients with evidence of abnormal liver synthetic function should be excluded from early phase trials (i.e., phase 1 and early proof-of-concept (POC) clinical trials). In addition, the sponsor should study the effects of hepatic impairment on the drug's pharmacokinetics early during the drug development program in a dedicated hepatic study to support appropriate dosing and dose adjustment across the spectrum of NASH liver disease.

B. Phase 2 Development Considerations

1. Early Phase 2 Trials

Sponsors should consider the following during early phase 2 trials for drug development for treatment of noncirrhotic NASH with liver fibrosis:

- FDA recognizes that, for sponsors, POC trials are desirable before embarking on extensive clinical development programs. Sponsors should provide adequate rationale and justification for the design of POC trials, including enrollment criteria, duration of the trials, and the choice of endpoints. Sponsors can seek proof of concept in respect to improvement on markers of steatohepatitis, fibrosis, or both.

- Noninvasive, disease-specific biomarkers; standard measures of liver injury (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)); and imaging modalities that assess liver stiffness or hepatic fat content are acceptable as POC study endpoints as long as the sponsor can scientifically justify them.

- In these early trials, baseline histologic documentation of NASH may not always be needed, depending on the endpoints to be assessed. Sponsors can enroll patients based on either a known histological diagnosis of NASH or a combination of biochemical criteria

and/or imaging evidence of steatosis/steatohepatitis/fibrosis in addition to known risk factors for NASH.

- The sponsor should ensure that these early trials capture the same or similar patient populations as those planned for the phase 3 development program. The sponsor can accomplish this via careful selection of inclusion and exclusion criteria.

- Duration of the trial will depend on the known mechanism of action of the drug and the anticipated effect on the efficacy assessment of interest.

- Evaluation of multiple dose levels is advisable at this early stage of development to inform dose selection for subsequent trials.

- If an early trial uses a histological endpoint, the trial should be of long enough duration to ensure that an anticipated effect can be observed (see section IV. B. 2., Late Phase 2 Trials).

- Such early trials offer a good opportunity for concomitant evaluation of histological and biochemical markers to characterize noninvasive biomarkers.

2. Late Phase 2 Trials

Sponsors should consider the following during late phase 2 trials for drug development for treatment of noncirrhotic NASH with liver fibrosis.

- Once proof of pharmacological activity has been demonstrated in a NASH population of interest, the phase 2 program should explore the treatment effect on histological endpoints.

- A successful phase 2 program that supports initiation of phase 3 trials should provide the following:

  - Evidence of efficacy on a histological endpoint (i.e., reduction of inflammatory changes, improvement in fibrosis, or both).

  - Adequate characterization of the treatment effect size and variability around the histological assessment of interest to support planning of statistical analyses and powering for phase 3 trials.

  - Adequate dose response information to support phase 3 program dose selection.

  - Time course of treatment response to inform an appropriate duration of the phase 3 program. Given that histological changes take time, the duration of phase 2 trials should be at least 12–18 months. Sponsors should provide clear scientific justification for trials of shorter durations.

- The sponsor should provide information supporting the proposed biomarker strategy for the late phase 2 program. This can include, but is not limited to, the following:

  – Inclusion of biomarkers that can reliably predict the histopathological evidence of NASH with or without liver fibrosis and, as such, can increase the likelihood of a confirmatory liver biopsy, reduce the number of screening failures, and expedite the screening of eligible patients

  – Inclusion of diagnostic biomarkers that may provide evidence of progression to cirrhosis

  – Inclusion of prognostic biomarkers that may robustly predict liver-related complications

- Sponsors could use innovative designs to combine phase 2 and phase 3 trials (e.g., a trial design with an initial dose response exploration phase followed by continuation at a selected dose or doses). Before initiating the trials, the sponsor should discuss with the FDA specific trial design issues and statistical topics (e.g., multiplicity control, alpha spending).

- Given the appreciable overlap of NASH and metabolic conditions (e.g., obesity, type 2 diabetes mellitus (T2DM)), the proportion of patients with these comorbidities to be included in clinical trials should be reflective of the target population and should be discussed with the FDA before the sponsor initiates phase 2/3 trials.

C. Phase 3 Development Considerations

This section addresses phase 3 drug development for treatment of noncirrhotic NASH with liver fibrosis, which includes clinical trials intended to support a marketing application.

1. Patient Population/Main Enrollment Criteria

a. Patient inclusion criteria

Sponsors should consider the following patient inclusion criteria for clinical trials in drug development for treatment of noncirrhotic NASH with liver fibrosis.

- Patients should have a histological diagnosis of NASH with liver fibrosis made close to the time of trial enrollment (i.e., no more than 6 months before enrollment). Because baseline histology is critical for efficacy evaluation, liver biopsies obtained more than 6 months before enrollment may not represent an accurate status of the disease at the beginning of the trial.

- FDA has accepted as critical inclusion criteria in NASH trials a NASH activity score (NAS) greater than or equal to 4 with at least 1 point each in inflammation and ballooning *along with* a NASH Clinical Research Network (CRN) fibrosis score greater

than stage 1 fibrosis but less than stage 4 fibrosis. These two criteria ensure that patients have evidence of steatohepatitis and significant liver fibrosis without cirrhosis at enrollment. Depending on the drug's mechanism of action and anticipated effect on inflammation and/or fibrosis, the sponsor can propose for discussion with the FDA alternatives to the NAS and NASH/CRN fibrosis score. The sponsor should provide adequate scientific justification for the alternatives.

- Patients with a baseline Model for End-Stage Liver Disease (MELD) score less than or equal to 12 can be enrolled.

- Patients with a documented history of Gilbert's syndrome can be enrolled if the direct bilirubin is within normal reference range.

- Patients with T2DM can be enrolled if they have been on stable doses of antidiabetic medication for at least 3 months before enrollment and can demonstrate that the T2DM is at least moderately controlled. If patients with diabetes are enrolled, the randomization should be stratified by the presence or absence of T2DM.

- Because some NASH patients are treated with vitamin E or pioglitazone, enrollment of such patients in clinical trials may confound treatment effects. Therefore, such NASH patients should either discontinue vitamin E or pioglitazone or be on stable doses for 6–12 months before enrollment. Stratified randomization may be necessary to avoid imbalances between treatment arms for concurrent treatment with vitamin E or pioglitazone.

- A patient's standard of care, background therapy for other ongoing chronic conditions, and weight should be stable for at least 3 months before trial enrollment. Stable weight is defined as no more than a 5 percent change.

- Patients who have had a biopsy more than 3 months before trial enrollment should have stable weights between the time of the biopsy and trial initiation.

b. Patient exclusion criteria

Sponsors should consider the following patient exclusion criteria for clinical trials in drug development for treatment of noncirrhotic NASH with liver fibrosis:

- Sponsors should rule out other causes of chronic liver disease for trial patients, including alcoholic liver disease, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, human immunodeficiency virus, etc.

- The protocol should clearly state the criteria for exclusion (e.g., biochemical, histopathological, clinical) of patients with cirrhosis. Currently, the FDA recommends excluding patients with bilirubin greater than or equal to 1.3 milligrams per deciliter and an international normalized ratio (INR) greater than or equal to 1.3.

- Evidence of portal hypertension (e.g., low platelet counts, esophageal varices, ascites, history of hepatic encephalopathy, splenomegaly), elevated bilirubin, or prolonged INR should disqualify patients from trial enrollment.

- Elevations of the liver enzymes such as ALT and AST are expected in NASH. However, an ALT and AST elevation greater than five times the upper limit of normal (ULN) (approximately 250 units per liter (U/L)) would indicate the possibility of other concomitant liver diseases (e.g., alcohol-associated liver disease, autoimmune hepatitis). Therefore, such patients should not be enrolled. Similarly, bilirubin levels should not exceed the ULN. Alkaline phosphatase should be less than 2 ULN (less than 250–300 U/L).

2. Trial design and efficacy endpoints

Sponsors should consider the following trial design and efficacy endpoints for clinical trials in drug development for treatment of noncirrhotic NASH with liver fibrosis:

- Sponsors should evaluate drugs for the treatment of NASH in double-blind, placebo-controlled clinical trials of sufficient duration and size.

- The ultimate goal of NASH treatment is to slow the progress of, halt, or reverse disease progression and improve clinical outcomes (i.e., prevent progression to cirrhosis and cirrhosis complications, reduce the need for liver transplantation, and improve survival).

- Because of the slow progression of NASH and the time required to conduct a trial that would evaluate clinical endpoints such as progression to cirrhosis or survival, the FDA recommends sponsors consider the following liver histological improvements as endpoints reasonably likely to predict clinical benefit to support accelerated approval under the regulations:[4]

  – Resolution of steatohepatitis on overall histopathological reading **and** no worsening of liver fibrosis on NASH CRN fibrosis score. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis;

  OR

  – Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) **and** no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis);

[4] 21 CFR 314.500 et seq. for new drugs and 21 CFR 601.40 et seq. for biological products. See the guidance for Industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

OR

- Both resolution of steatohepatitis and improvement in fibrosis (as defined above).

- Because the relationship between liver histological improvement and clinical outcomes has not been characterized, sponsors can propose and justify specific degrees of histological improvement anticipated to be beneficial based on the mechanism of action of the specific drug under development (i.e., drugs that predominantly address the inflammatory process, treat the fibrosis, or both).

- For NASH drugs approved on the basis of liver histology under the accelerated approval pathway, randomized, double-blind, placebo-controlled clinical trials designed to describe and verify the drug's clinical benefit should be underway at the time of submission of the marketing application. Clinical benefit can be verified by demonstrating superiority to placebo in delaying disease progression measured by a composite endpoint that includes the following:

  - Progression to cirrhosis on histopathology.

  - Reduction in hepatic decompensation events (e.g., hepatic encephalopathy, variceal bleeding, ascites). These events should be adjudicated by a committee of experts.

  - Change in MELD score from less than or equal to 12 to more than 15. (This endpoint approximates listing for liver transplant.)

  - Liver transplant.

  - All-cause mortality.

- FDA encourages sponsors to identify biochemical or noninvasive imaging biomarkers that could eventually replace liver biopsies. Sponsors could use such biomarkers, once characterized and agreed upon by the FDA, either for patient selection or for assessing efficacy in clinical trials.

- Sponsors have multiple ways to design and implement phase 3 and postapproval confirmatory clinical trials. Sponsors should discuss these designs and implementations with the FDA before initiating trials.

3. Safety Considerations

FDA recommends the following safety considerations for clinical trials in drug development for treatment of noncirrhotic NASH with liver fibrosis:

- The specific number of patients for each drug development program will require an individualized approach and should be discussed with the FDA. Regardless of the

approach, the safety database for approval should include patients who have been exposed to the drug in multiple-dose trials at the relevant dose(s).

- NASH is associated with elevation of liver enzymes, and assessment of potential drug-related liver toxicity can be very challenging given the patients' background of chronic liver disease. FDA encourages sponsors to develop a specific approach (e.g., an algorithm) for liver monitoring in patients with abnormal liver function at baseline, including criteria for drug discontinuation for individual patients and trial stopping rules (temporary or permanent). The protocol should specify a plan for diagnostic evaluation for such liver enzyme elevations. Sponsors should establish an expert committee to adjudicate cases that meet protocol-defined criteria for hepatic decompensation events and possible cases of drug-induced liver injury.

- Given the growing evidence of a link between NAFLD and cardiovascular disease, cardiovascular safety should be adequately monitored in clinical trials. FDA encourages sponsors to establish an expert committee to adjudicate cases that meet protocol-defined criteria for major adverse cardiac events.

D. Pediatric Considerations

Pediatric NASH appears to have different histological characteristics as well as a different natural history when compared to adult NASH. For reasons that are currently unknown, disease characteristics and progression in pediatric patients may be different. In addition, the common histologic findings of ballooning degeneration, classic zone-3 fibrosis, and parenchymal inflammation observed in adult NASH are less common in children with NASH. Therefore, applying the adult scoring system to children with NASH may be challenging. Sponsors of drugs for the treatment of noncirrhotic NASH with liver fibrosis should consider the following for pediatric studies:

- Given all the differences mentioned, extrapolation of efficacy from adults to pediatric patients solely on pharmacokinetic or pharmacodynamic information is not appropriate at this time. However, gathering robust exposure-response information during adult trials can be critical to inform the ability to extrapolate in the future.

- Longitudinal natural history data in pediatric patients are needed to better characterize the disease course, identify inclusion/exclusion criteria for future clinical studies, and support choice of endpoints for pediatric studies.

- The risk/benefit of each drug will determine the overall timing of the pediatric studies in relation to the adult clinical trials. Sponsors should consider initiating pediatric studies once sufficient information about dosing, safety, and efficacy in adults is obtained.

- Pediatric studies in noncirrhotic NASH pose additional challenges. FDA plans to provide recommendations addressing drug development for pediatric noncirrhotic NASH in a future guidance.