Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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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 nonalcoholic steatohepatitis (NASH) with compensated cirrhosis.

This guidance describes the Food and Drug Administration's (FDA's) current recommendations regarding the important components of a drug development program for compensated NASH cirrhosis. This guidance focuses on the enrollment criteria, trial design, efficacy endpoints, and safety considerations for phase 3 trials. This guidance also identifies knowledge gaps that represent important challenges in the development of drugs for this indication.

This guidance does not address the clinical development of drugs for the treatment of decompensated cirrhosis resulting from NASH. This guidance also does not address drug development for patients with noncirrhotic NASH or provide general recommendations on early drug development in NASH, such as use of animal models and approaches to monitoring for potential liver toxicity. These are both addressed in the draft guidance for industry *Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (December 2018).[2]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] When final, this guidance will represent the FDA's current thinking on this topic. For 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 features that range from simple fatty infiltration of the liver to chronic liver inflammation with or without fibrosis and cirrhosis. Cirrhosis is broadly divided into two main stages, compensated and decompensated.

Patients with compensated NASH cirrhosis have significant scar formation that is evident by histopathology, with hepatocytes clustered in nodules surrounded by dense extracellular matrix. Despite this, patients may appear clinically healthy. However, patients with compensated NASH cirrhosis can progress to decompensated cirrhosis, defined primarily by complications related to portal hypertension and impaired synthetic function that results in end-stage liver disease, the primary manifestation of decompensated cirrhosis.[3]

The goals of treatment for compensated NASH cirrhosis are to halt or slow progression of fibrosis, prevent clinical decompensation, reduce the need for liver transplantation, and improve survival. There are currently no FDA-approved drugs for compensated NASH cirrhosis.

III. PHASE 3 PROGRAM CONSIDERATIONS

A. Patient Population/Enrollment Criteria

Sponsors of drugs to treat compensated NASH cirrhosis should consider the following when enrolling patients in phase 3 clinical trials:

- Sponsors should be careful to enroll in clinical trials only patients whose cirrhosis is secondary to NASH and not caused by other etiologies. Patients should have histological diagnoses of NASH, and other causes of chronic liver disease should be ruled out (e.g., alcoholic liver disease, viral hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1-antitrypsin deficiency, HIV).

- The protocol should specify the following criteria used to establish a diagnosis of compensated cirrhosis:

  – A diagnosis of cirrhosis can be supported by histology (e.g., a NASH Clinical Research Network fibrosis score of 4); the sponsor can propose and discuss other histological criteria with the FDA.

  – Non-histologic criteria for the diagnosis of cirrhosis have not been established, but the sponsor can propose non-histologic criteria that could be acceptable, if

[3] Agopian VG, Kaldas FM, Hong JC, Whittaker M, Holt C, Rana A, Zarrinpar A, et al., 2012, Liver Transplantation for Non-Alcoholic Steatohepatitis: The New Epidemic, *Ann Surg,* 256(4):624–633.

scientifically supported. The FDA encourages sponsors to identify biochemical or imaging noninvasive biomarkers that can replace liver biopsies.

- The protocol should specify criteria to exclude patients with decompensated cirrhosis. The criteria can include, but are not limited to, the following:

  – Evidence of portal hypertension (e.g., low platelet counts, esophageal varices, ascites, history of hepatic encephalopathy, splenomegaly)

  – Elevated bilirubin

  – Elevated international normalized ratio or prolonged prothrombin time.

- Patients who develop manifestations of hepatic decompensation between screening and enrollment should not be randomized.

- Sponsors can enroll patients with documented history of Gilbert's syndrome if the direct bilirubin is within normal reference range.

- Sponsors can enroll patients with type 2 diabetes mellitus (T2DM) if they are adequately controlled on a stable dose or doses of antidiabetic medication(s) for at least 3 months before trial enrollment.

- Some patients with compensated NASH cirrhosis can be treated with vitamin E or pioglitazone. Such patients should either (1) discontinue vitamin E or pioglitazone or (2) be on a stable dose for 6 months before trial enrollment, and the dose should be held constant during the trial.

- Elevations of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be expected in NASH. However, ALT or AST elevation greater than 5 times the upper limit of normal (ULN) would indicate the possibility of concomitant liver disease(s) (e.g., alcohol-associated liver disease, autoimmune hepatitis). Therefore, sponsors should not enroll patients with evidence of such transaminase elevations. Similarly, bilirubin levels should not exceed ULN. Alkaline phosphate should be less than 1.5 times the ULN.

- Sponsors should exclude the following patients from trial enrollment:

  – Patients listed for living-related or orthotopic liver transplantation.

  – Patients with a baseline Model for End-Stage Liver Disease (MELD) score greater than 12.

  – Patients with a history of hepatocellular carcinoma (HCC) or history of HCC treatment.

B. Trial Design/Efficacy Endpoints

Sponsors of drugs to treat compensated NASH cirrhosis should consider the following for trial design and efficacy endpoints:

- Drugs for the treatment of compensated NASH cirrhosis should be evaluated in randomized, placebo-controlled, double-blind clinical trials. Sponsors can propose stratification factors (e.g., T2DM, vitamin E, pioglitazone) and discuss with the FDA before initiating phase 3 trials.

- The drug development program should evaluate the effect of the investigational drug relative to placebo on the composite endpoint of time from randomization to the first of any one of the following outcome events:

  - Complication of ascites including any of the following: spontaneous bacterial peritonitis, diuretic-resistant ascites (refractory ascites), hepato-pleural effusion, etc.

  - Variceal hemorrhage

  - Hepatic encephalopathy

  - Worsening in the MELD score to greater than or equal to 15 (this endpoint approximates listing for liver transplant)

  - Liver transplantation

  - Death from any cause

- The FDA strongly recommends clinical outcome trials to support a marketing application. Histological improvements in fibrosis can be proposed and justified; however, at present the relationship between histological changes in cirrhosis and clinical outcomes has not been characterized, and further, reversal of cirrhosis (e.g., fibrosis stage F4) may not be feasible. Because currently there is insufficient evidence to support the use of histological improvements as a surrogate endpoint that is reasonably likely to predict clinical benefit to support accelerated approval, in general, the FDA expects to evaluate drugs for the treatment of compensated NASH cirrhosis under the traditional approval pathway.

C. Safety Considerations

Assessment of potential drug-related liver toxicity can be challenging in patients with chronic liver disease. The FDA encourages the sponsor to develop a specific approach (e.g., an algorithm) for monitoring liver function 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 guidelines for monitoring liver function. The sponsor should establish an expert committee to adjudicate cases that meet protocol-defined

175 criteria for drug-induced liver injury. Given the growing evidence for an association between
176 NAFLD and cardiovascular disease, cardiovascular safety should be adequately monitored
177 during the clinical trial.