
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DRAFT GUIDANCE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)**

**June 2019
Clinical/Medical**

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Contains Nonbinding Recommendations
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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	PHASE 3 PROGRAM CONSIDERATIONS.....	2
A.	Patient Population/Enrollment Criteria	2
B.	Trial Design/Efficacy Endpoints.....	4
C.	Safety Considerations	4

1 **Nonalcoholic Steatohepatitis with Compensated Cirrhosis:**
2 **Developing Drugs for Treatment**
3 **Guidance for Industry¹**
4
5

6
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
12

13
14
15 **I. INTRODUCTION**
16

17 The purpose of this guidance is to assist sponsors in the clinical development of drugs for the
18 treatment of nonalcoholic steatohepatitis (NASH) with compensated cirrhosis.
19

20 This guidance describes the Food and Drug Administration's (FDA's) current recommendations
21 regarding the important components of a drug development program for compensated NASH
22 cirrhosis. This guidance focuses on the enrollment criteria, trial design, efficacy endpoints, and
23 safety considerations for phase 3 trials. This guidance also identifies knowledge gaps that
24 represent important challenges in the development of drugs for this indication.
25

26 This guidance does not address the clinical development of drugs for the treatment of
27 decompensated cirrhosis resulting from NASH. This guidance also does not address drug
28 development for patients with noncirrhotic NASH or provide general recommendations on early
29 drug development in NASH, such as use of animal models and approaches to monitoring for
30 potential liver toxicity. These are both addressed in the draft guidance for industry *Noncirrhotic*
31 *Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment* (December
32 2018).²
33

34 In general, FDA's guidance documents do not establish legally enforceable responsibilities.
35 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only
36 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
37 the word *should* in Agency guidances means that something is suggested or recommended, but
38 not required.
39
40

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>.

41 **II. BACKGROUND**

42
43 Nonalcoholic fatty liver disease (NAFLD) includes a spectrum of histological features that range
44 from simple fatty infiltration of the liver to chronic liver inflammation with or without fibrosis
45 and cirrhosis. Cirrhosis is broadly divided into two main stages, compensated and
46 decompensated.

47
48 Patients with compensated NASH cirrhosis have significant scar formation that is evident by
49 histopathology, with hepatocytes clustered in nodules surrounded by dense extracellular matrix.
50 Despite this, patients may appear clinically healthy. However, patients with compensated NASH
51 cirrhosis can progress to decompensated cirrhosis, defined primarily by complications related to
52 portal hypertension and impaired synthetic function that results in end-stage liver disease, the
53 primary manifestation of decompensated cirrhosis.³

54
55 The goals of treatment for compensated NASH cirrhosis are to halt or slow progression of
56 fibrosis, prevent clinical decompensation, reduce the need for liver transplantation, and improve
57 survival. There are currently no FDA-approved drugs for compensated NASH cirrhosis.

58
59

60 **III. PHASE 3 PROGRAM CONSIDERATIONS**

61

62 **A. Patient Population/Enrollment Criteria**

63

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

66

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

73

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

76

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

80

81 – Non-histologic criteria for the diagnosis of cirrhosis have not been established, but
82 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.

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- 83 scientifically supported. The FDA encourages sponsors to identify biochemical or
84 imaging noninvasive biomarkers that can replace liver biopsies.
85
- 86 • The protocol should specify criteria to exclude patients with decompensated cirrhosis.
87 The criteria can include, but are not limited to, the following:
88
 - 89 – Evidence of portal hypertension (e.g., low platelet counts, esophageal varices, ascites,
90 history of hepatic encephalopathy, splenomegaly)
 - 91
 - 92 – Elevated bilirubin
 - 93
 - 94 – Elevated international normalized ratio or prolonged prothrombin time.
 - 95
 - 96 • Patients who develop manifestations of hepatic decompensation between screening and
97 enrollment should not be randomized.
98
 - 99 • Sponsors can enroll patients with documented history of Gilbert’s syndrome if the direct
100 bilirubin is within normal reference range.
101
 - 102 • Sponsors can enroll patients with type 2 diabetes mellitus (T2DM) if they are adequately
103 controlled on a stable dose or doses of antidiabetic medication(s) for at least 3 months
104 before trial enrollment.
105
 - 106 • Some patients with compensated NASH cirrhosis can be treated with vitamin E or
107 pioglitazone. Such patients should either (1) discontinue vitamin E or pioglitazone or (2)
108 be on a stable dose for 6 months before trial enrollment, and the dose should be held
109 constant during the trial.
110
 - 111 • Elevations of liver enzymes such as alanine aminotransferase (ALT) and aspartate
112 aminotransferase (AST) can be expected in NASH. However, ALT or AST elevation
113 greater than 5 times the upper limit of normal (ULN) would indicate the possibility of
114 concomitant liver disease(s) (e.g., alcohol-associated liver disease, autoimmune
115 hepatitis). Therefore, sponsors should not enroll patients with evidence of such
116 transaminase elevations. Similarly, bilirubin levels should not exceed ULN. Alkaline
117 phosphate should be less than 1.5 times the ULN.
118
 - 119 • Sponsors should exclude the following patients from trial enrollment:
120
 - 121 – Patients listed for living-related or orthotopic liver transplantation.
 - 122
 - 123 – Patients with a baseline Model for End-Stage Liver Disease (MELD) score greater
124 than 12.
 - 125
 - 126 – Patients with a history of hepatocellular carcinoma (HCC) or history of HCC
127 treatment.
 - 128

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129 **B. Trial Design/Efficacy Endpoints**

130

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

133

134 • Drugs for the treatment of compensated NASH cirrhosis should be evaluated in

135 randomized, placebo-controlled, double-blind clinical trials. Sponsors can propose

136 stratification factors (e.g., T2DM, vitamin E, pioglitazone) and discuss with the FDA

137 before initiating phase 3 trials.

138

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

142

143 – Complication of ascites including any of the following: spontaneous bacterial

144 peritonitis, diuretic-resistant ascites (refractory ascites), hepato-pleural effusion, etc.

145

146 – Variceal hemorrhage

147

148 – Hepatic encephalopathy

149

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

152

153 – Liver transplantation

154

155 – Death from any cause

156

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

166

167 **C. Safety Considerations**

168

169 Assessment of potential drug-related liver toxicity can be challenging in patients with chronic

170 liver disease. The FDA encourages the sponsor to develop a specific approach (e.g., an

171 algorithm) for monitoring liver function in patients with abnormal liver function at baseline,

172 including criteria for drug discontinuation for individual patients and trial stopping rules

173 (temporary or permanent). The protocol should specify guidelines for monitoring liver function.

174 The sponsor should establish an expert committee to adjudicate cases that meet protocol-defined

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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.