



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-D-1516]

Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled “Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment.” The purpose of this draft guidance is to provide the Agency’s current recommendations regarding the important components of a drug development program for nonalcoholic steatohepatitis (NASH) with compensated cirrhosis. This draft guidance focuses on the enrollment criteria, trial design, efficacy endpoints, and safety considerations for phase 3 trials.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-D-1516 for "Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for

Treatment.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the

prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Frank A. Anania, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5387, Silver Spring, MD 20993, 240-402-9725.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment.”

This draft guidance focuses on the design of clinical trials to study patients who have compensated cirrhosis secondary to NASH. This draft guidance is in addition to a draft guidance published in 2018 which discusses the Agency’s thinking for the design of clinical trials for patients who have NASH but do not have cirrhosis (see the draft guidance for industry entitled “Noncirrhotic Nonalcoholic Steatohepatitis with Liver Fibrosis: Developing Drugs for Treatment” available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm627376.pdf>).

NASH is the hepatic manifestation of insulin resistance syndrome and is associated with type 2 diabetes, hypertension, hypertriglyceridemia, and obesity, among other diseases. NASH-related cirrhosis is becoming a major public health problem and is anticipated to be the leading indication for orthotopic liver transplantation within a decade.

This draft guidance applies only to compensated cirrhosis and specifically excludes patients with decompensated cirrhosis, i.e. patients who have already experienced any of several clinical events (e.g., variceal bleeding, ascites, hepatic encephalopathy) that are associated with high morbidity and significantly reduce their life expectancies. This draft guidance describes the criteria for enrolling patients with compensated cirrhosis in clinical trials, including the histologic criteria to establish the pathological diagnosis of cirrhosis.

This draft guidance provides recommendations on the selection of primary efficacy endpoints in clinical trials intended to study pharmacological treatments for compensated NASH cirrhosis. Finally, the Agency discusses the rationale for recommending that sponsors conduct clinical outcome trials for drugs treating compensated NASH cirrhosis. The Agency also provides recommendations to help ensure safety in patients with hepatic impairment and strategies to deal with drug-induced liver injury during a compensated NASH cirrhosis clinical trial.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking of FDA on "Nonalcoholic Steatohepatitis with Compensated Cirrhosis: Developing Drugs for Treatment." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information under 21 CFR part 312 (Investigational New Drug Application) have been approved under OMB control number 0910-0014. The collections of information in 21 CFR parts 50 and 56 (Protection of Human Subjects: Documentation of Informed Consent; Institutional Review Boards) have been approved under OMB control number 0910-0755. The collection of information under 21 CFR part 314, including the submission of information under subpart H (“Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses”), has been approved under OMB control number 0910-0001. The collection of information under the guidance for industry entitled “Expedited Programs for Serious Conditions--Drugs and Biologics” (available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm358301.pdf>) has been approved under OMB control number 0910-0765.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <https://www.regulations.gov>.

Dated: June 3, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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