Attribution of Nonalcoholic Steatohepatitis as an Etiology of Cirrhosis for Clinical Trials Eligibility: Recommendations from the Multi-stakeholder Liver Forum[Ω]

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Naga Chalasani has ongoing consulting activities (or had in preceding 12 months) with NuSirt, Abbvie, Allergan (Tobira), Madrigal, Siemens, Foresite, Genentech, Axcella, Zydus, and Galectin. Dr. Chalasani receives research grant support from Intercept, Galectin Therapeutics and Exact Sciences where his institution receives the funding.

Mazen Noureddin has been on the advisory board or a speaker for Allergan, Gilead, Intercept, Pfizer, Novartis, Blade, EchoSens North America, OWL, Simply Speaking, Terns, Fractyl, Siemens, Roche Diagnostics, and Abbott; has received research support from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Novartis, Shire and Zydus; is a minor shareholder or has stocks in Anaetos and Viking.

Arun Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland and Novartis. He receives royalties from Elsevier and UptoDate.

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Jean L. Chan was an employee of Conatus Pharmaceuticals during the preparation of this manuscript.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as a major public health threat and it is dynamic in its natural history of disease progression. The burden of end-stage liver disease due to this condition is projected to increase by 200-300% over the next two decades.[1] This has led to intense drug development efforts to establish effective therapy for this condition.[2] Two major approaches are being taken to treat nonalcoholic steatohepatitis (NASH): 1) targeting the metabolic underpinning of the disease and other upstream drivers of disease activity[2] and 2) targeting downstream elements of disease course such as fibrosis to reduce disease progression.[2] The greatest and most urgent unmet need is to develop effective therapy for those patients who already have developed cirrhosis and are thus at the highest risk of liver-related adverse outcomes.

A major challenge, however, in conducting clinical trials for NASH cirrhosis is an accurate case definition for eligibility into such trials. It may be straightforward in clinical practice to attribute NASH as the likely cause of cirrhosis in patients without competing etiologies. However, the stringent case definitions required to standardize trial enrollment across clinical trials of investigational drugs or lifestyle interventions are currently lacking for NASH-related cirrhosis. NASH is a histological diagnosis and yet many patients with NASH-related cirrhosis do not have histological confirmation at the time of their clinical presentation. If a liver biopsy is performed in patients with NASH cirrhosis, liver histology may not display typical histological lesions such as steatosis and hepatocyte ballooning in ~40% of patients.[3]

The Liver Forum has identified the development of consensus definitions for NASH cirrhosis as an important step towards developing effective therapies for this condition. The

Liver Forum is a multi-stakeholder group including academic investigators from around the world, members of professional organizations (American Association for the Study of Liver Diseases and European Association for Study of the Liver), representatives from regulatory agencies (U.S. Food and Drug Administration and European Medicines Agency), drug developers from the pharmaceutical industry, and patient advocates. This manuscript summarizes the work of the NASH Cirrhosis Working Group to specifically focus on case definitions that would allow attribution of NASH as the etiology for compensated cirrhosis. This document summarizes the current consensus of the working group, which will revisit this topic and update recommendations as new data become available. The general diagnosis of cirrhosis was addressed in a previous document of the Liver Forum[4] and thus will not be addressed here.

Methodology: A formal and consistent methodology was followed to reach consensus recommendations. First, the literature, existing guidelines, and previous and ongoing clinical trials were all reviewed by the Working Group (**Appendix**). A standardized discussion format was established, and data summarized in an objective and measurable fashion. Multiple conference calls and correspondence were held to establish consensus when there was divergence of opinion. The steps involved in developing these consensus-based recommendations are described in **Supplemental Table 1**. These steps were in line with what has been utilized by other internationally regarded organizations[5], and by the Liver Forum to develop recommendations for baseline parameters[6], case definitions[4], endpoints[7], and pediatric trials[8].

Definition of NASH as the cause of cirrhosis

Liver biopsy is currently the reference standard to determine NASH as the cause for cirrhosis based on specific histological features including steatosis, inflammation, and hepatocyte ballooning, in addition to the presence of cirrhosis. In the context of NASH clinical trials, a NAFLD Activity Score (NAS) of 4 points or higher has been used to identify patients with clinically significant disease activity.[9] However, some of the histological features indicating disease activity may not always be readily apparent or easily identified in NASH patients with cirrhosis, and thus, the NAS can be lower than 4. This may lead to a higher percentage of screen failures in NASH cirrhosis trials due to the inability to detect active steatohepatitis in such patients.[10] In clinical practice, when a patient presents with clinically evident cirrhosis, there is less enthusiasm to recommend a liver biopsy, when the clinical picture is consistent with fatty liver disease, either due to concern for heightened risk of complications or due to patient's reluctance. If a patient currently presenting with cirrhosis (but without a recent liver biopsy) has previously documented NAFLD, it is reasonable to consider NASH as the likely etiology, as long as other possible etiologies are comprehensively excluded. Some histological features (e.g., steatosis) disappear as cirrhosis develops and progresses, making identification of the underlying etiology of cirrhosis difficult (cryptogenic cirrhosis is considered in more detail below).[10]

The working group's consensus was that the case definition of NASH-related cirrhosis for inclusion in clinical trials may be qualitatively categorized according to a hierarchy based on the degree of certainty of NASH as the cause of cirrhosis, e.g. definitive, probable, and possible categories (see definitions below and **Table 1**). Within each category, the definitions are listed by decreasing order of confidence (e.g., 2a is considered more robust than 2b). When some of the histological evidence is absent, the presence of concomitant metabolic risk factors (history of

type 2 diabetes mellitus [T2DM], hypertension, dyslipidemia or obesity) strengthens the likelihood that NASH is the cause of cirrhosis. A diagnosis of NASH cirrhosis can be made only in the absence of other etiologies such as excessive alcohol intake, viral hepatitis, hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, alpha-1-antitrypsin deficiency, and autoimmune hepatitis. [4,9,11]

1. Definite NASH cirrhosis

The attribution of NASH as a definite cause of cirrhosis includes:

1a. Patients with current liver biopsy showing cirrhosis with steatohepatitis.

1b. Patients with a previous biopsy showing steatohepatitis, but now with evidence of cirrhosis, either by clinical history or current features, imaging, noninvasive tests, or biopsy.

Among individuals with a current biopsy, histological findings consistent with active steatohepatitis may have disappeared. In such instances, there should be at least one metabolic risk factor to support the likelihood of NASH as the underlying cause of cirrhosis.

1c. Patients with a current biopsy showing cirrhosis with steatosis (but no findings of active steatohepatitis) together with at least two co-existing or historical features of metabolic comorbidities including obesity and/or T2DM to corroborate a diagnosis of NASH as the cause of cirrhosis **(Table 1)**.

The 1a definition has the highest degree of certainty, while criteria for metabolic comorbidities were added to both 1b and 1c to increase the likelihood of diagnosing NASH

cirrhosis in the absence of a recent biopsy demonstrating cirrhosis and steatohepatitis. In the case where there is less histological evidence for NASH (e.g., 1c vs. 1b), requiring more than one comorbidity may increase the certainty of NASH diagnosis, a plausible conclusion which is supported by recent data from NASH cirrhosis studies (see **Table 1** for a list of comorbidities).[3, 12] Further, when individuals meeting such criteria undergo liver transplantation, there is ~88% recurrence of NAFLD over time, compared to ~20% incidence of NAFLD among those with cirrhosis due to other etiologies.[13]

NASH is strongly associated with metabolic syndrome, the definition of which has been harmonized across several academic societies.[14] However, both hypertension and dyslipidemia may be less evident once patients develop cirrhosis due to the dynamic nature and pathophysiological changes associated with cirrhosis.[15] For example, splanchnic vasodilatation associated with cirrhosis reduces systemic blood pressure[15], and history of T2DM and obesity has not only been associated with NAFLD but also with severity of the disease.[16, 17] It is currently unknown whether the duration of these comorbidities affects the disease progression to cirrhosis. Nevertheless, it is likely that the longer the duration of having these comorbidities, especially obesity and T2DM, the greater the likelihood of cirrhosis development. Although a complete agreement on this topic was not achieved, we suggest that a minimum of 5 years duration is reasonable to support that co-existing metabolic disease(s) contribute to NASH progression; however, this majority view will require validation and may require modification as relevant data emerge.

2. Probable NASH cirrhosis

2a. Patients with a previous biopsy with steatosis but not steatohepatitis, and current cirrhosis, either by a clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it may not show evidence of steatosis or steatohepatitis as these histological features may have disappeared. There must be at least two co-existing or history of metabolic comorbidities including obesity and/or T2DM to support NASH as an underlying cause of cirrhosis.

2b. Patients with cirrhosis (either by a clinical history or current features, imaging, or noninvasive tests) with current or previous imaging showing evidence of steatosis. There is no liver histology available. There are at least two co-existing or historical metabolic comorbidities including obesity and/or T2DM to support NASH as an underlying cause of cirrhosis.

2c. Patients with "cryptogenic cirrhosis" (either by a clinical history or current features, imaging, noninvasive tests, or biopsy) without current or previous evidence of steatosis by imaging or steatosis/steatohepatitis by histology. There are at least two co-existing or historical metabolic comorbidities including obesity and/or T2DM to support NASH as an underlying cause of cirrhosis.

Cryptogenic cirrhosis and its relationship to NASH is an area of ongoing research. In a recent clinical trial, Younossi, et al, found that 40% of cryptogenic cirrhosis patients had steatosis on their exit biopsy, although their baseline biopsy had no features to suggest NAFLD or NASH.[3] Similar to NASH patients, patients with cryptogenic cirrhosis had clustering of metabolic comorbidities, strengthening the rationale of including metabolic comorbidities in these case definitions.[3, 18] Indeed, it has been shown that a large number of these patients will have a

recurrence of NAFLD post-liver transplantation.[19 13] In addition, Younossi et al [3] showed that the cryptogenic cirrhosis group had higher fibrosis markers, more collagen content on biopsies and a higher risk of liver-related events than patient with definitive NASH cirrhosis. This plausibly suggests that these patients are further along in the course of their disease and likely in most need for effective therapies.

3. Possible NASH Cirrhosis

3a. Patients with "cryptogenic cirrhosis" (either by a clinical history or current features, imaging, noninvasive tests, or biopsy) without current or previous evidence of steatosis by imaging or steatosis/steatohepatitis by histology. There is one co-existing or history of metabolic comorbidity including obesity and/or T2DM.

3b. Patients with previously eradicated hepatitis C virus (HCV), or a remote history of heavy alcohol consumption, but who currently have evidence of cirrhosis and histological evidence of steatohepatitis. Patients with a remote history of heavy alcohol consumption should not have evidence of cirrhosis at the time of stopping alcohol.

Patients with cryptogenic cirrhosis may have minimal metabolic co-morbidities (See **Table 1**), which makes the likelihood of NASH as the cause of cirrhosis less certain. For this reason, we define this category as 'possible' and recommend further discussions between regulatory authorities and sponsors before enrolling such patients into a NASH cirrhosis clinical trial.

It is worth mentioning that establishing the duration of a comorbid condition can be challenging in terms of medical record documentation as well as delays in diagnosis due to lack of access to medical care. Previous medical records or a thorough history of a patient's medications may increase confidence in determining the duration of these conditions; however, documentation in medical records (e.g. duration of dyslipidemia; medication start/stop dates) is not always available. Further discussion with regulatory agencies during protocol development for the trial is warranted regarding whether patient self-reported history could be considered acceptable.

Finally, as HCV moved from being the leading cause of cirrhosis and indication for liver transplantation, many patients whose HCV has been eradicated following treatment with highly active anti-viral therapy, have concurrent metabolic comorbidities, resulting in concurrent NASH.[20, 21] If these patients did not have cirrhosis at the time of sustained virologic response (SVR) and subsequently develop cirrhosis, this can be attributed to NASH especially if enough time has elapsed since SVR. However, if these patients were known to have cirrhosis at the time of SVR, it is plausible that cirrhosis developed due to both conditions (NASH and HCV). Given the uncertainty as to what constitutes "enough time" since SVR, the following recommendations are provided, acknowledging that the level of evidence to support any decision is not substantial at this time. For testing anti-fibrotic drugs in patients with previous HCV infection, a 2-year time frame of SVR prior to enrollment[22] might be adequate to exclude the effects of HCV on those who currently have evidence of cirrhosis and histological evidence of steatohepatitis. A longer duration might be warranted in the case of HCV genotype 3 if anti-steatotic drugs are being considered; other causes of chronic liver disease should still be excluded. The area of NASH and

other co-existing chronic liver diseases requires further research and is beyond the scope of this document.

Summary

An accurate case definition of NASH cirrhosis is critical for enrolling appropriate patients into clinical trials as well as to maintain comparability across different clinical trials. Yet, there are no published criteria for defining NASH cirrhosis. This prompted the Liver Forum to develop consensus case definitions for NASH cirrhosis for clinical trial eligibility. Given that patients with cirrhosis may no longer have evidence of active steatohepatitis on biopsy at the time of enrollment and may not have a historical biopsy to establish the diagnosis, these case definitions provide recommendations, based on varying levels of confidence, on how to approach a range of clinical scenarios and determine the likelihood that NASH is the etiology of cirrhosis. The appropriate subgroups of participants (definite, probable, possible) for inclusion into a specific clinical trial in this patient population should be discussed with regulatory agencies prior to finalizing the study design.

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Table 1. NASH cirrhosis: Liver Forum Consensus Definitions for Clinical Trials

Definitive	Probable	Possible
1a. Current biopsy shows cirrhosis with steatohepatitis. There is no evidence for a competing etiology[#]. **1b.** Previous biopsy showed steatohepatitis, but now with cirrhosis either by clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it doesn't show evidence of steatosis or steatohepatitis as these histological findings may have disappeared (burn-out). There is no evidence for a competing etiology[#]. There is at least one co-existing or history of metabolic comorbidity^ to corroborate a diagnosis of NAFLD. **1c.** Current biopsy shows cirrhosis with steatosis. There is no evidence for a competing etiology[#]. There are at least two co-existing or history of metabolic comorbidities^ including obesity[&] and/or T2DM to corroborate a diagnosis of NAFLD.	**2a.** Previous biopsy shows steatosis, but now with cirrhosis, either by clinical history or current features, imaging, noninvasive tests, or biopsy. If there is a current biopsy, it does not show evidence of steatosis or steatohepatitis as histological findings may have disappeared (burn-out). There is no evidence for a competing etiology[#]. There are at least two co-existing or history of metabolic comorbidities^ including obesity[&] and/or T2DM to corroborate a diagnosis of NAFLD. **2b.** Patient with cirrhosis with current or previous imaging showing steatosis. There is no liver histology available. There is no evidence for a competing etiology[#]. There are at least two co-existing or history of metabolic comorbidities^ including obesity[&] and/or T2DM to corroborate a diagnosis of NAFLD. **2c.** "Cryptogenic cirrhosis" without current or previous evidence of steatosis by imaging or steatosis/steatohepatitis by histology. There is no evidence for a competing etiology[#] but there are at least two co-existing or history of metabolic comorbidities^ including obesity[&] and/or T2DM to corroborate a diagnosis of NAFLD.	**3a.** "Cryptogenic cirrhosis" without current or previous evidence of steatosis by imaging or steatosis/steatohepatitis by histology. There is no evidence for a competing etiology[#] but there is at least one co-existing or history of metabolic comorbidity^, including obesity[&] and/or T2DM. **3b.** Patients with previously eradicated HCV, or remote history of heavy alcohol consumption, but currently have evidence of cirrhosis and histological evidence of steatohepatitis.

Competing etiology: including alcohol, viral hepatitis, hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, Alpha-1-Antitrypsin deficiency and autoimmune hepatitis
^ Comorbidities: History of type 2 diabetes mellitus, hypertension, dyslipidemia or obesity. We suggest a duration of at least 5 years, however this can be discussed with regulators for each study protocol
[&] BMI $\geq$30 kg/m^2 or central obesity per consensus guidelines.
NASH, nonalcoholic steatohepatitis; **NAFLD,** nonalcoholic fatty liver disease; **T2DM,** Type 2 diabetes mellitus; **HCV**, chronic hepatitis C virus

Appendix: NASH Cirrhosis Case Definitions Subgroup Participants

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Supplementary Table 1: Consensus Development Protocol

Protocol followed for developing consensus recommendations proposed in this commentary
1. The working group scope was formulated and agreed by the working group chairs (MN, JC, KB, AJS and NC). 2. Discrepancies in inclusion criteria in patients' enrollment in clinical trials with NASH cirrhosis were identified via clinicaltrials.gov. 3. The literature was reviewed and summarized by the working group chairs (MN, JC, KB, AJS and NC). 4. Members from the Liver Forum were invited to participate in the working group and the chairs assured participation of the regulatory, industry, and academic experts. 5. Disagreement resolution was pre-defined as agreement of 2/3 of the group members. 6. The evidence was presented and discussed with the full working group (listed in the appendix). 7. Consensuses were reached during the course of multiple phone conferences as well as during Liver Forum conferences held in Paris, France in April 2018, and July 2019, and Washington DC in September 2019. 8. Disagreements were resolved via majority consensus based on interpretation of the literature. 9. Areas of uncertainty and unresolved disagreements were defined as future areas of research. 10. Summaries of conference calls were distributed to the full working group to provide documentation of group discussions and progress, and to allow review of the comments and assess for accuracy. 11. The document of recommendations was drafted by the chairs and was sent to the full working group for comments. 12. Additional authors were invited based on specific expertise and contributions required to complete the document. 13. All working group participants had the opportunity to review and comment on the final draft before submission.