

Consensus: guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis

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Summary

Background: The last decade has seen a rapid growth in the number of clinical trials enrolling patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis (NASH). Due to the underlying chronic liver disease, patients with NASH often require different approaches to the assessment and management of suspected drug-induced liver injury (DILI) compared to patients with healthy livers. However, currently no regulatory guidelines or position papers systematically address best practices pertaining to DILI in NASH clinical trials.

Aims: This publication focuses on best practices concerning the detection, monitoring, diagnosis and management of suspected acute DILI during clinical trials in patients with NASH.

Methods: This is one of several papers developed by the IQ DILI Initiative, comprised of members from 15 pharmaceutical companies, in collaboration with DILI experts from academia and regulatory agencies. This paper is based on extensive literature review, and discussions between industry members with expertise in drug safety and DILI experts from outside industry to achieve consensus on common questions related to this topic.

Results: Recommended best practices are outlined pertaining to hepatic inclusion and exclusion criteria, monitoring of liver tests, DILI detection, approach to a suspected DILI signal, causality assessment and hepatic discontinuation rules.

Conclusions: This paper provides a framework for the approach to assessment and management of suspected acute DILI during clinical trials in patients with NASH.

The complete list of author affiliations are listed in Appendix 2.

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1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is increasingly recognized as an important public health problem and a major cause of liver disease. Nonalcoholic steatohepatitis (NASH), a subset of NAFLD with a higher likelihood of progression to advanced liver disease, is presently the most common cause of chronic liver disease (CLD) and a leading indication for liver transplantation in Western countries.¹⁻³ Over the last decade, there has been an acceleration in the search for new therapies for NASH and the number of clinical trials enrolling NASH and NAFLD patients is growing rapidly.^{4,5} Simultaneously, the inclusion of patients with NAFLD/NASH into clinical trials in therapeutic areas other than NASH is increasing and will likely continue to increase as the obesity epidemic expands worldwide. For example, the search for new drugs for treatment of type 2 diabetes mellitus (T2DM) has led to a myriad of clinical trials enrolling T2DM patients that may have NAFLD in 60%-80% of the cases.^{6,7} As in other clinical trials, drug-induced liver injury (DILI) remains a major concern for drug developers and investigators in NASH trials. The well-recognized challenges in detection, assessment and management of DILI during drug development are amplified by the fact that a significant part of the target population may have varying degrees of hepatic fibrosis. However, there are no regulatory guidelines and position papers to provide information regarding DILI-related best practices for clinical trials enrolling patients with pre-existing NASH. As a result, clinical investigators and drug developers face considerable uncertainty when identifying and managing suspected DILI in these trials, and often use diverse approaches and practices for assessment and management of liver safety signals. Given the enormous prevalence of CLD related to NASH worldwide, and the growing number of clinical trials assessing new drugs for NASH, there is a great unmet need for consistent, evidence-based recommendations for best practices pertaining to suspected DILI in such patients.

The IQ DILI Initiative was launched in June 2016 within the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ consortium) to reach consensus and propose best practices on topics related to clinical DILI.⁸ The IQ Consortium is a science-focused, not-for-profit organisation addressing scientific and technical aspects of drug development and is comprised of 39 pharmaceutical and biotechnology companies. The IQ-DILI Initiative is an affiliate of the IQ Consortium, comprised of 15 IQ member companies, focused on establishing best practices for monitoring, diagnosing, managing and preventing DILI. This publication is based on an extensive literature review, and the consensus achieved in carefully structured discussions between IQ DILI members and academic and regulatory experts. The recommendations are based on the opinions of the authors, and do not imply a regulatory mandate. Although this publication focuses on DILI assessment during drug development, post-approval pharmacovigilance is an important part of the safety assessment of a new drug. This is especially important for assessment of DILI, which tends to be uncommon and might be missed during drug development. Most of the recommendations and best practices included in this publication are specific to

acute hepatocellular DILI. It is well recognized that some drugs may cause other types of acute DILI including cholestatic liver injury, mixed hepatocellular-cholestatic and acute steatosis with metabolic acidosis. It is also recognized that drugs may cause chronic liver injury including hepatic fibrosis, steatosis, steatohepatitis, cirrhosis, nodular regenerative hyperplasia, and vascular diseases.⁹ Cholestatic DILI will be discussed in detail in another paper by the IQ DILI initiative. Due to the scarcity of data in the published literature, other types of acute DILI and chronic DILI will not be discussed in this paper. However, it is strongly recommended that drug developers and investigators remain mindful of these less common types of DILI that could arise during drug development.

2 | ARE NAFLD PATIENTS SUSCEPTIBLE TO DILI?

Whether patients with pre-existing liver disease including NAFLD are more susceptible to DILI compared to individuals with healthy livers is still a matter of ongoing debate. Zimmerman was the first to opine that most drugs could be safely given to patients with underlying liver disease, although he recognized that if acute injury occurred, the outcome in such patients could be dire.^{10,11} Evidence in the medical literature concerning the specific risk of DILI in patients with NAFLD is limited and conflicting. While one study reported that NAFLD significantly increased the risk of DILI in middle-aged men, compared to men with hepatitis C,¹² several other reports have supported the safety of statins¹³⁻¹⁷ and of rosiglitazone¹⁸ in patients with NAFLD. In some of these studies, small sample sizes or significant methodologic issues limit the validity of these observations. Furthermore, the extremely low incidence of clinically significant statin-related liver injury in the general population makes it difficult to assess the specific effect of pre-existing NAFLD.^{19,20} Nevertheless, based on the available evidence, there is a strong consensus that statins are safe in patients with NAFLD.²¹ Several studies have demonstrated an association between NAFLD and increased activity of cytochrome P450 2E1 (CYP2E1).^{22,23} Since CYP2E1 plays a central role in the pathogenesis of acetaminophen-induced liver injury, the question of increased susceptibility of NAFLD patients to DILI due to acetaminophen overdose has been raised, although never examined directly. In studies of human liver samples, steatosis was associated with decreased hepatic cytochrome P450 3A (CYP3A) activity, and there appeared to be a relationship between the severity of hepatic steatosis and decreased CYP3A activity.^{22,24} Hepatic CYP3A is an important subfamily of drug-metabolizing enzymes that contributes to drug activation and to the control of endogenous hormone turnover; however, so far there is no evidence to suggest an association between decreased activity of CYP3A in NAFLD patients and DILI. Among authorities in the field of DILI there is still a general opinion that patients with CLD including NAFLD are not prone to develop DILI compared to the general population.²⁵⁻²⁷ However, it is also widely believed that patients with pre-existing CLD are at higher risk for complicated

course and adverse outcomes from DILI.^{25–28} A recent paper from the US Drug Induced Liver Injury Network (DILIN) showed that DILI in patients with pre-existing liver disease was associated with significantly higher frequency of adverse outcomes, including mortality.²⁹ The pre-existing CLDs were mainly hepatitis C and NAFLD or unexplained elevations in liver biochemistries.²⁹

2.1 | Consensus and Recommendations

1. There is no unequivocal evidence to suggest that patients with NAFLD/NASH are systematically predisposed to DILI. However, if DILI occurs in a patient with advanced liver damage due to NASH there may be an increased risk for serious liver injury and adverse outcome.

3 | HEPATIC EXCLUSION CRITERIA FOR PATIENTS WITH NONCIRRHOTIC NASH

Hepatic exclusion criteria depend on complex considerations and may vary according to the indication, target patient population, drug's mechanism of action, results of nonclinical or clinical studies, experience with similar molecules and geographic location. From the standpoint of liver safety, hepatic exclusion criteria aim to (a) minimise confusion between potential DILI and a fluctuation or exacerbations of a pre-existing liver disease; (b) decrease the risk of adverse outcome, if DILI occurs; (c) prevent accumulation of drugs that are eliminated by the liver. This section focuses on hepatic exclusion criteria in clinical trials conducted in patients with NASH who do not have apparent cirrhosis at enrolment. It should be noted that in patients with no apparent cirrhosis some might have undetected cirrhosis. Clinical trials in NASH patients with cirrhosis are outside the scope of this paper. There is a consensus among researchers and regulators in this field that these populations should be studied separately,^{30,31} and they will be discussed in a separate publication.

When designing a clinical trial for the treatment of patients with NASH, drug developers generally exclude patients with pre-existing liver disease other than NASH, or significant abnormalities in hepatic biochemical tests, that are outside the typical range for NASH.^{32–35} Several consensus papers have supported this approach in recent years.^{30,31} The main rationale for excluding these patients is to ensure a clean NASH population by avoiding a mix of different liver diseases that may respond differently to the study drug. An additional benefit is gained through decreasing confusion between potential DILI and a fluctuation or flare of the underlying liver disease. Most NASH clinical trials have excluded patients with viral hepatitis B and C, or any other cause of CLD, such as haemochromatosis, α 1 antitrypsin deficiency, autoimmune hepatitis (AIH), Wilson disease, primary sclerosing cholangitis or primary biliary cholangitis.^{32–37} This is consistent with recommendations of consensus meetings and clinical guidelines on NAFLD and NASH.^{30,38–41}

Patients with NAFLD usually have normal or mildly elevated serum levels of alanine aminotransferase (ALT),^{35,42–48} although ALT levels of more than 300 U/L occur rarely.⁴³ At diagnosis, ALT values in NAFLD patients typically range between low normal values and 250 IU/L, usually lower than fivefold (5 \times) upper limit of normal (ULN) (in most central laboratories, ULN for ALT is around 40–45 U/L). Aspartate aminotransferase (AST) values are typically lower than ALT, but with advanced fibrosis AST may be higher than ALT.^{45,49,50} Total bilirubin (TBL) is usually normal until advanced stages of disease, and alkaline phosphatase (ALP) levels are usually normal, although mild elevations (usually <2 \times ULN) may occur.⁴³ Gamma glutamyl transaminase (GGT) levels may range between low normal and >400 U/L.^{33,50,51} Of note, the majority of clinical trials use the ULN values of the central laboratory employed for the study. ULN values for ALT and other hepatic biochemical tests may vary among laboratories due to differences in reference populations and analytical variation among commercial assays.⁵² Most NASH studies have excluded patients with ALT levels considered to be higher than the typical range for NASH. ALT levels used as exclusion criteria vary considerably between different NASH studies ranging from 2.5 \times ULN to 300 U/L (approximately 8–10 \times ULN).^{34,35,37,53,54} GGT level has generally not been used as exclusion criterion. It is generally agreed that isolated elevation of GGT is a poor indicator of liver injury and insufficient to qualify as DILI.^{9,55} Several publications have reported a high prevalence of steatohepatitis in patients infected with human immunodeficiency virus (HIV). The mechanism for this association is poorly understood.^{56–58}

The extent to which workup should be performed prior to enrolment to exclude other diagnoses has not been clearly defined. Based on published clinical guidelines it has been recommended that at a minimum, a thorough medical history should be taken, including detailed alcohol consumption information, and serological tests for hepatitis B, C and AIH be performed prior to enrolment. In addition, NASH clinical trials often screen for HIV and exclude patients with positive HIV tests.^{35,59,60} Other tests such as iron studies, anti-mitochondrial antibody and evaluation for α 1 antitrypsin deficiency or Wilson disease, should be considered based on the nature of the hepatic biochemical tests abnormality, the investigator's clinical judgement, and published guidance for clinical practice.^{58,61}

Most NASH clinical trials have excluded patients with a history of significant alcohol use, aiming to avoid a mixed population of NASH and alcoholic liver disease. Cut-off levels for exclusion vary between trials and have included 14–21 standard drinks per week for men and 7–14 standard drinks per week for women.^{33–35,47,62–64} A standard drink contains roughly 14 g of pure alcohol, which is equivalent to a 12-ounce beer, a 4-ounce glass of wine or a 1-ounce shot of hard liquor. It should be noted that the National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines heavy or at-risk drinking as more than four standard drinks on any day or more than 14 drinks per week in men or more than three drinks on any day or seven drinks per week in women.⁶⁵ There is insufficient evidence to support the notion that patients who consume excessive alcohol are prone to develop DILI, but it is well established that patients who

consume large quantities of alcohol are more likely to develop alcoholic liver disease, which may be difficult to differentiate from DILI.²⁵

Most clinical trials in noncirrhotic NASH have also excluded patients with cirrhosis or evidence of decreased synthetic function (eg elevated TBL or INR), predominantly due to the differences in study objectives and clinical benefit endpoints.^{32,33,35,47,63,64,66} However, depending on the study drug and its mechanism of action, recently initiated clinical trials and future studies may strive to enrol patients with cirrhosis to allow assessment of the drug in this patient population. A recent consensus paper provides guidance regarding the inclusion of patients with NASH who have advanced disease or cirrhosis, especially in trials for therapeutics directed against fibrosis.³¹ This target population may need extensive evaluation to rule out other aetiologies, as typical histologic features pertaining to NASH (including steatosis) may be less prominent or absent.⁶⁷ Most clinical trials in noncirrhotic NASH have excluded patients with clinical evidence of hepatic decompensation or portal hypertension including decreased serum albumin (eg less than 32 g/L) increased INR (eg greater than 1.2 or 1.3), elevated direct bilirubin (eg direct bilirubin greater than 1.3 mg/dL, TBL higher than 1-1.2× ULN), low platelet count (<150 000/μL) or a history of oesophageal varices, ascites or hepatic encephalopathy.^{35,60,61} These exclusion criteria are in keeping with recommendations by a 2012 workshop on assessment and management of DILI during drug development.⁵⁵ Finally, most NASH studies excluded patients who were receiving drugs known to cause steatosis or steatohepatitis such as tamoxifen, amiodarone, methotrexate, 5-fluorouracil and corticosteroids, for more than 2 weeks in the year prior to enrolment.^{32,35,47,68}

3.1 | Consensus and Recommendations

- Clinical trials in patients with NASH should aim to exclude patients who have other acute or chronic liver diseases, to avoid confusion regarding response to the investigational drug, and to decrease uncertainty regarding diagnosis of DILI when abnormalities of liver blood tests occur.
- The extent of workup prior to enrolment to exclude other causes of chronic liver disease is not clearly defined. At a minimum, a thorough medical history, physical examination and serological testing for hepatitis B, C, HIV and AIH should be performed. Other tests (eg for haemochromatosis, α 1 antitrypsin deficiency, Wilson disease) should be based on the patient's history, physical examination, laboratory results and clinical judgement.
- It is recommended to exclude patients with evidence of active hepatitis B virus or hepatitis C virus infection.
- HIV infected patients should generally be excluded and need to be studied separately.
- Patients, who consume excessive amounts of alcohol, should be excluded. The cut-off for exclusion is not yet well defined but should not exceed 21 standard drinks per week in men and 14 standard drinks per week in women over a 2-year period prior to enrolment.

- Patients with baseline ALT or AST higher than 5× ULN or 250 U/L, should be excluded.
- Patients with elevated baseline levels of total bilirubin (higher than 1.2× ULN, or 1.3 mg/dL, (with exception of Gilbert's syndrome), with INR >1.2, or platelet count below the lower limit of normal (typically <150 000/μL), should generally be excluded. This recommendation does not apply to studies aiming to enrol patients with hepatic decompensation.
- Patients with elevated ALP, equal to or higher than 2× ULN or 250 U/L, should generally be excluded, unless the ALP elevation is not from a hepatic origin.

4 | MONITORING OF LIVER TESTS AND DILI DETECTION IN NASH CLINICAL TRIALS

As aminotransferases (ATs) (ALT and AST) often fluctuate as part of the natural course of the disease, detection of DILI signals during a clinical trial may be challenging in patients with NASH.^{38,46} While the degree of fluctuation of ATs during the natural history of NASH has not been clearly defined, the published data indicate that they typically do not fluctuate more than 1.5-2× baseline values.^{35,47,49,63} Furthermore, baseline AT levels may decrease in response to therapy or lifestyle modification, which may create a new reference baseline for ALT changes during the study.^{33,35,47,63} According to current regulatory guidance for patients participating in a clinical trial, who have no underlying liver disease and normal baseline ALT, treatment emergent ALT values exceeding 3× ULN should trigger close observation and workup for likely causes of hepatic injury other than the study drug.⁶⁹ In 2011, an international DILI Expert Working Group suggested that in the absence of liver-related symptoms or elevated TBL, a cut-off value of ALT >5× ULN would be a more appropriate threshold for a DILI signal. The main rationale for this proposal was that raising the cut-off level to 5× ULN is more likely to exclude clinically insignificant and/or self-limited drug related events, as well as AT fluctuations that normally occur in NASH and do not indicate a DILI signal.⁹ Many drug developers have adopted this threshold for studies enrolling patients with healthy livers; however, it may not be suitable for patients with NASH, who may have baseline ALT levels exceeding 3×ULN. Under these circumstances, it has been suggested to use multiples of baseline of ALT rather than multiples of ULN as a threshold for suspecting DILI.^{9,30,69,70}

The Food and Drug Administration (FDA) has recommended using ALT threshold values of >2× baseline in patients with elevated ATs at enrolment,⁶⁹ however, others have suggested an increase of >3× baseline and >5× baseline as more appropriate for hepatic safety signal detection.^{9,30} In the absence of large prospective comparative data, there is little evidence to support one suggested threshold over another. Recently, a combination of these approaches has been proposed as a more useful alternative⁷⁰ (Table 1). The actual cut-off values may need to be adjusted based on nonclinical data, mechanism of action or hepatic safety signals in early-phase trials. Finally, when designing liver-related monitoring and stopping

TABLE 1 Algorithm for monitoring and management of possible hepatocellular DILI in phase 2-3 NASH clinical trials in patients with normal or elevated baseline ALT^a

Treatment emergent ALT	Treatment emergent total bilirubin	Liver-related symptoms	Action ^b
Normal/near normal baseline ^a : ALT $\geq 5\times$ ULN Elevated baseline ^a : ALT $\geq 3\times$ baseline or ≥ 300 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome: No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 d. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
Normal/near normal baseline ^a : ALT $\geq 3\times$ ULN Elevated baseline ^a : ALT $\geq 2\times$ baseline or ≥ 300 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome: No change in baseline TBL	Severe fatigue, nausea, vomiting, right upper quadrant pain	Repeat ALT, AST, ALP, TBL, in 2-5 d. Follow-up for symptoms. Initiate evaluation for other etiologies of abnormal liver tests.
Normal/near normal baseline ^a : ALT $\geq 8\times$ ULN Elevated baseline ^a : ALT $\geq 5\times$ baseline or ≥ 500 U/L (whichever occurs first)	Normal Patients with Gilbert's syndrome: No change in baseline TBL	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another aetiology is identified and liver enzymes return to baseline.
Normal/near normal baseline ^a : ALT ≥ 3 ULN Elevated baseline ^a : ALT $\geq 2\times$ baseline or ≥ 300 U/L (whichever occurs first)	TBL $\geq 2\times$ ULN Patients with Gilbert's syndrome: Doubling of direct bilirubin or increased INR to >1.5	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another aetiology is identified and liver enzymes return to baseline.
Normal/near normal baseline ^{a,c} : ALT ≥ 5 ULN Elevated baseline ^a : ALT $\geq 3\times$ baseline or ≥ 300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another aetiology is identified and liver enzymes return to baseline.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; TBL, total bilirubin, ULN, upper limit of normal.

Modified from Chalasani and Regev.⁷⁰

^aBaseline ALT is derived from an average of two pre-treatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT $\geq 1.5\times$ ULN. In patients with a sizable stable decrease in ALT ($>50\%$ of the baseline value) during treatment, a new baseline, corresponding to the ALT nadir, should be established on an individual basis for subsequent determination of a DILI signal.

^bThe actions of close observation, monitoring, and drug interruption often overlap. Occasionally, workup is initiated after drug interruption.

criteria it is important to take into consideration the degree of variation that exists for ALT reference ranges between laboratories, where ULN values may vary between less than 30 U/L for some laboratories to more than 70 U/L for others.^{71,72}

How to determine baseline ALT is also a matter of debate. Since in patients with NASH, ALT levels can fluctuate even over a short period, a single measurement on a given day may not represent a true baseline. It has been suggested to take at least two ALT measurements prior to enrolment (at least 2 weeks apart) and use the average of the two values as the most appropriate baseline.^{55,70} These measurements can be performed at the "screening visit" (typically visit 1) and the "baseline visit" (typically visit 2 or 3). In cases of significant changes between two measurements (for example, $>50\%$ difference), it has been suggested to obtain a third measurement for a better estimate of the magnitude and trend of the ALT changes.⁷⁰ If a patient exhibits a sharp change prior to enrolment, it would be preferable to hold enrolment until the underlying cause is identified or ALT levels stabilize. This approach may be time consuming and may not be feasible for all clinical trials. To harmonise and simplify the definition of "elevated baseline ALT" some authors have recommended to use ALT $>1.5\times$ ULN as an empiric threshold (see Table 1).⁷⁰

As demonstrated in several studies, ALT levels may decrease during the treatment period in response to NASH treatment or life style modifications.^{33,35,47,63} However, in contrast to certain other liver diseases (eg AIH, chronic hepatitis C), in which the ALT decline in response to therapy often results in a new nadir, the decrease in ALT in NASH is typically not as abrupt or substantial. Changes from baseline in response to therapy have been reported in clinical trials to range between 12 and 20 U/L for ALT, 5-10 IU/L for AST and 5-14 U/L for GGT.^{33,35,47,63} However, in some instances, response to therapy in NASH patients may lead to more substantial improvement in liver enzymes.^{33,73} For studies in hepatitis C, several authors have suggested that ALT baseline should be adjusted according to the nadir attained during treatment.^{70,71,74} The IQ DILI working group recommended that a similar approach may be advisable in patients with NASH who experience a significant improvement in ALT level (eg a decrease of $>50\%$ of the original ALT baseline to a new stable level during the trial). For example, in a patient with a baseline ALT of 200 U/L, who experienced a decrease in ALT to a stable level of 100 U/L, future elevations of ALT should be viewed and managed as a change from the new ALT baseline of 100 U/L.

4.1 | Consensus and Recommendations

10. In patients with NASH who have normal or near normal baseline ALT (ie ALT $<1.5 \times$ ULN), ALT elevation of $\geq 5 \times$ ULN in the absence of hepatic symptoms (such as severe fatigue, abdominal pain, nausea or vomiting) or elevated TBL, is a reasonable threshold to suspect DILI and to initiate close observation and monitoring (Table 1).
11. In patients with normal or near normal baseline ALT, a combination of ALT $\geq 3 \times$ ULN plus TBL $\geq 2 \times$ ULN* or ALT $\geq 3 \times$ ULN plus hepatic symptoms should be considered as a signal of potential DILI (Table 1).
12. In patients with elevated baseline ALT ($\geq 1.5 \times$ ULN), ALT elevation of $>3 \times$ baseline or greater than 300 U/L (whichever comes first), even in the absence of hepatic symptoms or elevated TBL, is a reasonable threshold to suspect DILI and to initiate close observation and monitoring (Table 1). The threshold values may need to be adjusted based on nonclinical data, mechanism of action or hepatic safety signals in early-phase trials.
13. In patients with elevated baseline ALT ($\geq 1.5 \times$ ULN), a combination of ALT $\geq 2 \times$ baseline or ALT $\geq 300 \times$ ULN (whichever comes first) plus TBL $\geq 2 \times$ ULN* or hepatic symptoms, should be considered as a signal of potential DILI and require interruption of the study drug (Table 1).
14. In patients who meet the criteria for a DILI signal, assessment for hepatic symptoms and liver tests should be repeated within 2-5 days. The specific interval between the tests should be determined based on the patient's clinical condition.
15. Baseline values of ALT may need to be established based on an average of two consecutive tests performed at least 2 weeks apart prior to enrolment (preferably during the screening and baseline visits). If there is change in ALT level of $>50\%$ between the two tests, it may be prudent to perform a third test to determine the direction of the change, and to avoid enrolment until the cause is identified and ALT level stabilizes.
16. In patients with a sizable stable decrease in ALT level during treatment ($>50\%$ of the baseline value), a new baseline, corresponding to the ALT nadir, may need to be established for subsequent determination of a DILI signal.
17. When designing liver-related monitoring and stopping rules, it is important to take into consideration the variation of normal ALT range that exists among laboratories.

(*Does not apply to patients with Gilbert's syndrome.)

5 | SPECIAL CONSIDERATIONS FOR CAUSALITY ASSESSMENT OF SUSPECTED DILI IN PATIENTS WITH NASH

Causality assessment for suspected DILI is usually challenging during drug development, in part because there is insufficient information

on the hepatic safety profile of the drug, and it is often unknown whether a study subject is receiving the active drug or placebo.^{75,76} The difficulty increases when study subjects have pre-existing liver disease such as NASH, which may lead to fluctuation in hepatic biochemical tests.⁹ Causality assessment is required in NASH patients who meet the criteria for suspected DILI during a clinical trial (Table 1). A comprehensive discussion of the various methods of causality assessment is beyond the scope of this paper; however, several considerations, which are unique to drug development for NASH, are outlined. Patients with NASH are usually asymptomatic or report mild nonspecific symptoms such as fatigue or right upper abdominal discomfort.⁴² Therefore, new or worsening symptoms such as abdominal pain, severe fatigue, nausea or vomiting should raise suspicion of other diagnoses (including DILI). Changes in liver tests due to underlying NASH usually are hepatocellular in nature, and most NASH patients have normal to moderately elevated ALT levels. While the magnitude of "normal" fluctuation in ALT level in NAFLD/NASH is not well defined, ALT elevation of $\geq 5 \times$ ULN is rare, and usually should not be attributed to NASH during a clinical trial, especially if this elevation represents a significant change from the patient's baseline. In such patients, investigators should consider other causes such as viral hepatitis A-E, AIH, gallstone disease or DILI. Thorough history of concomitant medications, alcohol consumption and dietary and nutritional supplements is essential. Elevation of ALP or TBL to $\geq 2 \times$ ULN is also atypical of NASH and other causes (such as gallstone disease, hepatic tumour, pancreatic tumour or DILI) should be thoroughly investigated.^{77,78} Concomitant elevation of ALT and ALP increases the likelihood that the cause is DILI, which may be mixed, hepatocellular and cholestatic.^{77,78} According to a few publications, a small subset of NASH patients (predominantly women) may have isolated elevation in ALP (typically less than $2 \times$ ULN) instead of the more typical AT elevations.^{77,78} The clinical significance of this observation is not well understood and requires further study.

Patients with long-standing T2DM and other features of the metabolic syndrome have a higher risk of cholelithiasis, pancreatic carcinoma, cholangiocarcinoma and hepatocellular carcinoma compared to nondiabetic populations.^{79,80} Furthermore, patients with NASH often are started on low calorie diets as part of their treatment, which may further raise the risk of cholelithiasis, largely due to increased cholesterol flux through the biliary system.⁸¹ Patients undergoing rapid weight loss from dieting or gastric surgery are at particularly increased risk of gallstones and their complications. Passage of a gallstone or choledocholithiasis may closely resemble cholestatic DILI and occasionally acute hepatocellular DILI. Therefore, the assessment of a NASH patient with a treatment emergent abnormality in hepatic biochemical tests should take into account the possibility of gallstone-related disease. Importantly, intensive exercising (eg weight lifting), started in conjunction with other lifestyle changes for NASH can lead to an acute elevation in AST and ALT due to muscle injury, that can be mistaken for acute DILI. Patients receiving statins as concomitant therapy for dyslipidemia, may also have elevated ALT and AST due to statin-related muscle

injury. Testing for blood levels of creatine phosphokinase (CK), aldolase or other muscle-related enzymes can confirm the nonhepatic origin of this event.

Anti-nuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) are frequently positive with low titres in NASH patients and are generally considered an epiphenomenon of no clinical consequence.^{58,82} In an analysis from the NASH Clinical Research Network (NASH CRN), elevated serum autoantibodies levels (ANA $\geq 1:160$ or ASMA $\geq 1:40$ or both) were present in 21% of 864 patients with biopsy-proven NAFLD, in the absence of AIH.⁸² The finding of positive titres for ANA or ASMA may be confusing and is unhelpful for causality assessment of a potential DILI in patients with NASH. A liver biopsy may be helpful in ruling out idiopathic AIH, especially in patients with concomitant hypergammaglobulinemia or other clinical features suggesting AIH.^{58,75,83} Another potentially confounding biochemical finding in patients with NASH is an elevated serum ferritin level, however, iron overload disorders do not generally cause acute liver injury and therefore evaluation for iron overload is normally not necessary in a NASH patient with acute hepatocellular injury during a clinical trial.^{84,85}

As in other circumstances of suspected DILI, a liver biopsy is usually not required for causality assessment, but when performed, it can provide important and useful information on the pattern of injury and its severity. A liver biopsy may be particularly helpful in the setting of pre-existing NASH and an experimental agent in early development for which there is little prior information regarding liver injury. It may also be useful when there are multiple candidates as the causal agent, and for exclusion of AIH.⁸⁶

5.1 | Consensus and Recommendations

18. In NASH patients with normal or near normal baseline ALT, an increase of ALT to $\geq 5 \times$ ULN during a clinical trial should not be presumed due to underlying NASH, but should trigger an evaluation for an alternative aetiology including possible DILI. Similarly, the occurrence of ALT elevation $> 3 \times$ ULN with new onset or worsening hepatic symptoms (severe fatigue, abdominal pain, nausea, or vomiting) should prompt an evaluation for alternative aetiology (as well as interruption of the study drug).
19. In NASH patients with elevated baseline ALT ($\geq 1.5 \times$ ULN), an increase of ALT to $\geq 3 \times$ baseline, or ≥ 300 U/L (whichever comes first) during a clinical trial should not be presumed due to underlying NASH, and should prompt an evaluation for alternative aetiologies including possible DILI.
20. Elevated serum autoantibodies titres (ANA $> 1:160$ or ASMA $> 1:40$) may be encountered in NAFLD patients, and do not necessarily suggest AIH. The finding of autoantibody positivity associated with hypergammaglobulinemia should prompt further evaluation including consideration of a liver biopsy.
21. It is recommended to measure autoantibody titres (ANA and ASMA) prior to enrolment, to provide a baseline for subsequent comparison.
22. Elevated ferritin levels may be encountered in patients with NAFLD. This finding should not automatically prompt evaluation for iron overload unless associated with an elevated transferrin saturation.
23. Emergence of ALP $\geq 2 \times$ ULN is not typical of NASH and should prompt an evaluation for alternative aetiology including DILI.

6 | ASSESSMENT OF DILI RISK DURING DRUG DEVELOPMENT IN PATIENTS WITH NASH

Assessment of a candidate drug's potential to cause severe DILI relies predominantly on changes in routine hepatic biochemical tests (ALT, ALP, TBL and INR) during clinical phases of drug development.^{9,28,69} An imbalance (even as low as 1.2%) in the frequency of ALT elevation $> 3 \times$ ULN between active treatment and placebo/comparator during clinical development may sometimes be the first signal of a high risk of severe DILI post-marketing, although such imbalance may also appear in studies of drugs that have proven to be safe to the liver (for example, statins).^{69,75,87} In addition, a small imbalance of ALT $\geq 3 \times$ ULN may become insignificant when the study population includes a relatively high percentage (eg $> 20\%$) of patients with ALT $> 3 \times$ ULN prior to enrolment. Since this may be the case in clinical trials enrolling NASH patients, it has been recommended to adjust the approach to DILI risk assessment in such clinical trials.^{30,70} In patients enrolled with elevated ALT (ie ALT $> 1.5 \times$ ULN), searching for an imbalance in ALT $> 5 \times$ ULN or multiple of baseline ALT between the drug and comparator has been proposed as more informative.^{9,70}

Hy's law is currently the most specific tool available to the pharmaceutical industry and regulatory agencies for assessing a drug's potential to cause severe hepatocellular DILI.^{10,11} Its predictive value has been validated in DILI registries from Sweden,⁸⁸ Spain⁸⁹ and the US,⁹⁰ where the risk of death or need for liver transplantation from acute DILI causing jaundice, approximates 10%.^{10,11}

The current definition of Hy's law^{10,11} was intended to be applied in patients without underlying liver disease and thus presents a significant challenge when dealing with patients with NASH. According to current guidelines, a Hy's law case is defined by (a) ALT elevation $\geq 3 \times$ ULN; (b) TBL $\geq 2 \times$ ULN; (c) absences of significant cholestasis; and (d) no other cause explaining the elevation of ALT and TBL. In addition, the suspected drug should show a higher incidence of ALT $> 3 \times$ ULN compared to the control drug or placebo.⁶⁹ Yet, in studies enrolling patients with NASH, ALT elevation may be related to the underlying NASH and thus the test abnormalities may not meet the definition of Hy's law. As a result, the predictive value of Hy's law, based on its current definition, may be diminished. Nevertheless, it is widely agreed that the underlying concept of Hy's law remains valid, although the biochemical criteria may need to be modified. The optimal approach to using Hy's law in clinical trials in patients with NASH is still a matter of debate and clear guidelines and definitions are lacking. A few groups have suggested

improved predictive models based on modified definitions of Hy's law, however, these modified definitions have not been assessed for drug development or in a clinical trial setting in patients with elevated baseline liver tests, and will require further assessment and validation.^{91,92}

The Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plot, another widely used hepatic safety assessment tool by regulators and drug developers, allows scanning of large numbers of clinical trial patients for indicators of hepatocellular injury by serum ALT and TBL levels. However, eDISH was originally designed for patients who are enrolled into clinical trials with no underlying liver disease.^{28,93} The right upper quadrant of the eDISH plot, referred to as "Hy's law range," includes all study subjects with ALT $>3\times$ ULN and TBL $>2\times$ ULN. This quadrant identifies patients of special interest for which more clinical information should be sought for medical diagnosis of the most likely cause. These patients may potentially represent Hy's law cases, if there is no significant cholestatic abnormality, and the liver injury is caused by the study drug.^{28,93} While eDISH is still useful and effective in NASH clinical trials, it is more likely that patients in the Hy's law range may have had abnormal liver tests at baseline, and careful assessment of these patients is needed. There is an ongoing discussion on the best way to use the eDISH plot in patients enrolled in clinical trials with pre-existing CLD such as NASH. It is possible that future modification using different cut-off values may improve the use of eDISH in this patient population.

6.1 | Consensus and Recommendations

24. When peak levels of ALT $\geq 3\times$ ULN and TBL $\geq 2\times$ ULN are observed in a NASH patient enrolled in a clinical trial, the biochemical threshold levels of acute hepatocellular injury consistent with Hy's law may not be met, because of prior ALT elevation at baseline.
25. Recently suggested modified biochemical threshold criteria for Hy's law have not been assessed for drug development and require further assessment and validation for patients with underlying liver disease such as NASH.
26. eDISH remains useful in NASH clinical trials, however, patients in the Hy's law quadrant need careful assessment based on their baseline ALT and TBL values.
27. Presently, there is no evidence to support that existing modifications to eDISH are advantageous for clinical trials in patients with NASH.

7 | HEPATIC DISCONTINUATION RULES

In most idiosyncratic DILI cases, the only effective treatment is discontinuation of the causal agent. Delayed discontinuation can result in irreversible liver failure and death.^{10,90} On the other hand, automatic discontinuation of a study drug upon finding a mild

abnormality in liver enzymes (eg elevation of ALT or AST to $>3\times$ ULN without hepatic symptoms or elevated TBL) is usually unnecessary and may make it difficult to differentiate between a drug that is associated with benign self-limiting AT elevations and a drug that may cause clinically significant liver injury.^{28,69} Current regulatory recommendations regarding hepatic discontinuation rules focus on patients who are enrolled in clinical trials with healthy livers and normal hepatic biochemical tests.^{69,94} According to the US FDA guidelines, discontinuation of the study drug should be considered in any one of the following conditions: (a) ALT or AST $\geq 8\times$ ULN; (b) ALT or AST $\geq 5\times$ ULN for more than 2 weeks; (3) ALT or AST $\geq 3\times$ ULN with TBL $\geq 2\times$ ULN or INR >1.5 ; (4) ALT or AST $\geq 3\times$ ULN with symptoms such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash.⁶⁹ However, in some patients with NASH, ALT and AST may approach or cross these levels at baseline or during the trial, which may lead to premature discontinuations if these same stopping rules are applied.³²⁻³⁵ Several experts have suggested that in patients with NASH enrolled in clinical trials with elevated ALT, AST or TBL, discontinuation rules should be determined as multiples of baseline rather than multiples of ULN.^{30,70} For example, it has been suggested that in patients with NASH enrolled with elevated ALT discontinuation should be considered for ALT levels exceeding $5\times$ baseline or 500 U/L (whichever occurs first) (Table 1). Concurrent elevation of ALT and TBL should be viewed as a more specific indication of severe DILI and should lead to an earlier discontinuation. In such cases, patients who had normal TBL and ALT of $\geq 1.5\times$ ULN at baseline, may need to be considered for discontinuation when ALT is $\geq 2\times$ baseline, if TBL increases to $\geq 2\times$ ULN (Table 1). Of note: Occasionally in clinical trials the study drug has to be interrupted, but can then be resumed when a clear cause of liver injury other than the drug is identified and liver enzymes improve.

7.1 | Consensus and Recommendations

28. When considering study drug discontinuation in NASH patients with suspected DILI, who had elevated baseline ALT ($\geq 1.5\times$ ULN), it is recommended to assess the change from baseline rather than the change from ULN (Table 1).
29. In patients with normal baseline ALT and TBL, study drug discontinuation should conform to the current FDA stopping rules: (a) ALT $\geq 8\times$ ULN, (b) ALT $\geq 3\times$ ULN and TBL $\geq 2\times$ ULN or INR >1.5 , (c) ALT $\geq 3\times$ ULN and symptoms such as severe fatigue, fever, right upper quadrant pain, nausea, or vomiting.
30. In patients with elevated baseline ALT (ALT $>1.5\times$ ULN) study drug discontinuation should be considered if one of the following occurs: (a) ALT $\geq 5\times$ baseline or ≥ 500 U/L (whichever occurs first), (b) ALT $\geq 2\times$ baseline or ≥ 300 U/L (whichever occurs first) and TBL $\geq 2\times$ ULN, (c) ALT $\geq 2\times$ baseline or ≥ 300 U/L (whichever occurs first) and symptoms such as severe fatigue, fever, right upper quadrant pain, nausea, or vomiting.
31. When ALT and AST have improved considerably during treatment (eg a reduction of $>50\%$ of the baseline values), the new

nadir should be considered as the new baseline for monitoring and discontinuation decisions.

32. Occasionally, the study drug has to be interrupted because of acute biochemical changes, but can then be resumed when a clear cause other than the drug is identified, and liver enzymes improve.

8 | BIOMARKERS FOR DETECTION AND ASSESSMENT OF DILI IN PATIENTS WITH NASH

Despite intensive efforts to identify and develop new noninvasive biomarkers for detection and assessment of DILI, none of these future biomarkers is qualified or ready for routine use. Ongoing efforts are being spearheaded by groups such as TransBioline (under the Innovative Medicines Initiative), Predictive Safety Testing Consortium (under the Critical Path Institute), DILIN, and others. A detailed discussion of these biomarkers is outside the scope of this article.

9 | MONITORING AND ASSESSMENT OF DILI IN CIRRHOTIC NASH PATIENTS WITH OR WITHOUT HEPATIC DECOMPENSATION

While a complete discussion of the assessment and management of DILI occurring in patients with cirrhotic NASH is beyond the scope of this paper, a few points will be briefly addressed. Monitoring and assessment of DILI in patients with cirrhosis present drug developers and clinical investigators with unique challenges, which to date have not been addressed in existing regulatory guidance. It should be noted that patients with advanced liver disease can have normal AT values or only mild elevations. Importantly, the AST:ALT ratio may increase to >1 in such patients, and the ratio may increase as the disease progresses.⁹⁵ In general, DILI in patients with preexisting liver dysfunction may sometimes present with rapid deterioration of liver function (ie elevated direct bilirubin and prolonged INR), with only mild changes in ATs.⁹⁶⁻⁹⁸ Therefore, close monitoring is essential in such patients, to enable early detection of the first signs of DILI, and ensure early discontinuation of the drug. Such patients are often highly confounded and causality assessment may be very challenging. To date there are no published systematic reports of drug treatment in patients with NASH-related advanced liver disease or decompensated cirrhosis, although clinical trials are ongoing. In fact, relatively few publications discuss the management of DILI patients with preexisting liver dysfunction who participate in clinical trials.^{55,70}

10 | SUMMARY

The number of drug-development programs for NASH has grown considerably over the last decade. Moreover, the inclusion of patients with diagnosed or undiagnosed NASH into trials in other

therapeutic areas is increasing rapidly, and will likely continue to increase as the obesity and diabetes epidemic expands worldwide. There is a great need for consistent and evidence based recommendations for best practices to enable better monitoring, assessment, and management of suspected DILI in patients with NASH. This paper provides a framework for recommendations based on the collaborative work of the IQ DILI initiative with experts from academia and other experts in the DILI field.

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DISCLAIMER

The views expressed are those of the authors and do not necessarily represent the position of, nor imply endorsement from, the US Food and Drug Administration or the US Government.

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APPENDIX 1

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APPENDIX 2

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