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Nonalcoholic Steatohepatitis: Current Thinking from the Division of Hepatology and Nutrition at the Food and Drug Administration

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Abbreviations: DHN, Division **of Hepatology and Nutrition;** FDA, US Food **and Drug Administration;** NASH, n**onalcoholic steatohepatitis;** SOC, standard of care.

As part of a larger reorganization of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of New Drugs, the former Division of Gastroenterology and Inborn Errors Products (DGIEP) has been divided into three review divisions with more focused disease areas, including the new Division of Hepatology and Nutrition (DHN). DHN's review activities are focused on three general areas: (1) drug development and review of early and late phase clinical trials of drugs for treatment of specific diseases of the liver, (2) consultations from any FDA review division on drug-induced liver injury (DILI), and (3) development and review of early and late phase clinical trials for nutrition products.

DHN views nonalcoholic steatohepatitis (NASH) with liver fibrosis as a serious and life-threatening condition. NASH with liver fibrosis affects more than 5 million people in the United States and is an important area of investigational drug development. DHN reviews drug development programs for NASH and is committed to the collaborative work needed to fill this critical unmet medical need. Drug development for treatment of NASH can be challenging due to the gradual, slow progression of fibrosis in the liver over years to decades. The magnitude of the benefit a patient receives with lifelong treatment of NASH must be balanced with the safety profile of the drug. NASH patients are also vulnerable to other diseases [(1)], and the investigational drug should not worsen comorbidities, including cardiovascular disease, hyperlipidemia, metabolic disease, and diabetes, or cause liver injury.

The accelerated approval pathway for drugs intended to treat NASH with liver fibrosis is appropriate because of the seriousness of the condition. Accelerated approval relies on adequate and well-controlled clinical trials establishing that the drug affects a surrogate endpoint that is reasonably likely to predict clinical benefit. A post-marketing clinical outcomes trial to verify the drug's clinical benefit should be under way before the phase 3 trial data is submitted for review. The outcomes trial must also be adequate and well controlled and carried out with due diligence [(2)].

While many non-invasive biomarkers are under study for consideration as a surrogate marker, none to date have demonstrated reliability and consistency to be reasonably likely to predict clinical benefit, that is, can be used as a surrogate efficacy endpoint for accelerated approval while post-marketing trials

confirm clinical benefit based on how a patient feels, functions, or survives. Sponsors should use non-invasive biomarkers in clinical development, from proof-of-concept early phase 2 studies to their use as secondary or exploratory endpoints in late stages of drug development (i.e., dose-finding or phase 2b trials and phase 3 trials). We encourage use and evaluation of non-invasive biomarkers in any clinical development program with a goal to describe and characterize a non-invasive biomarker with reliable and consistent findings to be considered for use as a surrogate efficacy endpoint reasonably likely to predict clinical benefit.

DGIEP issued a 2018 draft guidance on developing drugs for treatment of NASH with liver fibrosis.[3] For NASH with moderate or bridging fibrosis (fibrosis stages 2 and 3 [F2 and F3]), the accelerated approval pathway was offered as a potential route for approval based on the following histologic endpoints: (1) resolution of steatohepatitis (on overall histopathological reading) and no worsening of liver fibrosis based on the NASH Clinical Research Network (CRN) fibrosis score, (2) improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis, or (3) both resolution of steatohepatitis and improvement in fibrosis (as defined above).

These surrogate endpoints were based on the published Kaplan-Meier curve demonstrating reduced overall survival and increased liver-related mortality that occurred with more advanced fibrosis.[3,4] Cirrhosis (fibrosis stage 4 [F4]) is highly predictive of a significantly increased mortality rate compared to F3 or F2, but both F3 and F2 are associated with substantially higher mortality rates compared to no fibrosis (stage 0 [F0]) or minimal fibrosis (stage 1 [F1]). Fibrosis also appears to predict liver-related clinical outcomes [3], and a strong association between histologic resolution of steatohepatitis and improvement in fibrosis has been observed and reported in the literature [4-6]. Therefore, the surrogate histologic endpoints in the draft guidance for NASH patients with F2 and F3 appear to be a reliable and consistent surrogate endpoint reasonably likely to predict clinical benefit. Sponsors and academia are encouraged to continue evaluation of potential noninvasive biomarkers with this capability.

The draft guidance on NASH represents DHN's current thinking on the development of drugs intended to treat NASH. DHN encourages sponsor engagement during the planning and conduct of NASH trials.

Despite well-recognized limitations, liver histology read by an experienced hepatopathologist remains the gold standard for the classification of patients with F2 or F3. These limitations include but are not limited to the following: (1) substantial (~40%) sampling error [7], that can result in disease severity being misclassified and (2) inadequate samples with respect to length of the biopsy [8] and the number of portal areas captured. Additional important challenges include differences in the interpretation of liver histology findings among several pathologists (e.g., potential for low inter-reader concordance rate) and even with their own previous interpretation of findings (intra-reader variability).

The inter-reader concordance rate for key components of both the nonalcoholic fatty liver disease score (NAS)[5] (inflammation, ballooning, and steatosis) as well as the NASH fibrosis score (or stage) can vary widely.[9] Conceivably, a high degree of discordance in liver histology interpretation could be improved by pathologists' training, for example, having an adjudication committee of central pathologists read baseline and treatment slides together and decide how each of the components of the NAS system will be interpreted. Such training efforts, along with inclusion of a placebo control in the trial design, should help to address many of the limitations of the histopathology reading of liver biopsies and have liver histology be considered as a reliable and consistent surrogate efficacy endpoint. We recommend sponsors review in detail their plan for liver biopsy procurement, processing, and interpretation before embarking on their phase 3 trial.

Furthermore, NASH is a common disease, and trials that provide a sufficiently large preapproval safety database will facilitate the assessment of risk and benefit. In accordance with the International Conference on Harmonization (ICH) E1A guidance [10] which recommends a minimum number of patients who should be enrolled in a trial for drugs intended for chronic administration, the size of the preapproval safety database should ensure that low-frequency adverse event(s) can be detected and appropriately described for an assessment of risk and benefit. Sponsors should be aware that the size of one placebo-controlled trial adequately powered for efficacy might not be sufficient to support the drug's safety and allow for the overall benefit-risk assessment that is necessary for drug approval; this is a particular concern in NASH, in which millions of patients would be treated with the new drug, once FDA approved.

Generally, premarketing trials for NASH plan to evaluate the histology surrogate endpoint at 12 to 18 months of treatment, and FDA's draft guidance endorses this approach. However, given the slow gradual progression or improvement in inflammatory changes and fibrosis observed on liver histopathology, sponsors might want to consider efficacy evaluations of the surrogate histopathologic endpoint at 2 or more years because of subtle changes in histologic features associated with the disease. Moreover, trials should be designed to follow patients who continue their randomized treatment assignments (e.g., investigational drug or placebo in a double-blinded fashion) for clinical outcome assessments in the post-market setting to be able to confirm clinical benefit following accelerated approval. There are obvious challenges associated with this approach, for example, reconsenting patients enrolled in the trials to ensure awareness of the availability of an FDA-approved drug under accelerated approval. However, drug labeling under accelerated approval is required to have cautionary statements that clinical benefit has not been confirmed, thereby demonstrating to patients, investigators, and institutional review board committees that it may be ethically appropriate, if not highly desirable, to continue randomized treatment assignments after an accelerated approval and minimize loss to follow-up. Furthermore, in phase 3 development programs with large enough trial(s), confirmation of clinical benefit and traditional approval could occur during a relatively short period of time after accelerated approval.

Clinical outcomes conferring benefit in post-marketing studies were listed in both the noncirrhotic NASH with fibrosis guidance [(2)], and the guidance for NASH-related compensated cirrhosis. [(11)] If a product merits accelerated approval for NASH based on the histologic efficacy endpoints, the accelerated approval pathway requires a phase 4 clinical outcomes trial to verify clinical benefit. The phase 4 trial is a randomized, double-blind, placebo-controlled study in which patients are followed on the drug to determine clinical outcome assessments. These outcome assessments include decompensation events associated with progression of NASH, such as a slowing of progression to cirrhosis, reduction in hepatic decompensatory events (variceal bleeding, ascites, hepatic encephalopathy, etc.), improvement in Model for End-Stage Liver Disease (MELD) score (from $\leq$12 to $\geq$15), reduction in death (all-cause mortality), and need for liver transplantation. Success of the phase 4 trial verifying clinical benefit

conveys full-market approval of the sponsor's drug.

Sponsors should be aware of the impact of how the standard of care (SOC) permitted in caring for all NASH patients enrolled in a clinical trial could impact a placebo response rate. This is likely within developed countries and could be influenced by cultural differences that may influence how individuals in a placebo cohort respond to or participate in SOC measures in NASH clinical trials. Published literature indicates that a substantial number of patients in placebo cohorts achieve histological improvement [12], on liver biopsies obtained during study treatment—that is, a substantial number of placebo-treated patients often meet a successful finding on the surrogate endpoint. Trial participation may represent a favorable environment for patients with NASH to receive and willingly follow dietary counseling advice and embark on exercise programs that result in weight reduction. As a result, trial participation could result in a higher than expected placebo response rate and a lower than expected observed treatment difference from the investigational drug. Therefore, it is important to ensure that the SOC is uniform across all treatment arms as described in published guidelines by authoritative scientific bodies[13], and differences in SOC should be considered when analyzing international trials (e.g., stratification by geographical/cultural areas).Sponsors should account for such differences in SOC across geographic areas to appropriately power their phase 3 studies and account for these issues.

Summary

FDA's draft guidance for noncirrhotic NASH, issued in December 2018, provides our current thinking on clinical trials conducted in the support of successful approval of new drugs for NASH with F2 and F3. Phase 3 studies demonstrating a successful treatment difference on liver histology surrogate endpoint(s) and an adequate safety profile can receive an accelerated approval with a requirement to verify and confirm clinical benefit after approval. For clinical trials in compensated cirrhosis secondary to NASH, we continue to recommend a traditional approval pathway based on improvement in clinical benefit outcomes. DHN is open to discussions with sponsors about other options for approval for this population.

Limitations in clinical trials for marketing approval of NASH drugs include a current lack of surrogate

endpoint biomarkers other than liver histology. Although liver histology remains the gold standard, the shortcomings of liver histology interpretation can lead to significant discordance among blinded hepatopathologists. Sponsors should provide additional reassurance that the histologic endpoint is reliable and consistent, for example, by use of an adjudication committee of at least two pathologists trained in evaluating liver biopsy. Study duration and follow-up of patients in liver histology trials can be challenging and impose undue burdens. Nonetheless, well-designed and adequately controlled trials are essential, not only for efficacy assessment but also for accruing a safety database that ensures that a thorough benefit-risk assessment can be conducted given the likelihood that any drug approved for NASH will be a lifelong therapy in patients. The published literature also suggests that patients in placebo treatment arms may have a higher than expected success rate in achieving primary histologic endpoints. Whether this is a result of clinical trial participation is not fully known. However, sponsors may want to be more explicit in standardizing SOC maneuvers across all treatment arms. Finally, because many patients with NASH have comorbid conditions that could be adversely affected by a potentially lifelong NASH treatment, clinical outcomes trials are essential for verifying and establishing the clinical benefit of successful findings on a surrogate endpoint resulting in accelerated approval. NASH with fibrosis is a serious condition, [14] and therefore sponsors are encouraged to meet with DHN at key stages of drug development and avail themselves of FDA's expedited drug development programs.

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