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Editorial

The Complex Pathophysiology of Metabolic Dysfunction-Associated SteatoHepatitis (MASH) may Complicate FDA Accelerated Approval Regulatory Paradigm

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Metabolic dysfunction-Associated SteatoHepatitis (MASH), previously known as NonAlcoholic SteatoHepatitis (NASH), continues to be the most common cause of chronic liver disease in the industrialized world [1] and can progress to liver fibrosis, as well as end-stage cirrhosis leading to death [2]. MASH is also associated with an increased risk of cardiovascular (CV) morbidity and mortality, as well as obesity and type 2 diabetes mellitus (T2DM) [3]. Cirrhosis associated with MASH increases the risk of hepatocellular carcinoma [4]. Most MASH clinical trials use liver biopsy [5] as the primary endpoint to support regulatory submissions to FDA, based upon the original NIH published guidelines for NASH Clinical Trial Design [6] which influenced the recommendations in the December 2018 Draft NASH FDA Guidance [7]. However, a growing number of trials include imaging and blood based biomarkers as secondary and/or exploratory endpoints, allowing for comparison with liver biopsy for calculations of their sensitivity, specificity and predictive values [8] to help support the move away from liver biopsy to these surrogate assessments for both initial MASH diagnosis and as clinical trial endpoints to support FDA approval [9].

Recent FDA approvals of drugs to treat patients with MASH have been applauded by patient advocacy groups [10] and supported by clinicians [11]. However, lost in the media headlines is the fact that these regulatory actions were "accelerated approvals" by FDA which then must be followed by successful Phase 4 confirmatory clinical outcomes trials in order for these drugs to stay on the U.S. market [12]. One can consider accelerated approvals as a contract between the pharmaceutical company and FDA. Under this initial approval, the agency allows the drug to be sold earlier, allowing broader patient access based upon surrogate or intermediate clinical endpoints ("biomarker") that is deemed to be "reasonably likely to predict clinical benefit" [12] in confirmatory clinical outcome studies to be conducted post-accelerated approval. FDA expectations are that the pharmaceutical company starts the outcomes trial before accelerated approval is granted, it then is fully enrolled, completed and submits the data to FDA and the submitted clinical data is viewed by the agency as "substantial evidence" [13] adequate to support conversion of the accelerated approval to a traditional (full) approval. Previously the agency had limited authority to withdraw accelerated approvals when confirmatory outcomes studies failed, but in 2022, Congress granted FDA additional authority to rapidly withdraw accelerated approval drugs from the U.S. market, as part of the Food and Drug Omnibus Report Act of 2022 (FDORA) [14]. However, prior to the withdrawal of any accelerated approval, FDA has to provide the pharmaceutical company with due notice and an explanation of the proposed withdrawal. This is followed by an opportunity for the company to have a meeting with the Commissioner or the Commissioner's designee and an opportunity for written appeal, including an advisory committee meeting on the proposed withdrawal [14]. It was soon after the granting of this new authority that FDA withdrew the accelerated approval of Pepaxto (melphalan flufenamide) [15]. The FDA decision memo stated that "the grounds for withdrawing approval have been met because: (1) the confirmatory study conducted as a condition of accelerated approval did not confirm Pepaxto's clinical benefit and (2) the available evidence demonstrates that Pepaxto is not shown to be safe or effective under its conditions of use" [16].

FDA Guidance "Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment" (December 2018) lists the various endpoints to be utilized to verify clinical benefit after demonstrating positive impact on liver history and receiving accelerated approval [7]. Each element of clinical benefit listed deserves individual analysis. The "Progression to cirrhosis on histopathology" [7] sounds promising on its face. A clinical trial design where the Phase 3 patients which supported accelerated approval are "rolled over" into the Phase 4 confirmatory outcomes trial with the primary endpoint measure by liver biopsy histology. However, a significant question is how long these patients should be treated and should the placebo group be followed for the same interval? The published literature describes various lengths of time for progression of fibrosis from early stages to later stages, with all in years. An article authored by Singh S et al. (2015) described "In this systematic review and meta-analysis of paired liver biopsy studies in patients with NAFLD, contrary to conventional paradigm, we found that both patients with

NAFL and NASH develop progressive hepatic fibrosis, progressing by 1 fibrosis stage (from baseline stage 0 fibrosis) over 14.3 and 7.1 years, respectively. A small subset of these patients may develop rapidly progressive hepatic fibrosis" [17]. Will patients want to be part of a placebo group for at best 7 years? Since some companies pushed back on the FDA desire for 18 month endpoints in Phase 3, the willingness to fund a confirmatory study that runs significantly longer than their Hatch-Waxman Exclusivity is less likely. Regardless, this design would require a third liver biopsy to be successful, which many patients do not want to undergo. "Reduction in hepatic decompensation events" [7] is an appealing endpoint since these are the types of clinical events (e.g., variceal bleeding, portal hypertension, hepatic encephalopathy, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hospitalizations, liver related deaths) that clinicians and patients want to avoid. However, many of these events can be impacted by the amount and quality of care these patients receive. If a patient is in a rural area, the hope is that they receive appropriate supportive care. In contrast, in some tertiary/academic centers, patients could have better outcomes by receiving state-of-the-art procedures and medications that minimize these adverse events [18].

There is hope that the MELD score (Model for End Stage Liver Disease) [7] will be an easy calculation using laboratory data and other patient information to derive a number that has demonstrated correlation with clinical status over time. The original publication by Wiesner R et al. (2003) was intimidating to some clinicians "The MELD equation used to calculate the severity score was as follows: MELD score = [9.57 × loge creatinine mg/dL + 3.78 × loge bilirubin mg/dL + 11.20 × loge INR + 6.43 (constant for liver disease etiology)]" [19]. Currently, this function has been automated and is available for anyone with internet access and the patient's laboratory values (e.g., bilirubin, serum sodium, INR, serum creatine, albumin0, along with their medical history [20]. In contrast, "Liver transplant" [7] has been a problematic endpoint in the past for FDA to interpret in the context of treatments of other liver diseases given the variability on timing, as well as heterogeneity of the transplant criteria and implementation within the U.S. and around the world. Despite changes to the organ allocation system over the years, continued variability in this transplant process makes it difficult to differentiate an improvement due to drug treatment versus seasonal or other variabilities within transplant centers or heterogeneity across centers [21]. It is possible for a drug to have a positive impact on either NASH Activity Score (NAS) and/or NASH Clinical Research Network (CRN) fibrosis score [7] but that efficacy signal is lost in the noise of the liver transplant system.

Finally, "All-cause mortality" [7] prized as the most desirable endpoint for support of clinical efficacy in confirmatory drug trials, is the most difficult to obtain. In the case of MASH, the underlying factors that contribute to fatty liver with resulting hepatic inflammation and fibrosis, are also risk factors for hyperlipidemia [22] obesity and T2DM, all of which contribute to cardiovascular (CV) risk, including myocardial infarction (MI) and stroke (CVA) [23]. The specific mechanism of action for any MASH drug may provide either a selective advantage or disadvantage in confirmatory clinical outcome trials depending upon that drugs impact on a patient's weight, LDL cholesterol, fasting blood glucose, blood pressure and emerging factors related to inflammation and thus the degree to which they are able to "reasonably likely to predict clinical benefit" [12] in confirmatory trials. From a practical perspective, how can such an accurate prediction be made if the drug is effective in a significant percentage over placebo, but under 50% of patients treated? Even if the drug produces complete resolution of NASH and reduction of hepatic fibrosis, what if the many years of untreated risks have produced coronary artery disease (CAD) which remains unaffected by even the most potent MASH drug, resulting in a fatal CV event during the confirmatory clinical outcome study. With the occurrence of a number of such CV events, the confirmatory trial could be labeled a "failure". This simplistic perspective would do a disservice to MASH patients, since given the complex nature of this disease it is unlikely that any one drug would significantly treat all of its aspects. It is reasonable to assume that combinations of drugs with different mechanisms of action will be necessary to completely treat MASH, just as combinations of various drugs are routinely used for the effective treatment of T2DM [24]. FDA has approved MASH treatments based upon the accelerated approval pathway which has been in effect since the early 1990's. Given that FDA law undergoes Congressional revision every five years with Prescription Drug User Fee Act (PDUFA) renewals [25] there have been multiple opportunities for Capitol Hill to modify use of the accelerated approval provisions. FDA has used the regulatory tools it has been provided and the results are MASH drug approvals. Although these initial drugs have been described as "modest" and "incremental advances", their availability on the U.S. market has raised both patient and practitioner awareness, increasing screening programs and thus MASH diagnosis of patients who are then able to enroll in clinical trials to study new therapeutic agents. I hope that these benefits to underserved patients with MASH will not be forgotten during a future "drug failure" news cycle, questioning FDA and their use of the accelerated approval pathway.

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References

1. Diehl AM, Day C (2017) Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *New England Journal of Medicine*. [crossref]
2. Ekstedt M, Franzén LE, Mathiesen UL (2006) Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology*. [crossref]
3. Targher G, Day CP, Bonora E (2010) Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *New England Journal of Medicine*. [crossref]
4. Ratziu V, Bellentani S, Cortez-Pinto H (2010) A position statement on NAFLD/NASH based on the EASL 2009 special conference. *Journal of Hepatology*. [crossref]
5. Anania FA, Dimick-Santos L, Mehta R (2021) Nonalcoholic steatohepatitis: current thinking from the FDA Division of Hepatology and Nutrition. *Hepatology*. [crossref]
6. Sanyal AJ, Brunt EM, Kleiner DE (2011) Endpoints and clinical trial design for nonalcoholic steatohepatitis. *Hepatology*. [crossref]
7. U.S. FDA (2018) Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment. *FDA Guidance*. [crossref]
8. Di Mauro S, Scamporrino A, Filippello A (2021) Clinical and molecular biomarkers for diagnosis and staging of NAFLD. *International Journal of Molecular Sciences*. [crossref]

9. Harvey BE (2022) NASH: regulatory considerations for clinical drug development and FDA approval, *Acta Pharmacologica Sinica*. [crossref]
10. Global Liver Institute (2024) Annual Report. *GLI*. [crossref]
11. Harvey BE (2025) Improvements in FDA regulatory process leading to first drug approval for common liver disease. *Acta Pharmacologica Sinica*. [crossref]
12. U.S. FDA (2024) Expedited Programs for Serious Conditions — Accelerated Approval of Drugs and Biologics. *FDA Guidance*. [crossref]
13. U.S. FDA (2023) Demonstrating substantial evidence of effectiveness with one adequate and well-controlled clinical investigation. *FDA Guidance*. [crossref]
14. U.S. Congress (2022) Accelerated Approval Update under FDORA. *Federal Report*. [crossref]
15. U.S. FDA (2024) Final decision to withdraw approval of Pepaxto. *FDA Announcement*. [crossref]
16. U.S. FDA (2024) Final decision on proposal to withdraw approval of Pepaxto. *FDA Documentation*. [crossref]
17. Singh S, Allen AM, Wang Z (2015) Fibrosis progression in NAFLD vs NASH: systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. [crossref]
18. Liu YB, Chen MK (2022) Epidemiology of liver cirrhosis and associated complications. *World Journal of Gastroenterology*. [crossref]
19. Wiesner R, Edwards E, Freeman R (2003) MELD and allocation of donor livers. *Gastroenterology*. [crossref]
20. OPTN (2025) MELD Calculator. *Organ Procurement and Transplantation Network*. [crossref]
21. Goldberg DA, Gilroy R, Charlton M (2016) New organ allocation policy in U.S. liver transplantation. *Clinical Liver Disease (Hoboken)*. [crossref]
22. Loomba R, Friedman SL, Shulman GI (2021) Mechanisms and disease consequences of NAFLD. *Cell*. [crossref]
23. Khoshbaten M, Maleki SH, Hadad S (2023) NAFLD and carotid intima-media thickness: systematic review and meta-analysis. *Health Science Reports*. [crossref]
24. Fleming GA, Harvey BE (2019) Regulatory considerations for early clinical development of drugs for diabetes, obesity, NASH and cardiometabolic disorders. *Springer Nature*. [crossref]
25. U.S. FDA (2025) Prescription Drug User Fee Amendments. *FDA Guidance*. [crossref]

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