# Experts Advise Against Approval of Obeticholic Acid for NASH

An FDA advisory committee expressed concerns about the safety of the fatty liver disease treatment.

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[Update: On June 22, 2023, the FDA followed the advisory committee's recommendation and denied approval of obeticholic acid for NASH for a second time.]

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A Food and Drug Administration (FDA) advisory committee recommended that the agency again decline approval of obeticholic acid (OCA) as a treatment for non-alcoholic steatohepatitis (NASH), meaning there will be a longer wait for the first safe and effective medication for the condition.

The Gastrointestinal Drugs Advisory Committee voted 15 to 1 against accelerated approval of OCA, asking for more clinical trial data. What's more, the experts voted 12 to 2 (with two abstentions) that the drug's modest benefits do not appear to outweigh its risks, citing concerns about serious drug-induced liver injury. This week's vote is the second blow for Intercept Pharmaceuticals' farnesoid X receptor (FXR) agonist. The FDA previously declined to approve the drug in June 2020, asking for more data on its long-term health effects.

Non-alcoholic fatty liver disease (NAFLD) and NASH, its more severe form, are responsible for a growing burden of advanced liver disease worldwide. Over time, the buildup of fat in the liver can lead to fibrosis, cirrhosis and liver cancer. Linked to obesity and diabetes, fatty liver disease is increasingly recognized as a metabolic disorder. With no effective approved therapies, management depends on lifestyle changes such as diet, exercise and weight loss.

Several treatment approaches aim to target metabolic abnormalities to improve liver fat accumulation and fibrosis. FXR agonists, for example, regulate bile acid synthesis and play a role in lipid and glucose metabolism and inflammation. But developing effective NASH treatments has proved challenging, and numerous candidates that appeared promising in early studies did not show significant benefits in larger clinical trials.

At one point, OCA—which is currently approved as a treatment for primary biliary cholangitis under the brand name Ocaliva—appeared to be a front-runner in the race to become the first

approved NASH treatment, thanks to promising findings from the ongoing Phase III REGENERATE trial.

REGENERATE enrolled people with NASH and either moderate to advanced fibrosis (Stage F2 to F3) or mild fibrosis (F1) with certain comorbidities. They were randomly assigned to receive one of two doses of OCA or a placebo once daily. Liver biopsies were done at the start of the study and 18 months later. Interim results were published in The Lancet in 2019.

While OCA increased the likelihood of fibrosis improvement without worsening NASH—part of the FDA's two-prong metric for effectiveness—it failed to meet the other main endpoint of NASH improvement without worsening fibrosis. It is too soon to know whether a one-stage reduction in liver fibrosis will prevent long-term complications, such as cirrhosis, liver decompensation or death.

The researchers described the treatment as generally safe, but side effects, including itching (pruritus), were common. Worse, an estimated 1 in 1,000 people taking OCA might develop severe drug-induced liver injury. "Trial results for obeticholic acid indicate it causes multiple off-target effects that require multiple risk mitigation strategies with low likelihood of effectiveness," according to an FDA briefing document released ahead of the advisory meeting. The document also noted concerns related to diabetes risk, elevated cholesterol and potential kidney and gallbladder problems.

"We have clear evidence of safety risks," said advisory committee member James Floyd, MD, of the University of Washington in Seattle. "It's impossible, in my mind, to ensure a good risk-benefit profile based on this surrogate endpoint data; we need to see the full clinical outcomes."

But Intercept still believes the treatment holds promise for NASH. The company has implemented a plan for monitoring and mitigating adverse events among trial participants, though it is unclear how well this would work in the real world with long-term OCA use.

"We continue to disagree with the FDA on certain characterizations of OCA's efficacy and safety in pre-cirrhotic fibrosis due to NASH and the role of noninvasive tests [NITs], as discussed in today's meeting," Intercept president and CEO Jerry Durso said in a press release. "The robust body of evidence provided by Intercept was underscored by public testimony from the liver community, who supported OCA as an option to address the urgent treatment need in NASH and the use of NITs to manage this devastating disease in clinical practice."

The FDA is expected to make a decision on OCA by June 22. The agency is not required to follow advisory committee recommendations, but it usually does so. "The FDA initially concluded that OCA was associated with an unfavorable benefit/risk profile, and in the resubmission our assessment of efficacy has remained unchanged," Ruby Mehta, medical team leader for FDA's Division of Hepatology and Nutrition, said at the meeting.

If the FDA rejects accelerated approval, it would take another three years to accumulate enough data to try for traditional approval. But Intercept is a small company, and continuing the trial for

that long might not be “economically feasible,” according to Intercept chief medical officer M. Michelle Berrey.

Several other companies are also in the NASH race. Madrigal’s resmetirom, a selective thyroid hormone receptor agonist, reduced liver fat and improved fibrosis in a Phase III clinical trial. The company expects to file for approval this quarter. 89bio and Viking Therapeutics recently announced promising Phase II data for their NASH candidates, pegozafermin and VK2809.

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