FDA Delays Approval of Ocaliva for Fatty Liver Disease

The regulatory agency requested further data to show whether its benefits outweigh its risks.

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The Food and Drug Administration (FDA) indicated in late June that it would not approve Intercept Pharmaceuticals' Ocaliva (obeticholic acid) for the treatment of fibrosis related to non-alcoholic steatohepatitis until more data are available, the company announced. This delays the debut of a first approved therapy for the increasingly common and potentially serious liver condition.

However, as Arun Sanyal, MD, of Virginia Commonwealth University noted at a fatty liver disease symposium sponsored by the Nutrition Obesity Research Center at Harvard, if the agency thought the drug was "ineffective or toxic," they likely would have stopped an ongoing clinical trial of the drug.

Non-alcoholic steatohepatitis (NASH) and its less severe form, non-alcoholic fatty liver disease (NAFLD), are responsible for a growing proportion of advanced liver disease. The buildup of fat in the liver triggers inflammation, which over time can lead to the development of fibrosis (scarring), cirrhosis and liver cancer. With no effective medical therapies currently approved—and with several candidates recently missing the mark—management relies on lifestyle changes such as weight loss and exercise.

Ocaliva is a farnesoid X receptor agonist that activates receptors that regulate glucose and lipid metabolism and inflammation. It is currently FDA-approved for primary biliary cholangitis, a disease of the bile ducts.

Intercept's application for approval was based on findings from the Phase III REGENERATE trial, which evaluated Ocaliva in people with diagnosed NASH and mild to advanced fibrosis (Stage F1 to F3). They were randomly assigned to receive 10 or 25 milligrams of Ocaliva or a placebo once daily. Liver biopsies were done at the start of the study and 18 months later.

Interim results, presented at the 2019 International Liver Congress and published in The Lancet last December, showed that while Ocaliva did significantly improve NASH-related fibrosis, it did not lead to NASH resolution.

This interim analysis included more than 900 people with moderate to advanced fibrosis who received at least one dose of Ocaliva. After 18 months, 23% of participants in the 25 mg Ocaliva group, 18% in the 10 mg group and 12% in the placebo group experienced fibrosis improvement without worsening of NASH. However, a NASH resolution endpoint showed that a reduction in liver fat and inflammation did not occur significantly more often in the Ocaliva groups compared with the placebo group (12%, 11% and 8%, respectively).

Treatment was described as generally safe, but side effects were common. The most common side effect was itching (pruritus), reported by 51% in the Ocaliva 25 mg group, 28% in the 10 mg group and 19% in the placebo group. This was usually mild to moderate, but 9% of people in the higher-dose Ocaliva group stopped treatment for this reason. Of perhaps more concern, Ocaliva recipients saw about a 20% increase in harmful LDL cholesterol, which could have implications for cardiovascular disease risk.

These data in hand, Intercept requested approval of the drug for NASH last September. It was the first such submission for a NASH treatment, according to the company.

But the FDA is not yet convinced. In a complete response letter to the company, regulatory officials said that the predicted benefit of Ocaliva based on surrogate endpoints "remains uncertain and does not sufficiently outweigh the potential risks to support accelerated approval" of the drug.

"The FDA recommends that Intercept submit additional post-interim analysis efficacy and safety data from the ongoing REGENERATE study in support of potential accelerated approval and that the long-term outcomes phase of the study should continue," officials wrote.

Yet Intercept remains undaunted.

"At no point during the review did the FDA communicate that Ocaliva was not approvable on an accelerated basis, and we strongly believe that the totality of data submitted to date both meet the requirements of the agency's own guidance and clearly support the positive benefit-risk profile of Ocaliva," Intercept president and CEO Mark Pruzanski, MD, said in a company news release.

In the midst of the COVID-19 crisis, the FDA cancelled an advisory committee meeting schedule for early June to review the Ocaliva data, which is typically part of the approval review process.

"We are disappointed to see the determination the agency has reached based on an apparently incomplete review, and without having provided medical experts and patients the opportunity to be heard at the anticipated [advisory committee meeting] on the merits of Ocaliva," Pruzanski said.

"The FDA has progressively increased the complexity of the histologic endpoints, creating a very high bar that only Ocaliva has so far met in a pivotal Phase III study," he continued. "On behalf of the hepatology community, we are very concerned that the agency's apparently still evolving expectations will make it exceedingly challenging to bring innovative therapies to NASH patients with high unmet medical need. We plan to meet as soon as possible with the FDA to review the

[complete response letter] and discuss options for an efficient path forward to approval."

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