Resmetirom Improves NASH and Liver Fibrosis in Phase III Trial

The findings could potentially lead to the first FDA approval of a treatment for fatty liver disease.

June 23, 2023 By Liz Highleyman

Resmetirom, a leading contender in the race to become the first approved treatment for non-alcoholic steatohepatitis (NASH), reduced liver fat accumulation and improved inflammation and liver fibrosis in a Phase III clinical trial, according to results presented this week at the EASL Congress in Vienna.

Stephen Harrison, MD, of Pinnacle Clinical Research and Oxford University, reported that both tested doses of resmetirom led to NASH resolution and a reduction in fibrosis over 52 weeks in people who underwent liver biopsies. What's more, the drug was safe and generally well tolerated.

"This is the first treatment to achieve meaningful effects on both primary liver biopsy endpoints that are reasonably likely to produce clinical benefit" for people with NASH, Harrison said at an EASL press briefing.

Non-alcoholic fatty liver disease (NAFLD) and NASH, its more severe form, are responsible for a growing burden of advanced liver disease worldwide. Experts estimate that around one third of Americans have fatty liver disease. The buildup of fat in the liver can lead to inflammation, 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.

Fat and glucose metabolism, inflammation and fibrosis are not fully understood, and developing treatments for fatty liver disease has proved challenging. Several treatment approaches aim to target metabolic abnormalities to improve liver fat accumulation and fibrosis. For example, glucagon-like peptide-1 agonists—such as the popular diabetes and weight loss drug semaglutide (Ozempic and Wegovy)—mimic hormones that regulate appetite and glucose metabolism.

But the Food and Drug Administration's dual benchmark of NASH improvement without worsening of fibrosis and fibrosis improvement without worsening of NASH has been difficult to meet. Numerous candidates that showed promise in early studies have not panned out in larger clinical trials.

Resmetirom (formerly MGL-3196), from Madrigal Pharmaceuticals, is a selective thyroid hormone receptor-beta agonist. Thyroid hormones play a role in metabolism, and agents that promote receptor-beta activity can reduce blood lipids and liver fat by breaking down fatty acids.

At the 2021 EASL Congress, Harrison presented initial findings from the MAESTRO-NAFLD1 trial (NCT04197479) showing that resmetirom reduced liver fat and fibrosis according to biomarkers and noninvasive imaging. The MAESTRO-NASH trial (NCT03900429), which enrolled people with more advanced fatty liver disease, aimed to determine whether the benefits held up in a biopsy study. Liver biopsies are considered the gold standard for liver disease research, but repeat biopsies are hard to implement in a real-world clinical setting.

This MAESTRO-NASH analysis included 966 people with biopsy-confirmed NASH, fibrosis and at least three metabolic risk factors. More than half were women, most were white and the average age was 57 years. Many had obesity, type 2 diabetes, high blood pressure and abnormal blood fat levels, and about half were taking statin medications. About 60% had advanced fibrosis.

The participants were randomly assigned to receive once-daily oral resmetirom at a dose of 80 or 100 milligrams or a placebo. After 52 weeks of treatment, they had a liver biopsy. The dual primary endpoints were NASH resolution—no inflammation or "ballooning" of liver cells and at least a two-point improvement in the NAFLD activity score—with no worsening of fibrosis, and at least a one-stage decrease in fibrosis with no worsening of NASH.

As Madrigal announced last December, resmetirom met both primary endpoints. After 52 weeks of treatment, nearly a third of participants (30%) who received the 100 mg dose and 26% of those who received the 80 mg dose experienced NASH resolution without worsening of fibrosis, compared with 10% of placebo recipients. Fibrosis improvement without worsening of NASH was observed in 26%, 24% and 14%, respectively. Half of participants taking the higher resmetirom dose experienced either NASH resolution or fibrosis improvement.

Liver fat content decreased by 51% and 42% in the two resmetirom groups, but by just 10% in the placebo group. Improvements in liver stiffness according to FibroScan imaging, liver enzyme levels and blood lipid levels were also observed. The drug worked well regardless of baseline fibrosis severity (moderate or advanced), the presence of diabetes or whether participants lost weight. Follow-up is continuing to see whether it helps prevent progression to cirrhosis and decompensated liver disease.

Resmetirom was generally safe and well tolerated. Adverse effects, including transient diarrhea and nausea, were generally mild to moderate. Rates of serious adverse events were statistically similar in all three groups (approximately 12%). More people stopped treatment due to adverse events in the high-dose group during the first few weeks of treatment, but discontinuation rates were similar across groups during the remainder of follow-up, Harrison said. There were no cases of drug-induced liver injury.

"The new data being presented at EASL build on the impressive topline efficacy findings for both NASH and fibrosis reported last December, reinforce the safety and tolerability profile of

resmetirom and provide important insights for community clinicians seeking to understand the effects of resmetirom on the noninvasive tests that are used to manage patients in real world clinical practice," Harrison said in a Madrigal press release.

These findings could potentially pave the way for accelerated approval of resmetirom, but the FDA has set a high bar. This week, the agency declined to approve Intercept Pharmaceuticals' obeticholic acid (Ocaliva), as recommended by an advisory committee in May, citing safety concerns related to drug-induced liver injury. Intercept announced that it will abandon its work on NASH.

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