Resmetirom Improved Liver Fat and Fibrosis in Late-Stage NASH Trial

Positive results announced in a Madrigal press release could potentially lead to the first drug approval for fatty liver disease.

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Madrigal's experimental drug resmetirom reduced liver fat accumulation and improved fibrosis in a Phase III clinical trial that compared liver biopsies from patients with non-alcoholic steatohepatitis (NASH) before and after treatment, according to a company press release.

At 52 weeks, nearly 30% of study participants showed NASH resolution with no worsening of fibrosis, and about one quarter showed improvement in fibrosis with no worsening of NASH.

Based on these findings—which have not yet been published or presented at a scientific conference—Madrigal intends to file for Food and Drug Administration (FDA) accelerated approval during the first half of 2023. If granted, resmetirom could be the first therapy for this hard-to-treat condition to hit the market.

"NASH with liver fibrosis puts patients at risk of progressing to liver failure, liver cancer, need for liver transplant and premature mortality," study investigator Stephen Harrison, MD, of Pinnacle Clinical Research and Summit Clinical Research in San Antonio, said in the press release. "With no approved treatment, this disease represents one of the most urgent unmet needs in health care today. These unprecedented results from the MAESTRO-NASH clinical trial signal a major turning point for the field."

NASH and its less severe form, non-alcoholic fatty liver disease (NAFLD), are a growing cause of advanced liver disease in the United States and worldwide. Experts estimate that around one third of Americans have NAFLD. In many cases, liver fat accumulation is associated with obesity and diabetes. The buildup of fat in the liver triggers inflammation, which over time can lead to liver fibrosis (scarring), cirrhosis and liver cancer. With no effective approved medical therapies, management depends on lifestyle changes such as weight loss and exercise.

Developing treatments for NAFLD and NASH has been challenging. Fat and glucose metabolism, inflammation and fibrosis are highly complex, and their interaction is not fully understood. Several drugs that have produced favorable biomarker changes in early studies did not show significant

clinical benefits in larger clinical trials. The FDA's benchmark of NASH improvement without worsening of fibrosis and fibrosis improvement without worsening of NASH has proved difficult to meet.

Resmetirom (formerly known as MGL-3196) is a selective thyroid hormone receptor 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. Selective agonists aim to stimulate the beta-receptor activity without triggering alpha-receptor activity, which can lead to side effects.

At the 2021 EASL International Liver Congress, Harrison presented initial findings from the MAESTRO-NAFLD-1 trial (NCT04197479), showing that resmetirom reduced liver fat and fibrosis according to biomarkers and noninvasive imaging. He presented further results at this year's AASLD Liver Meeting.

The follow-up MAESTRO-NASH trial (NCT03900429) aimed to determine whether these benefits held up in a biopsy study, considered the gold standard of liver disease research.

MAESTRO-NASH enrolled more than 950 patients with biopsy-confirmed NASH and fibrosis. More than half (56%) were women, 89% were white, 21% were Latino and the average age was 56 years. Many had obesity, diabetes, high blood pressure and abnormal blood fat levels. About 60% had advanced fibrosis, and the rest had moderate 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 underwent a second liver biopsy. The dual primary endpoints were NASH resolution (no "ballooning" of liver cells and absent or minimal inflammation) with at least a two-point reduction in the NAFLD Activity Score (NAS) and no worsening of fibrosis or at least a one-point decrease in fibrosis with no worsening of the NAS. Achievement of either endpoint was considered a successful outcome.

Resmetirom met both primary endpoints, Madrigal announced. NASH resolution without worsening fibrosis was seen in 26% of participants who received the 80 mg dose, 30% of those who received the 100 mg dose and 10% of placebo recipients. Fibrosis improvement without worsening NAS was observed in 24%, 26% and 14%, respectively. These results were statistically significant.

Resmetirom also reduced low-density lipoprotein ("bad cholesterol") levels by 12% and 16% in the two resmetirom groups, compared with just 1% in the placebo group. Liver enzyme levels declined and noninvasive imaging tests showed improvement in the resmetirom groups. The drug worked well regardless of fibrosis severity or diabetes.

Resmetirom was generally safe and well tolerated, with similar rates of serious adverse events in all three study groups, according to Madrigal. Study discontinuation rates were 2.8%, 7.7% and 3.7%, respectively, in the 80 mg, 100 mg and placebo groups. Harrison previously reported that side effects were generally mild, including transient diarrhea and nausea, with no notable changes in thyroid function.

The FDA has indicated that these liver biopsy measures would be “reasonably likely to predict clinical benefit,” paving the way for potential accelerated approval of resmetirom, according to Madrigal. Another ongoing trial, MAESTRO-NASH-OUTCOMES (NCT05500222) is looking at how resmetirom affects clinical outcomes in people with early compensated NASH cirrhosis; that trial, if successful, could support full approval.

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