Resmetirom Could Be First Approved MASH Treatment

Resmetirom (brand name Rezdiffra) is the first drug to show both MASH resolution and fibrosis improvement in a late-stage clinical trial.

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UPDATE: On March 14, 2024, the Food and Drug Administration approved resmetirom (brand name Rezdiffra) for people with MASH and moderate to advanced liver fibrosis.

Resmetirom, the leading contender in the race to become the first approved treatment for metabolic dysfunction-associated steatohepatitis (MASH), reduced liver fat buildup and improved liver fibrosis in a Phase III clinical trial. The results, previously presented at last year's EASL Congress, were published this week in The New England Journal of Medicine. The Food and Drug Administration (FDA) will consider resmetirom approval next month.

"MAESTRO-NASH is a landmark study in a disease that has historically been very challenging for drug development," Stephen Harrison, MD, of Pinnacle Clinical Research and Oxford University, said in a news release. The publication "will provide clinicians with valuable information about the medication that may soon become the first approved therapy for patients with [MASH]."

MASH, the new name for non-alcoholic steatohepatitis (NASH), and its earlier stage, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), are responsible for a growing proportion of advanced liver disease worldwide. The new names emphasize the link with obesity, type 2 diabetes and other metabolic abnormalities. Over time, the buildup of fat in the liver can lead to inflammation, fibrosis, cirrhosis and liver cancer.

With no effective approved medical therapies, disease management has relied on lifestyle changes such as weight loss and exercise. Developing treatments for fatty liver disease has proved challenging. The FDA's dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH has been difficult to meet, and several drug candidates that looked promising in early studies did not pan out in larger trials.

MAESTRO-NASH (NCT03900429) is evaluating resmetirom (formerly MGL-3196), a selective thyroid hormone receptor-beta agonist from Madrigal Pharmaceuticals. 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, which showed that resmetirom reduced liver fat and fibrosis in people with MASLD according to biomarkers and noninvasive imaging. MAESTRO-NASH enrolled people with more advanced fatty liver disease and evaluated outcomes using liver biopsies.

This analysis included 966 people with biopsy-confirmed MASH, at least moderate (Stage F1B to Stage 3) fibrosis and metabolic risk factors. More than half were women, most were white, about 20% were Latino (a group with a high rate of fatty liver disease) and the average age was about 57 years. A majority had obesity, diabetes, high blood pressure and abnormal blood fat levels. About 60% had advanced fibrosis. (Another ongoing trial, MAESTRO-NASH-OUTCOMES [NCT05500222] is evaluating resmetirom for people with compensated cirrhosis, or Stage F4 fibrosis.)

Study participants were randomly assigned to receive once-daily oral resmetirom at a dose of 80 or 100 milligrams or a placebo. After 52 weeks, they had a follow-up liver biopsy. The dual primary endpoints were: 1) MASH resolution (no inflammation or "ballooning" of liver cells) with at least a two-point improvement in the NAFLD activity score and no worsening of fibrosis; and 2) at least a one-stage reduction in fibrosis with no worsening of MASH.

Resmetirom met both endpoints. Nearly a third of participants (30%) who received the 100 mg dose and 26% of those who received the 80 mg dose experienced MASH resolution without worsening fibrosis, compared with 10% of placebo recipients. About a quarter of patients in the two resmetirom groups (26% and 24%) experienced fibrosis improvement without worsening MASH, compared with 14% in the placebo group. All these comparisons were statistically significant. About half of people who received the higher resmetirom dose experienced either MASH resolution of fibrosis improvement at 52 weeks.

Participants taking resmetirom also saw improvements in fibrosis biomarkers, liver stiffness (a noninvasive measure of fibrosis), liver enzyme levels and LDL cholesterol levels. The drug worked well regardless of baseline fibrosis severity (moderate or advanced), the presence of diabetes or whether participants lost weight. Follow-up will continue for more than four years to see whether resmetirom helps prevent progression to cirrhosis and other complications of advanced liver disease.

Resmetirom was generally safe and well tolerated. Transient diarrhea and nausea, generally mild to moderate, were more common in the two resmetirom groups versus the placebo group. 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 resmetirom group during the first few weeks of treatment, but discontinuation rates were similar across groups during the remainder of follow-up. There were no cases of drug-induced liver injury.

Resmetirom is the first drug to achieve both the MASH resolution and fibrosis improvement endpoints in a Phase III clinical trial, and these findings could pave the way for accelerated

approval. An FDA decision is expected by March 14 without an advisory committee meeting.

Approval of the first MASH medication would be welcome news, especially after the FDA last year declined to approve another one-time front-runner, obeticholic acid (Ocaliva). That drug led to fibrosis improvement without worsening MASH, but it failed to meet the second endpoint of MASH improvement without worsening fibrosis, and there were safety concerns regarding the drug.

In an editorial accompanying the MAESTRO-NASH report, Kenneth Cusi, MD, of the University of Florida Gainesville, suggested that the long-awaited approval of resmetirom could encourage screening as part of primary care to identify people with MASH and fibrosis who might benefit from the new treatment.

If approved, resmetirom might not remain the sole MASH treatment for long. Weight-loss medications, for example, also show promise for fatty liver disease. Eli Lilly recently announced that tirzepatide (branded as Mounjaro for diabetes and Zepbound for obesity) led to MASH resolution with no worsening of fibrosis in 74% of participants in the Phase II SYNERGY-NASH trial. Other investigational drugs, including efinopegdutide and retatrutide, also look promising for MASLD or MASH.

However, as is the case for weight-loss medications and direct-acting antivirals for hepatitis C, high cost and limited access could be a concern for fatty liver disease treatment as well.

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