

# Resmetirom Appears to Cut Liver Fat and Improve Fibrosis

A companion study will look at liver biopsy results to confirm these findings from noninvasive tests.

June 30, 2021 By [Liz Highleyman](#)

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The experimental drug resmetirom appeared to reduce liver fat and fibrosis based on changes in biomarkers and noninvasive imaging in people with [fatty liver disease](#), according to results from a Phase III study presented last week at the International Liver Congress. But these findings will need to be confirmed in a controlled trial that includes liver biopsies.

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH), are a growing concern worldwide. Now that a vaccine can prevent [hepatitis B](#) and direct-acting antivirals can cure [hepatitis C](#), fatty liver disease accounts for a rising proportion of advanced liver disease. Linked to obesity and diabetes, NAFLD is increasingly recognized as a manifestation of metabolic syndrome. The buildup of fat in the liver triggers inflammation and the production of scar tissue (fibrosis), which over time can lead to cirrhosis, [liver cancer](#) and the need for a liver transplant. With no approved medications, treatment currently relies on lifestyle changes, such as exercise and weight loss.

Developing treatments for NAFLD and NASH [has proved challenging](#). Fat and glucose metabolism, inflammation and fibrosis are complex, and researchers have studied a variety of approaches to target these processes. But several drugs that have produced favorable biomarker changes in early studies did not show significant clinical benefits in larger clinical trials.

“We are clearly in a race against time to develop new drugs and treatment for NAFLD before the epidemic worsens,” Philip Newsome, MD, general secretary of the European Association for the Study of the Liver, said in an [EASL press release](#). “News that resmetirom appears to make inroads against NASH is most welcome—we are hopefully beginning to draw a line in the sand on the treatment of fatty liver disease.”

Resmetirom (formerly known as MGL-3196), from Madrigal Pharmaceuticals, is a selective thyroid hormone receptor-beta agonist. Thyroid hormones play an important role in metabolism, and agents that promote receptor-beta activity can reduce blood lipids and liver fat by breaking down fatty acids. Selective agonists like resmetirom aim to stimulate receptor-beta without triggering receptor-alpha activity, which can lead to side effects.

At last week's virtual conference, Stephen Harrison, MD, of Pinnacle Clinical Research in San Antonio, presented findings from the Phase III MAESTRO-NAFLD-1 trial ([NCT04197479](#)). Three years ago, Harrison [presented promising results](#) from a smaller Phase II trial of resmetirom.

MAESTRO-NAFLD-1 enrolled around 1,200 people with NASH, as determined by noninvasive biomarker and imaging tests, at some 65 sites in the United States. Harrison described this as a "real-life" NASH study that doesn't require liver biopsies to verify eligibility or monitor outcomes.

Participants had to have at least three metabolic risk factors, FibroScan imaging showing at least some fibrosis (5.5 kiloPascals or higher) and substantial liver fat (CAP score of at least 280) and MRI-PDFF (magnetic resonance imaging estimation of proton density fat fraction) showing at least 8% liver fat.

Three quarters of the participants were randomized to receive 80 or 100 milligrams of resmetirom or a placebo for 52 weeks. The rest directly entered an open-label arm in which they all received 100 mg of resmetirom; this group included those found to have compensated cirrhosis.

Harrison presented results for the open-label arm, which included 115 people who completed 52 weeks of treatment and underwent follow-up laboratory tests, FibroScan, magnetic resonance elastography (MRE) and MRI-PDFF imaging. Just over 70% were women, 26% were Latino—a group more prone to fatty liver disease—and the average age was approximately 58 years. The mean body mass index was in the range for obesity, and a majority of participants had metabolic conditions, including type 2 diabetes (41%), hypertension (64%) and abnormal blood lipids (over 70%). At study entry, the average MRI-PDFF fat fraction was 18%.

Resmetirom potently reduced liver fat as determined by both MRI-PDFF and CAP at week 52, Harrison reported. MRI-PDFF fell by an average of 53% overall, with a 63% decline among those who lost at least 5% of their pretreatment body weight.

Looking at fibrosis, FibroScan imaging showed an overall reduction of -2.8 kPa, or 26%. MRE showed a 11.9% reduction. Harrison noted that about half of the participants saw at least a 25% FibroScan reduction or a 15% MRE reduction.

Various fibrosis and inflammation biomarkers showed improvements. This was also the case for biomarkers of cardiovascular risk, including reductions in LDL ("bad") cholesterol, triglycerides and blood pressure. While 21% of participants lost at least 5% of their baseline body weight, 9% gained a similar amount.

Resmetirom was safe and well tolerated; only one person withdrew from the study due to adverse events. Side effects were generally mild, including transient loose stools. There were no notable changes in thyroid function or vital signs.

Noninvasive imaging and biomarker tests can provide only an estimate of liver pathology, but Harrison said the observed improvements could reflect favorable changes that would be apparent

in liver biopsies. A companion Phase III trial, MAESTRO-NASH ([NCT03900429](#)), is currently enrolling NASH patients with moderate to advanced fibrosis. That trial will include pre- and posttreatment biopsies, considered the gold standard for assessing liver disease.

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