Lanifibranor Both Resolves NASH and Reduces Liver Fibrosis

The experimental therapy improved liver inflammation, fibrosis and metabolic parameters in six months.

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The experimental drug lanifibranor led to improvement in several indicators of liver and metabolic health in people with non-alcoholic steatohepatitis (NASH), according to research presented at the AASLD virtual Liver Meeting.

Treatment led to resolution of NASH without worsening of fibrosis and improvement in fibrosis without worsening of NASH, a dual goal that has proved difficult to achieve in clinical trials of therapies for fatty liver disease.

Non-alcoholic fatty liver disease (NAFLD) and NASH, its more severe form, are responsible for a growing burden of advanced liver disease. Associated with obesity and diabetes, NAFLD and NASH are increasingly recognized as manifestations of the metabolic syndrome, a cluster of conditions linked to increased cardiovascular risk. The buildup of fat in the liver triggers cell death and inflammation, which over time can lead to fibrosis, cirrhosis and liver cancer.

Developing treatments for NAFLD and NASH has proved challenging, and management currently relies on lifestyle changes, such as weight loss and exercise. Several drugs that appeared promising in early studies did not show significant benefits in larger clinical trials. Because multiple biological processes play a role in the development of fatty liver disease, many experts think successful treatment will require a combination approach.

Lanifibranor, from Inventiva, is a peroxisome proliferator-activated receptor (PPAR) agonist that regulates the production of proteins involved in fat metabolism, inflammation and blood glucose control. It targets all three known PPAR types—alpha, gamma and delta—and therefore has multiple mechanisms of action.

Sven Francque, MD, PhD, of Antwerp University Hospital in Belgium presented results from the NATIVE study, a Phase IIb trial of lanifibranor for people with biopsy-proven NASH who did not yet have cirrhosis. Inventiva released top-line results from the study in a press release last July.

More than half of the participants were women, most were white and the average age was about

54 years. Three quarters had moderate to advanced (Stage F2 or F3) fibrosis, about 40% had diabetes and the average body weight was within the range for obesity.

At study entry, they had a high steatosis-activity-fibrosis (SAF) score—a new combined outcome measure for NASH—indicating substantial liver fat accumulation, “ballooning” of liver cells, inflammatory activity and scar tissue buildup. More than 70% had a NAFLD activity score of 6 or above, indicating highly active NASH using an older measure used in prior studies.

The 247 participants were randomly assigned to receive lanifibranor at doses of 800 or 1,200 milligrams or a placebo, all taken as a once-daily pill for 24 weeks. They received a second liver biopsy four weeks after completing treatment.

In the study population as a whole, 49% of people in the 1,200 mg lanifibranor group and 41% in the 800 mg group saw at least a two-point decrease in their SAF score with no worsening of fibrosis—the study’s primary endpoint—compared with 27% in the placebo group. The difference between the higher-dose lanifibranor and placebo groups was statistically significant, meaning it was probably not attributable to chance. Response rates were similar in people with moderate to advanced fibrosis.

In a subgroup of 194 people who remained on treatment for the whole study and underwent a second liver biopsy, the response rates were 55%, 51% and 34%, respectively. The substantial response in the placebo group, which has not been seen in previous NASH studies, remains unexplained.

Looking at various other endpoints, people taking the higher dose of lanifibranor were about twice as likely as those in the placebo group to experience NASH resolution with no worsening of fibrosis (45% versus 19%) and to achieve at least a one-stage reduction in fibrosis with no worsening of NASH (42% versus 24%). Nearly a third of people in the higher-dose lanifibranor group and 21% in the lower-dose group experienced both NASH resolution and fibrosis improvement, compared with just 7% in the placebo group.

What’s more, people receiving either dose of lanifibranor saw decreases in liver enzymes (ALT, AST and GGT) and biomarkers of fibrosis, cell death and inflammation. In addition, triglyceride levels fell, harmful LDL cholesterol remained stable and beneficial HDL cholesterol rose. However, lanifibranor recipients gained an average of about 5 pounds, which Francque suggested might reflect a shift from visceral abdominal fat to subcutaneous fat under the skin. Little change in these measures was seen in the placebo group.

Another late-breaking analysis showed that the improvements seen in the study population as a whole, including NASH resolution, fibrosis regression and improved lipid profiles, were similar for people with diabetes. Measures of glucose control, including fasting glucose, HbA1c and insulin levels, improved in both lanifibranor dose groups.

Treatment was generally well tolerated, and the higher dose of lanifibranor did not lead to more side effects than the lower dose. The most common adverse events were diarrhea, fatigue and

nausea. Few participants in any group discontinued treatment due to adverse events. This is promising news, as some other NASH drugs can cause side effects that are difficult to tolerate, including gastrointestinal symptoms and itching.

The researchers concluded that lanifibranor is the first therapy to demonstrate both NASH resolution and improvement in fibrosis.

Inventiva recently announced details of a follow-up Phase III trial of lanifibranor, which aims to enroll 2,000 participants, after meeting with the Food and Drug Administration to discuss the Phase II findings. Like the NATIVE study, the new trial will compare 800 mg and 1,200 mg doses of lanifibranor against a placebo. The primary endpoint will again be a composite measure combining NASH resolution and fibrosis improvement. But the second biopsies will be performed at 18 months, allowing for longer follow-up.

As noted, promising Phase II results for NASH therapies have not always been borne out in larger trials. Another PPAR agonist, elafibranor—which targets the alpha and gamma types but not delta—also produced NASH resolution without worsening of fibrosis in about 20% of participants and reduced liver enzymes and inflammation biomarkers in a Phase II study. However, it failed to meet its primary endpoint in the Phase III RESOLVE-IT trial, and its development for NASH was halted. (It is still being studied as a treatment for primary biliary cholangitis.)

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