Experimental NASH Drug Fails in Late-Stage Study

Selonsertib did not improve liver fibrosis more than a placebo.

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Selonsertib, one of Gilead Sciences' investigational therapies for non-alcoholic steatohepatitis (NASH), failed to outperform a placebo when used as a stand-alone treatment in a Phase III clinical trial, according to a statement from the company.

Selonsertib joins a growing list of drug candidates for fatty liver disease that do not work well alone; however, some may still have potential as components of combination therapy.

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, NASH, are responsible for a growing proportion of advanced liver disease. The buildup of fat in the liver triggers inflammation, which over time can lead to the development of scar tissue (fibrosis), cirrhosis (severe scarring) and liver cancer. With no effective approved therapies, management of the disease currently relies on lifestyle changes, such as weight loss and exercise.

Having conquered the hepatitis C market with its direct-acting antivirals—and seeing a decline in revenue as more people with hep C are cured and other companies have developed competing drugs—Gilead is making a big push into fatty liver disease.

Selonsertib is an inhibitor of apoptosis signal-regulating kinase 1 (ASK1), which promotes inflammation, cell death and fibrosis.

The Phase III STELLAR-3 trial evaluated selonsertib as a stand-alone treatment for people with NASH-related Stage F3 bridging fibrosis, an advanced stage of liver scarring that falls short of cirrhosis. Previously, the STELLAR-4 trial showed that selonsertib did not work better than a placebo in people with NASH-related Stage F4 cirrhosis.

STELLAR-3 included 802 participants who were randomly assigned to receive 6 milligrams or 18 mg of selonsertib or a placebo taken by mouth once daily for up to five years.

The primary endpoints of the study were the proportion of people who saw at least a one-stage improvement in fibrosis without worsening of NASH at 48 weeks. The proportion who experienced NASH resolution without worsening of fibrosis was a secondary endpoint.

After 48 weeks of treatment, 12.1% of people treated with the lower dose of selonsertib and 9.3% of those who received the higher dose had at least a one-stage improvement in fibrosis. These percentages were not significantly different from that of the placebo group, 13.2%, meaning the differences could be attributable to chance.

Selonsertib was generally well tolerated and safety results were consistent with prior studies, according to the Gilead press release. The company indicated that it is now working to conclude the trial "in a manner consistent with the best interests of each patient."

"While we had hoped for different outcomes from the STELLAR program, we remain focused and committed to developing highly effective treatments for patients living with advanced fibrosis due to NASH," said Gilead chief scientific officer John McHutchison, MD. "We believe that effective therapy for NASH will ultimately require a combination approach that targets distinct pathways involved in the pathogenesis of this disease."

The Phase II ATLAS trial is currently evaluating selonsertib in various combinations with two other Gilead drug candidates that act on different pathways involved in NASH: the nonsteroidal farnesoid X receptor agonist cilofexor (GS-9674) and the acetyl-CoA carboxylase inhibitor firsocostat (GS-0976). The farnesoid X receptor regulates bile acid synthesis and plays a role in lipid metabolism, while acetyl-CoA carboxylase is involved in de novo lipogenesis, or conversion of carbohydrates into fatty acids in the liver.

Click here to read Gilead's press release about the study results.

Click here to learn more about NAFLD and NASH.
