Companies Announce More NASH Drug Disappointments

Three fatty liver disease candidates miss the mark for effectiveness or safety.

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Two experimental medications evaluated for non-alcoholic steatohepatitis (NASH) did not improve liver fibrosis as intended, while another was discontinued because of its potential for drug interactions, according to recent company announcements.

The failure of these three candidates, along with disappointing results presented last month at The Liver Meeting, underscore the difficulty of treating this complex but increasingly common metabolic condition.

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

Gilead Sciences this month announced topline results from its Phase II ATLAS trial, which compared three of the company's NASH candidates in various combinations.

Firsocostat is an acetyl-CoA carboxylase inhibitor that blocks an enzyme that helps convert carbohydrates to fatty acids in the liver. Cilofexor is an agonist, or activator, of farnesoid X receptor (FXR), which regulates bile acid synthesis and plays a role in lipid metabolism. Selonsertib inhibits apoptosis signal-regulating kinase 1 (ASK1), which promotes inflammation, liver cell injury and fibrosis.

ATLAS included 392 patients with advanced bridging fibrosis or cirrhosis (stage F3 or F4) due to NASH. They were randomly assigned to receive firsocostat alone, cilofexor alone, firsocostat plus selonsertib, cilofexor plus selonsertib or firsocostat plus cilofexor.

Earlier this year, Gilead announced that in two Phase III trials, selonsertib alone was not significantly more likely than a placebo to improve fibrosis by at least one stage without worsening NASH, as determined by liver biopsies. Up to 12.1% of STELLAR-3 participants and up to 14.4% of STELLAR-4 participants treated with selonsertib monotherapy achieved this primary endpoint,

compared with about 13% of placebo recipients.

According to the new results, firsocostat or cilofexor alone did not perform better. At 48 weeks, 12.1% of those who received firsocostat monotherapy and 11.8% of those who used cilofexor monotherapy achieved this endpoint.

Participants who received combination therapy fared somewhat better: 15.5% of those taking firsocostat plus selonsertib, 19.1% of those taking cilofexor plus selonsertib and 20.9% of those taking firsocostat plus cilofexor achieved the endpoint. But these figures did not differ significantly from that of the placebo group (10.5%), meaning the results could have been driven by chance. NASH resolution without worsening of fibrosis was uncommon in all treatment groups.

Participants treated with firsocostat plus cilofexor did see significant improvements in various biopsy-based secondary endpoints, including at least a two-point reduction in NAFLD activity score and at least a one-point reduction in steatosis (liver fat accumulation), liver cell ballooning and inflammation. They also saw significant improvements in liver enzyme levels and noninvasive measures of fibrosis compared with placebo recipients.

All three drugs alone or in combination were generally safe and well tolerated. The most common adverse events in people treated with firsocostat plus cilofexor were itching (pruritus), headache, diarrhea and nausea. About twice as many participants in this group compared with the placebo group experienced itching (28.2% versus 15.4%), but this was usually mild to moderate and led to no treatment discontinuations. About 4% experienced severe (Grade 3) but asymptomatic triglyceride elevations.

Given the many different biological processes that play a role in the development of fatty liver disease, optimal treatment may involve combining multiple drugs that work by different mechanisms.

“This trial provides novel data showing consistent improvements in liver histology and noninvasive tests, demonstrating the value of a combination approach to deliver meaningful changes in fibrosis, the key determinant of disease severity in NASH,” Rohit Loomba, MD, of University of California at San Diego, said in a Gilead press release.

In related news, Boehringer Ingelheim and Pharmaxis announced this month that they have abandoned development of their experimental therapy BI 1467335 for NASH because of potential interactions with other drugs.

BI 1467335 is a SSAO/VAP-1 inhibitor that interferes with leukocyte (white blood cell) tissue infiltration, a key step in inflammation. This approach differs from most other NASH candidates, many of which target glucose or fat metabolism.

In a 12-week Phase IIa study of 114 participants with NASH, BI 1467335 appeared to work as intended, led to favorable changes in NASH biomarkers and was generally well tolerated with no drug-related serious adverse events.

However, the companies said they would discontinue the development of BI 1467335 for this indication due to the risk of drug interactions in NASH patients. The compound is still being studied for diabetic retinopathy.

Click here to see the Gilead press release about the ATLAS results.

Click here to see the Boehringer Ingelheim press release about BI 1467335.

Click here to learn more about NAFLD and NASH.
