Elafibranor Wins Accelerated Approval for Primary Biliary Cholangitis

A second PPAR agonist, seladelpar, has also done well in clinical trials and is under FDA review.

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On June 10, the Food and Drug Administration (FDA) granted accelerated approval of elafibranor (brand name Iqirvo), a new type of treatment for primary biliary cholangitis (PBC), a rare autoimmune disease affecting the bile ducts and liver.

The approval comes just days after researchers presented promising results for elafibranor at the European Association of the Study of the Liver's EASL Congress 2024. Other presentations touted good results for another PBC drug candidate, seladelpar, which is scheduled for an FDA decision in August.

Primary biliary cholangitis is characterized by chronic inflammation and progressive destruction of the bile ducts, which carry bile from the liver and gallbladder to the small intestine to aid digestion. Early symptoms may include fatigue and pruritus (itching). If left untreated, PBC can lead to liver fibrosis, cirrhosis, liver cancer and the need for a liver transplant.

Two medications were previously approved to treat PBC, ursodeoxycholic acid (Actigall) and obeticholic acid (Ocaliva). These do not cure the disease, but they may improve liver function and slow fibrosis progression. Ursodeoxycholic acid often does not relieve itching, however, and obeticholic acid can make it worse.

Elafibranor (developed by Genfit and marketed by Ipsen) and seladelpar (developed by CymaBay Therapeutics, which was recently acquired by Gilead Sciences) are PPAR agonists that activate proteins that play a role in bile acid synthesis and transport, fat metabolism, glucose regulation and inflammation. Both therapies have also been evaluated for metabolic dysfunction-associated steatohepatitis (MASH), but they did not meet the FDA's dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH. Last year, the FDA denied approval of Ocaliva for fatty liver disease.

Elafibranor

This week's accelerated approval is for elafibranor in combination with ursodeoxycholic acid for adults with PBC who have an inadequate response to ursodeoxycholic acid alone, or as

monotherapy for people who can't tolerate ursodeoxycholic acid. Drugs that receive accelerated approval based on surrogate endpoints are expected to undergo further testing to confirm that they offer clinical benefits, and the FDA can rescind the approval if they fail to measure up.

The approval was supported by results from the Phase III ELATIVE trial (NCT04526665), which tested elafibranor for PBC patients with inadequate response or unacceptable side effects on ursodeoxycholic acid. The study included 161 participants with elevated alkaline phosphatase (ALP) and bilirubin levels, which are biomarkers of cholestasis, or bile blockage. They were randomly assigned to receive oral elafibranor (80 milligrams) or a placebo once daily for at least a year.

Researchers reported results from the primary analysis at last year's AASLD Liver Meeting and in The New England Journal of Medicine showing that elafibranor led to rapid and sustained improvement in ALP and bilirubin levels. At 52 weeks, 51% of patients who received elafibranor had a biochemical response, compared with just 4% of placebo recipients; 15% and zero, respectively, experienced ALP normalization. Elafibranor recipients were more likely to experience gastrointestinal side effects. Among participants with moderate to severe pruritus, scores on the Worst Itch Numeric Rating Scale improved somewhat more in the elafibranor group, but the difference did not reach statistical significance.

Two late-breaking posters at the EASL Congress described follow-up results from the trial. After the primary analysis, study participants continued on their assigned regimen until everyone reached the 52-week mark or for a maximum of 104 weeks, whichever came first. About a quarter of the participants reached the 78-week mark.

Christopher Bowlus, MD, of the University of California Davis School of Medicine, and colleagues reported that 70% of patients assigned to elafibranor, but none of those who received the placebo, achieved a biochemical response at 78 weeks, meaning a substantial reduction in ALP and a normal bilirubin level. The average reduction in ALP was four times greater in the elafibranor group, and some people who had not achieved ALP normalization by week 52 did so by week 78.

Using two other measures of itching, Andreas Kremer, MD, PhD, of University Hospital Zurich, and colleagues reported that elafibranor may have a beneficial effect on itch-related quality of life, including sleep disturbances and emotional impact. Among the 66 patients with moderate to severe pruritus at baseline, elafibranor led to greater reductions in the 5-D itch score (degree, duration, dimension, disability and distribution) and the itch domain of the PBC-40 quality-of-life questionnaire. For instance, 58% of elafibranor recipients reported reduced duration of itching compared with 27% of placebo recipients.

"When you have a patient with PBC, it's vital to manage disease progression, to prevent or delay liver damage or failure. You also want to provide relief from distressing symptoms because they can have a very detrimental impact on quality of life," Bowlus said in an Ipsen news release. "These new data from ELATIVE provide further evidence that elafibranor has the potential to address the two priority treatment goals by demonstrating longer-term improvements in the

prognostic markers of disease progression as well as potential improvements in pruritus-symptom severity and impacts on the quality of life."

Seladelpar

In February, researchers published results from the Phase III RESPONSE trial (NCT04620733), which provided pivotal data for the pending FDA review of seladelpar.

The study included 193 people with PBC who had an inadequate response or unacceptable side effects on ursodeoxycholic acid. They were randomly assigned to receive once-daily oral seladelpar (10 mg) or a placebo; more than 90% were also taking ursodeoxycholic acid.

As in the elafibranor trial, the primary endpoint was biochemical response, defined as a substantial decrease in ALP and normal bilirubin after a year of treatment. At 52 weeks, significantly more people in the seladelpar group met this endpoint compared with the placebo group (62% versus 20%). ALP normalization was also more common in the seladelpar group (25% versus zero). Those in the seladelpar group saw about a twofold greater reduction in scores on a pruritus rating scale. A similar proportion in both groups experienced serious adverse events (7% and 6%, respectively).

In another late-breaking poster at the EASL Congress, Palak Trivedi, PhD, MBBS, of the University of Birmingham, and colleagues presented two-year results from the ASSURE trial (NCT03301506), an ongoing open-label study evaluating long-term outcomes among people who participated in earlier trials of seladelpar for PBC, including efficacy, safety, tolerability and impact on quality of life.

As of January 2024, ASSURE had enrolled 158 patients from the RESPONSE trial who either continued on seladelpar or crossed over from the placebo group. The analysis also included 179 participants from other legacy studies, a majority of whom had a gap of at least a year between their prior trial and enrollment in ASSURE. About one in five already had cirrhosis. Participants received once-daily seladelpar for up to three years.

Among prior RESPONSE participants who continued on seladelpar without interruption, 62% saw a reduction in ALP and bilirubin normalization after 18 total months on the drug, and 72% did so after 24 months. Among those who crossed over from the placebo, the biochemical response rates were 75% at six months and 94% at 12 months. Among participants from other legacy studies, 73% had a biochemical response at 12 months, and 70% did so at 24 months; 42% achieved ALT normalization at both time points. Participants in all groups reported a reduction in itching similar to that seen in RESPONSE. The safety profile of seladelpar was favorable with no treatment-related serious adverse events.

"The long-term efficacy and safety interim results from ASSURE demonstrate that seladelpar may meaningfully raise the bar in PBC," Trivedi said in a Gilead news release. Seladelpar can help people achieve significant reduction and, in some cases, normalization of liver blood tests. At the same time, seladelpar can also help lower itch intensity."

Finally, Stuart Gordon, MD, of Henry Ford Health, presented interim results from a subset of ASSURE participants who had compensated liver cirrhosis. Consistent with the overall findings, a majority saw improvements in biochemical markers of cholestasis and liver injury. Even in this sicker group, there were no serious drug-related adverse events.

The approval of elafibranor and the pending review of seladelpar offer hope for the approximately 100,000 people with PBC in the United States who need better treatment options.

“People living with PBC can feel like the symptoms they experience are dismissed by family members, friends or even their doctors, because they have not experienced something similarly disruptive in their lives,” said Carol Roberts, executive president of the patient advocacy group PBCers. “People with PBC may also feel uncertainty around the disease progression and if, or when, their liver health may deteriorate. Earlier diagnosis and education about PBC, along with new treatment options, are important to meet the current needs of people living with PBC.”

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