Emricasan Proves a Disappointment as NASH Treatment

Nevertheless, researchers are hoping to learn more from the study of the pan-caspase inhibitor among people with non-alcoholic steatohepatitis.

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Conatus Pharmaceuticals' oral pan-caspase inhibitor emricasan proved disappointing as a potential treatment for non-alcoholic steatohepatitis (NASH) in a 72-week trial. The treatment did not meet its primary endpoint of an improvement in liver fibrosis (scarring) of at least one stage without any worsening of NASH.

Stephen A. Harrison, MD, of Pinnacle Clinical Research in San Antonio, presented findings from the trial at The Liver Meeting, the Annual Meeting of the American Association for the Study of Liver Diseases, this week in Boston.

The randomized, placebo-controlled, double-blind study enrolled people at 87 sites in the United States, Spain and Germany. The participants had to have NASH, a non-alcoholic fatty liver disease activity score (NAS) of 4 or greater and a fibrosis stage of F1, F2 or F3. No more than 20% of the study population could have fibrosis Stage 1, and if they did, they also had to have diabetes or metabolic syndrome. If participants were taking vitamin E or pioglitazone, they had to be on a stable dose for at least three months.

The participants were randomized evenly into three groups to receive 5 milligrams or 50 mg of emricasan or a placebo twice daily for 72 weeks. They received liver biopsies at the start of the study and at the 72-week mark.

A total of 318 people were randomized, with 107 in the 5 mg group, 106 in the 50 mg group and 105 in the placebo group. A respective 95, 97 and 94 people in each group completed the study; and a respective 94, 96 and 92 provided evaluable biopsies.

The characteristics of the members of the three groups were generally balanced. Overall, the average age was 54 years old and the average body mass index (BMI) was 34.6 (a BMI of 30 or greater is obese). Fifty-six percent of the participants were female, 94% were white, 51% had type 2 diabetes and 60% had metabolic syndrome.

Twenty-one percent of the participants had Stage 1 of fibrosis while 42% had Stage 2 and 37%

had Stage 3. The average NAS score was 5.5, the average ALT liver enzyme was 64 and the average AST liver enzyme was 59.

The proportion of each group that reached the primary endpoint of at least one stage of fibrosis improvement and no worsening of NASH was 11.2% in the 5 mg group, 12.3% in the 50 mg group and 19.0% in the placebo group.

As for the key secondary endpoint of NASH resolution without worsening of fibrosis, this was achieved by 3.7% of the 5 mg group, 6.6% of the 50 mg group and 10.5% of the placebo group.

In other words, the study met neither its primary nor its secondary endpoints.

Fewer people in the placebo group experienced worsening of fibrosis. The proportion of each study arm that saw their fibrosis improve, remain stable and worsen after 72 weeks of treatment was a respective 41.1%, 45.3% and 13.7% in the 5 mg group, a respective 38.1%, 48.5% and 13.4% in the 50 mg group and a respective 20.4%, 58.1% and 21.5% in the placebo group.

Those who received the placebo experienced a better response than those who received emricasan when it came to liver inflammation and ballooning of liver cells. That said, steatosis improvement was more frequent among those who received emricasan.

The study saw a dose-dependent—meaning the effect was greater with a higher dose of emricasan—decrease in ALT and caspase 3/7 liver enzymes. This indicated that the drug was still hitting its desired target in the liver, even if it did not succeed in this trial.

Rates of adverse health events during the study were similar across the three groups, with 90.1% of those who received emricasan and 86.7% of those in the placebo group experiencing an adverse event. A respective 11.3% and 6.7% of the participants experienced serious adverse health events.

The most common side effects among all participants were diarrhea, upper respiratory infection, nausea, sinusitis, back pain, fatigue, upper abdominal pain, general abdominal pain, painful joints, diabetes, headache, the common cold, urinary tract infection, vomiting and acid reflux disease.

The study authors concluded that emricasan was well tolerated. They hope that further evaluation of the mechanisms underlying the drug’s effects in this trial will yield valuable insights into the death of liver cells that drives NASH.

To read the study abstract, click here.

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