Tropifexor Shows Promise as Treatment for NASH

Initial 12-week results of a 48-week treatment period showed the drug led to a significant decline in weight and liver enzymes.

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Tropifexor, a highly potent FXR agonist, led to a significant decline in weight and liver enzyme levels 12 weeks into a 48-week study among people with non-alcoholic steatohepatitis (NASH).

Arun Sanyal, MD, of Virginia Commonwealth University School of Medicine in Richmond, presented interim findings from the ongoing, randomized, double-blind, placebo-controlled Phase II FLIGHT-FXR study of tropifexor at The Liver Meeting, the Annual Meeting of the American Association for the Study of Liver Diseases, this month in Boston.

The previously reported interim results from parts A and B of the study, in which participants received between 10 and 90 micrograms of tropifexor daily, showed evidence that the drug affected the intended targets and reduced both inflammation and the level of fat in the liver without causing major changes in blood lipids.

In Boston, Sanyal presented findings from part C of the study, in which participants received higher doses of tropifexor.

The participants in part C needed to have a minimum hepatic fat fraction, or the fat content in the liver, of 10%; an ALT liver enzyme level of at least 43 international units per liter among men and 28 IU/l among women; and biopsy-confirmed presence of NASH with moderate to severe liver fibrosis (scarring) and no other chronic liver disease.

The study excluded those who had received a liver transplant or had uncontrolled diabetes, cirrhosis, severe liver impairment, any history of major alcohol consumption and previous exposure to FXR agonists, including tropifexor. Women who were pregnant or nursing were also excluded.

A total of 152 participants in part C were randomized evenly into three groups to receive a placebo (51 people), 140 micrograms of tropifexor (50 people) or 200 micrograms of tropifexor. They are scheduled to receive daily treatment for 48 weeks and then to receive a liver biopsy followed by an additional four weeks of follow-up.

The characteristics of the three treatment groups were generally similar. The average age was between 54 and 56 years old; 40% to 43% were younger than 65 years old. Fifty-seven percent to 72% were women, and 74% to 75% were white. The average body mass index was 34 to 35 (30 or greater is obese). Seventy-eight percent to 84% had diabetes. The average ALT enzyme level was 62 to 75 units per liter. Forty percent to 43% had moderate liver fibrosis, and 57% to 60% had severe fibrosis. The average hepatic fat fraction was 6.3% to 7.8%.

The interim analysis presented at the liver conference was conducted at the study's 12-week mark. By that time, one person, based upon a physician's decision, discontinued treatment in the placebo group, leaving a group of 50; three people discontinued in the 140 microgram group, including two because of adverse health events and one because of a personal or guardian's decision, leaving a group of 47; and five people from the 200 microgram group discontinued treatment, including four because of adverse health events and one because of a personal or guardian's decision, leaving a group of 46.

After 12 weeks of treatment, tropifexor had caused a rapid and sustained decline in ALT enzymes. In the placebo, 140 microgram and 200 microgram groups, the average decline in ALT was 8.9, 20.1 and 23.6 IU/l, with no statistically significant difference between the two treatment groups, meaning the difference may have been driven by chance. The difference between higher-dose group and the placebo group, however, was statistically significant.

The change in gamma-glutamyl transferase liver enzymes was also significant between the placebo and treatment groups. The average decline in units per liter was 2.5 in the placebo group, 39.2 in the 140 microgram group and 40.9 in the 200 microgram group.

The decline in hepatic fat fraction was 10% in the placebo group, 17% in the 140 microgram group and 31% in the 200 microgram tropifexor group. The difference between the placebo and treatment groups was significant.

A significant difference was seen in weight loss between the placebo and tropifexor groups. The average weight decline was 2.4 pounds in the placebo group, 5.5 pounds in the 140 microgram group and 7.1 pounds in the 200 microgram group.

C4 levels, a measure of a group of proteins in the blood that aid the immune system, remained steady in the placebo group and declined by just under 80% in each of the treatment groups.

In the placebo, 140 microgram and 200 microgram groups, a respective 71%, 88% and 86% experienced at least one adverse health event; 2%, 0% and 2% experienced at least one serious adverse health event; and 2%, 4% and 10% had any adverse health event that led to discontinuation of treatment.

Itching, a concern with this type of treatment, was reported by 12%, 34% and 39% of the placebo, 140 microgram and 2000 microgram groups, respectively. Of those who experienced itching, all of those in the placebo group and a respective 64% and 63% of those in the 140 microgram and 200 microgram groups experienced mild (Grade 1) itching. In the two treatment groups, a respective

32% and 30% experienced moderate (Grade 2) itching and a respective 4.5% and 7.4% experienced severe (Grade 3) itching.

There were no deaths in the study, and there was no evidence of liver injury among those who received tropifexor.

Further findings from the study and from ongoing and planned studies of tropifexor in combination with other treatments will, according to the study authors, “define the role of tropifexor in the treatment of fibrotic NASH.”

To read the conference abstract, click here.

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http://beta.docker.hepmag.com/article/tropifexor-shows-promise-treatment-nash