IONIS™ InBrief
17 June 2020

Lancet Gastroenterology and Hepatology: innovative antisense therapy shows potential to be safe and efficacious for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH)

Findings of first-in-class trial of IONIS-DGAT2$_{Rx}$ validate DGAT2 as a novel, potential therapeutic target for NAFLD and NASH

IONIS-DGAT2$_{Rx}$ is an antisense oligonucleotide inhibitor of diacylglycerol acyltransferase 2, or DGAT2, that is under clinical investigation for the treatment of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). The study results published in Lancet Gastroenterology and Hepatology examined the safety, tolerability, and efficacy of IONIS-DGAT2$_{Rx}$ in reducing liver fat in patients with type 2 diabetes and NAFLD. This Phase 2 study represents a first-in-class trial in this patient population.

NAFLD is the leading cause of chronic liver disease worldwide. NASH is a more progressive form and is considered a "silent" liver disease. Some patients are unaware of their symptoms during the early stages of disease until a buildup of excessive fat in the liver (steatosis) causes inflammation and cellular damage. Patients with NASH are also at a higher risk for both liver cirrhosis and liver cancer. As an enzyme that catalyzes the final step in liver triglyceride synthesis, reducing the production of DGAT2 is believed to reduce overall liver fat thereby preventing subsequent inflammation and cell damage.

NAFLD is prevalent in 25 percent of adults globally and NASH is present in 59 percent of patients biopsied to identify NAFLD, signifying an unmet need for these patient populations. Currently, a liver transplant is the only therapeutic option for patients with liver cirrhosis and advanced stages of this disease.

KEY TAKEAWAYS

The findings from this study suggest that DGAT2 antisense inhibition could be a safe and effective strategy for treatment of the broader population of patients with NAFLD and support further investigation in patients with biopsy-proven NASH.

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The data from 44 patients enrolled in the Phase 2 study show that treatment with IONIS-DGAT2$_{Rx}$ led to significant reduction in absolute liver fat content compared with placebo without adversely affecting liver function, plasma lipid profiles, or glycemic control. The mean absolute reduction of liver fat from baseline was –5.2 percent with the study drug (n=25) compared to –0.6 percent with the placebo (n=12). Further, the mean relative change from baseline in liver fat content was also significantly greater in the treatment group (–25.5 percent) compared to the placebo group (–2.4 percent). Nearly 50 percent of patients treated with IONIS-DGAT2$_{Rx}$ had a relative reduction in liver fat content of 30 percent or greater, which has been associated with improvement in histological features associated with NASH. Overall, IONIS-DGAT2$_{Rx}$ was well tolerated in the Phase 2 study. There were no drug-related serious adverse events in the study.

The double-blind, randomized, placebo-controlled, Phase 2 study was conducted at 16 clinical research sites in Canada, Poland and Hungary. All patients participated in a 2-week screening period, a run-in period of up to 4 weeks, a 13-week treatment period of once-weekly dosing, and a 13-week post-treatment follow-up period. Enrolled patients received a once weekly subcutaneous injection of 250 mg of study drug or placebo during the treatment period. The primary endpoints were the safety, tolerability, and pharmacodynamic effect of IONIS-DGAT2$_{Rx}$ on hepatic steatosis. There were also several secondary and exploratory endpoints detailed in the publication. The results demonstrate the safety and efficacy of IONIS-DGAT2$_{Rx}$ in improving hepatic steatosis after 13 weeks of treatment.

Investigators noted that longer-term studies may reveal additional beneficial effects on key markers of glycemic control in patients with type 2 diabetes. They also described confines of the current study, including a small sample size, short duration, and the study population.

NEXT STEPS

*Given the robust expression of the DGAT2 enzyme in liver hepatocytes and the clinical success of Ionis' proprietary **LI**gand **C**onjugated **A**ntisense (LICA) technology, investigators are currently developing, ION224, a N-acetylgalactosamine (GalNAc)-conjugated form of IONIS-DGAT2$_{Rx}$. Ionis' LICA technology increases potency up to 30-fold compared with unconjugated antisense oligonucleotides in humans, allowing for less frequent and substantially lower doses. ION224 is currently in a Phase 1 study with plans to initiate a Phase 2 study in first half of 2021.*

Read the University of California San Diego Health's release on the study here.