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An international, randomized, placebo-controlled phase 2 trial demonstrates novel effects of DGAT2 antisense inhibition in reducing steatosis without causing hypertriglyceridemia in T2DM patients

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An international, randomized, placebo-controlled phase 2 trial demonstrates novel effects of DGAT2 antisense inhibition in reducing steatosis without causing hypertriglyceridemia in T2DM patients
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Background and aims: DGAT2 catalyzes the terminal step in the synthesis of triacylglycerols from de novo synthesized fatty acids and newly formed diglycerides. We previously reported that specific inhibition of DGAT2 caused a marked improvement in hepatic steatosis (Hepatology 2005; 42: 362-371). In this clinical trial we examined the efficacy of a novel antisense inhibitor of DGAT2, IONIS-DGAT2$_{RX}$ versus placebo in T2DM patients with MRI-PDFF ≥ 10% in a double-blind placebo-controlled design.
Method: This international trial included 44 patients with NAFLD and T2DM, HbA1c, 8.1% BMI, 34.3 kg/m^2 and mean baseline MRI-PDFF of 18.8% who were randomized 2 :1 (Active: PBO) to either a once weekly subcutaneous injection of IONIS-DGAT2$_{RX}$ 250 mg or PBO (0.9% saline solution) for 13 weeks. MRI-PDFF was conducted prior to initiation of dosing and 2 weeks after the last dose. Primary end point was absolute reduction in liver fat content by MRI-PDFF.
Results: Treatment with IONIS-DGAT2$_{RX}$ resulted in a significant absolute reduction in liver fat of -5.37% (± 5.4) compared to -0.04% (± 5.8) in patients treated with placebo (p = 0.003). The relative percent reduction from baseline was also significantly higher -26.4% in ISIS-DGAT2$_{RX}$ treated patients compared to 1.0% in placebo treated patients (p = 0.003). Importantly, 50% (13/26) of the treated patients had at least a 30% relative reduction in liver fat (p = 0.02), Table 1; 30% or higher fat reduction has been associated with histologic improvement in NASH in longer term studies. IONIS-DGAT2$_{RX}$ was well tolerated. There were no treatment related deaths or serious adverse events, no changes in hepatic or renal function and no thrombocytopenia. Liver fat reduction was not accompanied by hypertriglyceridemia or GI side effects and no elevations in serum transaminases, plasma glucose or body weight.
Conclusion: These data suggest that DGAT2 inhibition may be a novel, safe and effective strategy for treatment of NAFLD and associated disorders. These data support further investigation of this agent's efficacy in biopsy-proven NASH.

Table 1.

	Randomized Population (N = 44)	
	Placebo	**ISIS DGAT2$_{RX}$**
	(N = 15)	**(N = 29)**
Number of Patients who had Post-Treatment Liver Fat Percentage Assessment	**15**	**26**
Percent Reduction in Liver Fat Percentage ≥ 20%	**2 (13.3%)**	**15 (57.7%)**
p =		**0.0052**
Percent Reduction in Liver Fat Percentage ≥ 30%	**2 (13.3%)**	**13 (50.0%)**
p =		**0.0188**
Percent Reduction in Liver Fat Percentage ≥ 40%	**1 (6.7%)**	**8 (30.8%)**
p =		**0.0804**