ND-630, a Potent and Liver-Directed Acetyl-CoA Carboxylase Inhibitor, Reduces Hepatic Steatosis and Improves Dyslipidemia in Diet-Induced Obese and Diabetic Rat Models of Non-Alcoholic Fatty Liver Disease

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ABSTRACT

Simultaneous inhibition of the acetyl-CoA carboxylase isozymes, ACC1 and ACC2, results in concomitant inhibition of fatty acid synthesis (FASyn) and stimulation of fatty acid oxidation (FAOxn) and may favorably affect fatty liver diseases such as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Using state-of-the-art structure-based drug design technologies and crystal structures of human ACC biotin carboxylase (BC) domain, we identified a unique series of allosteric inhibitors that binds to the BC domain of the enzyme to prevent dimerization and inhibit enzymatic activity, distributes preferentially to the liver (the pharmacologic target organ), and exhibits functional activity in cultured cells and acute and chronic in vivo efficacy in experimental animals. The representative series analog, ND-630, inhibited human ACC1 & ACC2 (IC_{50} 2.0–7.0 nM), inhibited HepG2 cell FASyn (EC_{50} 0.14 mg/kg), and stimulated rat whole body FAOxn (MED 3 mg/kg, 2-fold). When administered chronically by once-daily oral gavage, ND-630 demonstrated dramatic and dose-dependent reductions in hepatic steatosis in high-fat diet-induced obese (DIO) rats, high-sucrose DIO rats, and Zucker diabetic fatty (ZDF) rats. When evaluated chronically in high-sucrose DIO rats, ND-630 also markedly and dose-dependently reduced plasma triglycerides, free fatty acids, and cholesterol. These observations suggest that ND-630 and related analogs may favorably affect the hepatic steatosis, dyslipidemia, and sequelae of fatty liver diseases such as NAFLD and NASH.

1. Acetyl CoA Carboxylase (ACC): Master Regulator of Fatty Acid Synthesis & Oxidation

2. Nimbus Solves ACC Druggability Challenge by Targeting Allosteric Site in BC Domain

3. ND-630: Hepatotropic ACC Inhibitor for NASH/Metabolic Disease

4. ACC1/2 Allosteric Inhibitor ND-630 Favorably Modulates Key Metabolic Parameters In Vivo

5. Data Summary of ND-630 in High Fat and High Sucrose DIO Rat Studies

6. Weight Neutral Profile; Well Tolerated. Reduction in Weight Gain at High Dose

7. ND-630 Favorably Modulates Key Metabolic Parameters In Vivo

8. Liver Triglycerides Lowered Across 14-Day DIO and ZDF Studies

CONCLUSIONS

• ND-630 is a potent ACC1/2 inhibitor with good drug-like properties
• It is well tolerated and effective in three models of hepatic steatosis and dyslipidemia
• ND-630 was also effective at modulating several parameters of metabolic syndrome
• ND-630, designed to have hepatoselective bio-distribution, was shown to reduce hepatic steatosis and improve dyslipidemia in DIO and ZDF diabetic rat models of non-alcoholic fatty liver disease