NDI-010976, A Potent, Liver-Directed, Oral Inhibitor of Acetyl CoA Carboxylase for Non-Alcoholic Steatohepatitis: Pharmacodynamic Effects on Hepatic De Novo Lipogenesis in Obese but Otherwise Healthy Adult Male Volunteers

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Background and Aims:
NDI-010976 is a small molecule allosteric inhibitor that acts at the protein-protein homodimer interface of acetyl-CoA carboxylases (ACC) ACC1 and ACC2 to prevent dimerization. Nonclinical pharmacodynamic and efficacy studies indicate that NDI-010976 favorably affects dyslipidemia and hepatic de novo lipogenesis, steatosis, inflammation, and subsequent fibrosis in models of fatty liver disease. NDI-010976 is being developed for the treatment of metabolic disorders characterized by dysregulated fatty acid metabolism, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Methods:
This study was a randomized, double-blind, placebo-controlled trial evaluating the pharmacodynamic effects of a single oral dose of NDI-010976 on hepatic de novo lipogenesis (DNL) in obese, but otherwise healthy, adult male subjects. Three cohorts of 10 subjects were evaluated. In each cohort, subjects were randomized in Period 1 to receive either NDI-010976 or matching placebo followed by a washout and administration of the opposite study medication in Period 2. Fractional DNL was determined using a stable isotope tracer technique (^{13}C-acetate) and hepatic lipogenesis was stimulated with oral fructose administration.

Results:
NDI-010976 was well tolerated. Overnight infusion of ^{13}C-acetate led to incorporation of the ^{13}C label into the hepatic pool of acetyl CoA. Periodic oral fructose administration over a 10 hr period stimulated hepatic DNL an average of 31±7% over baseline in placebo treated subjects. Assessment of the available data demonstrated that all subjects administered NDI-010976 at doses of 20, 50, and 200 mg had substantial inhibition of de novo lipogenesis (mean inhibition 71%, 87%, and 98%, respectively). Following a single dose of 50 mg NDI-010976, all subjects had greater than 70% inhibition of DNL as determined by baseline normalized AUC over the 10 hr period as compared to the matched placebo period. Moreover, all subjects administered 200 mg NDI-010976 had complete, or near complete, inhibition of DNL.

Conclusions:
This clinical pharmacodynamic study demonstrates that ACC target engagement by NDI-010976 resulted in substantial dose-dependent inhibition of fractional de novo lipogenesis in the liver of adult male subjects who are overweight and/or obese, but otherwise healthy. Therefore, NDI-010976 has the potential to contribute considerable value to the treatment algorithm of NASH.