Background and Aims

Non-Alcoholic Steatohepatitis (NASH) is characterized by high unmet medical need and the lack of approved therapies. Due to its unique position in intermediary metabolism, pharmacologic inhibition of acetyl-CoA carboxylase (ACC) presents an attractive approach to limiting fatty acid synthesis in lipogenic tissues while simultaneously starving fatty acid oxidation in oxidative tissues. The results of non-clinical pharmacodynamic and efficacy studies indicate that NDI-010976 inhibits multiple pathogenic mechanisms of NASH including hepatic steatosis, inflammation, and fibrosis.

Methods

This study was a first-in-human randomized, double-blinded, placebo-controlled, single ascending dose study conducted at a single center in the United States. Six cohorts of 8 subjects (6 active and 2 placebo) received a single oral dose of NDI-010976 (range 30-1000 mg) or placebo under fasting conditions, with 1 cohort spanning over to receive a single oral dose of NDI-010976 or placebo under fed conditions.

Results

Single oral doses of NDI-010976 in the fasted and fed state were safe and well tolerated across the dose range studied when administered to healthy adult subjects. There were no deaths, SAEs, or subject discontinuations due to adverse events. There were no clinically important changes in laboratory or vital sign-related trends or dose-related trends in the treatment-emergent adverse events, clinical laboratory, vital sign, ECG, or physical examination assessments. Plasma NDI-010976 exposure generally increased proportionally with dose in the 30-500 mg range. Maximal plasma exposure of NDI-010976 (C₀) following a 200 mg dose was approximately 68% lower under fed compared to fasting conditions. However, overall plasma exposure (AUC) of NDI-010976 was highly nonlinear Increase in NDI-010976 at Highest Doses (Cohort 2) (N=6)a Nonlinear Increase in NDI-010976 at Highest Doses (Cohort 4) (N=6)a Nonlinear Increase in NDI-010976 at Lowest Doses (Cohort 1) (N=6)a. NDI-010976 was rapidly absorbed following an oral dose, with median t₁/₂ values of 1.3 to 1.5 hrs across dose levels. NDI-010976 was eliminated in a multi-phasic manner, with mean t₁/₂ of 25.2 ± 1.8 hrs at 200-500 mg dose levels. Under fed conditions, there was a delay in the first quantifiable plasma NDI-010976 concentrations and a prolonged absorption/distribution phase compared to fed conditions. Primary metabolite exposure was <10%.

Conclusions

Single oral doses of NDI-010976 were well tolerated up to 1000 mg with generally dose-proportional pharmacokinetics. NDI-010976 has the potential to contribute valuable data to the treatment algorithm of NASH.

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