NDI-010976, A Potent, Liver-Directed, Oral Inhibitor of Acetyl-CoA Carboxylase for Non-Alcoholic Steatohepatitis: A Phase 1 Single Ascending Dose Study in Healthy Volunteers

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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 stimulating fatty acid oxidation in oxidative tissues. The results of nonclinical 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-blind, 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 crossing over to receive a single oral dose of NDI-010976 or placebo under fed conditions.

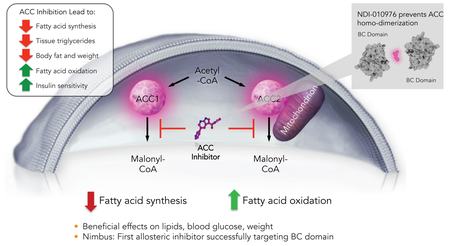
Results

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 treatment-related 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 proportional with dose in the 30-500 mg range. Maximal plasma exposure of NDI-010976 (C_{max}) following a 200 mg dose was approximately 68% lower under fed compared to fasted conditions; however, overall plasma exposure (AUC) of NDI-010976 was highly similar under fed and fasted conditions. NDI-010976 was rapidly absorbed following an oral dose, with median plasma t_{max} values of 1.3 to 2.5 hrs across dose levels. NDI-010976 was eliminated in a multi-phasic manner, with mean $t_{½}$ values ranging from 8.2 to 11.7 hrs at 200-1000 mg dose levels. Under fed conditions, there was a delay in the first quantifiable plasma NDI-010976 concentration and a prolonged absorption/distribution phase compared to fasted conditions. Primary metabolite exposure was <10%.

Conclusions

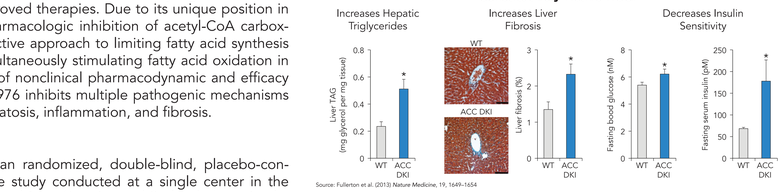
Single oral doses of NDI-010976 were well tolerated up to 1000 mg with generally dose-proportional pharmacokinetics. NDI-010976 has the potential to contribute considerable value to the treatment algorithm of NASH.

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



- Beneficial effects on lipids, blood glucose, weight
- Nimbus: First allosteric inhibitor successfully targeting BC domain

2. Constitutive Activation of ACC Leads to NASH Phenotype in Mice

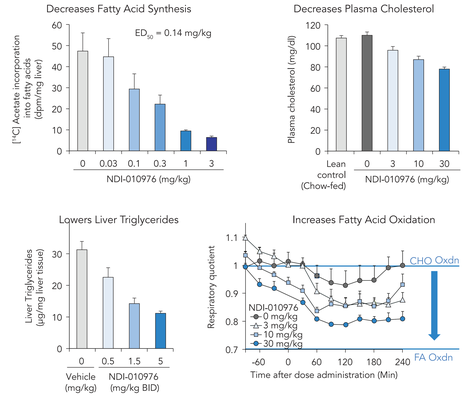


Source: Fullerton et al. (2013) *Nature Medicine*, 19, 1649–1654

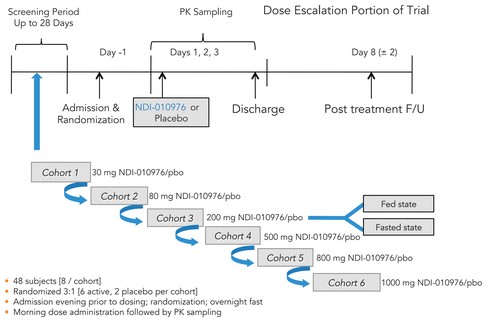
3. Allosteric Approach Enables Outstanding Potency and Exquisite Selectivity of NDI-010976

	Compound	NDI-010976
Cellular Enzyme	ACC1 (IC_{50})	2 nM
	ACC2 (IC_{50})	7 nM
	HepG2 FASyn EC_{50} (serum free)	9 nM
	HepG2 FASyn EC_{50} (10% FBS)	62 nM
In Vivo	Rat and human plasma free fraction	1.4%, 1.5%
	Inhibition of hepatic malonyl CoA (ED_{50})	0.8 mg/kg
	Inhibition of muscle malonyl CoA (ED_{50})	3 mg/kg
	Inhibition of hepatic FASyn (ED_{50})	0.14 mg/kg
	Respiratory exchange ratio lowering (ED_{50})	3 mg/kg

4. NDI-010976 Favorably Modulates Key Metabolic Parameters in Preclinical Models



5. Phase 1a Single Ascending Dose Study



- 48 subjects [8 / cohort]
- Randomized 3:1 [6 active, 2 placebo per cohort]
- Admission evening prior to dosing; randomization; overnight fast
- Morning dose administration followed by PK sampling

6. Key Entry Criteria

Inclusion:

- Healthy adult male or female (non-childbearing potential only), 19-50 years of age
- BMI ≥ 18.5 and ≤ 32.0 (kg/m²) and weight ≥ 50.0 kg at screening

Exclusion:

- History or presence of alcoholism or drug abuse within the past 2 years, confirmed at screening
- Positive results human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV)
- History or presence of malignancy within past 5 years other than localized basal cell skin cancer or cervical cancer that has been successfully treated
- Anticipated use of prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to dosing of study medication and throughout the study

7. Nimbus Clinical Study 0976-101 Demographics

Trait	Category	Statistics N=48	Number of Subjects
Gender	Female	4%	2
	Male	96%	46
Race	Asian	4%	2
	Black or African American	25%	12
	Multiple Races	2%	1
	White	69%	33
Ethnicity	Hispanic or Latino	10%	5
	Non Hispanic or Latino	90%	43
Age		31.9 ± 9.1	48
Weight (kg)		81.4 ± 13.0	48
Height (cm)		178.3 ± 7.6	48
BMI (kg/m²)		25.5 ± 3.1	48

Mean ± SD

8. Nimbus Clinical Study 0976-101 Disposition

	Fasting (n)		Fed (n)	
Disposition	Total NDI-010976	Total Placebo	Total NDI-010976	Total Placebo
Dosed	36	12	6	2
Completed Study	35	12	6	2
Discontinued Early	1	0	0	0
Due to Non-compliance	1	0	0	0
Included in Safety	36	12	6	2
Included in PK	36	0	6	0

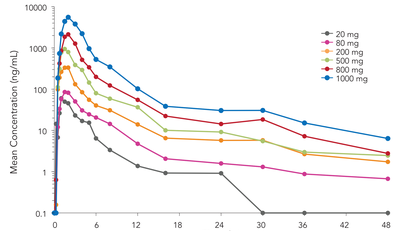
9. Nimbus Clinical Study 0976-101 Plasma PK Parameters

Pharmacokinetic Parameters	NDI-010976 Dose Mean ± SD						
	30 mg (Cohort 1) (N=6)[a]	80 mg (Cohort 2) (N=6)[a]	200 mg Fasting (Cohort 3a) (N=6)[a]	200 mg Fed (Cohort 3b) (N=6)[a]	500 mg (Cohort 4) (N=6)	800 mg (Cohort 5) (N=6)	1000 mg (Cohort 6) (N=6)
AUC_{0-t} (ng*hr/mL)	176.3 ± 104.1	3623.0 ± 215.4	1209.2 ± 536.6	1157.1 ± 613.4	2930.8 ± 2438.5	6423.6 ± 3183.9	17419.1 ± 8403.1
AUC_{0-inf} (ng*hr/mL)	179.0 ± 114.9	401.8 ± 224.9	1254.0 ± 615.8	1255.3 ± 683.1	2963.5 ± 2458.0	6463.7 ± 3185.6	17508.9 ± 8413.4
C_{max} (ng/mL)	79.7 ± 65.9	101.3 ± 47.8	416.3 ± 210.8	133.9 ± 70.1	1112 ± 1148.6	2571 ± 1875.1	8375 ± 3206.6
t_{max} (hr)[b]	1.26 (0.23, 2.00)	2.00 (1.50, 2.00)	1.50 (1.01, 4.00)	2.00 (1.50, 24.0)	1.75 (1.01, 3.00)	2.01 (1.01, 3.00)	2.50 (1.02, 4.01)
$t_{½}$ (hr)	4.47 ± 1.56	6.98 ± 2.81	11.67 ± 1.35	8.70 ± 2.10	10.18 ± 2.13	8.24 ± 3.26	9.46 ± 2.60
V/F (L)	1732.1 ± 1512.4	2362.1 ± 1389.0	3154.8 ± 1267.3	2498.9 ± 1293.8	4186.5 ± 2573.6	1622.6 ± 560.5	903.7 ± 468.9

[a] N=5 for AUC_{0-inf}, $t_{½}$
[b] t_{max} is presented as median (minimum, maximum)

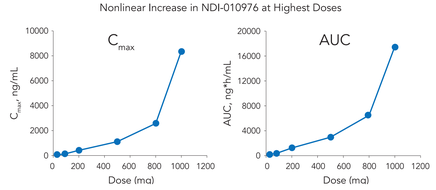
10. Nimbus Clinical Study 0976-101 Ph.1a SAD Study

Fasted Plasma PK Concentration vs Time Curves

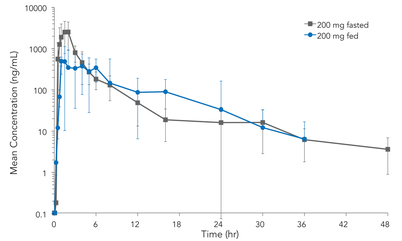


11. Nimbus Clinical Study 0976-101 Ph.1a SAD Study

Human Pharmacokinetics



12. Nimbus Clinical Study 0976-101: Plasma Concentrations after a Single 200 mg Dose under Fasted and Fed Conditions



13. Nimbus Clinical Study 0976-101 Treatment Emergent Adverse Events by Treatment

Number of Subjects Reporting Events (% of Subjects Dosed)

	Fasting								Fed	
Adverse Event*	Placebo	NDI-010976 30 mg	NDI-010976 80 mg	NDI-010976 200 mg	NDI-010976 500 mg	NDI-010976 800 mg	NDI-010976 1000 mg	Combined NDI-010976	Placebo	NDI-010976 200 mg
Dosed	12 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	6 (100%)	36 (100%	2 (100%)	6 (100%)
With TEAEs	3 (25%)	3 (50%)	1 (17%)	1 (17%)	2 (33%)	1 (17%)	2 (33%)	10 (28%)	0 (0%)	2 (33%)
Without TEAEs	9 (75%)	3 (50%)	5 (83%)	5 (83%)	4 (67%)	5 (83%)	4 (67%)	26 (72%)	2 (100%)	4 (67%)
With at Least 1 TE-SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
With at Least 1 Related TEAE	1 (8%)	1 (17%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
With at Least 1 Grade 3 or higher TEAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Eye disorders	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Visual impairment	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders	1 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Abdominal discomfort	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Constipation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Dyspepsia	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Faeces discoloured	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Nausea	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
General disorders and administration site conditions	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	2 (6%)	0 (0%)	0 (0%)
Vessel puncture site pain	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	2 (6%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	1 (17%)
Back pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Limb discomfort	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Nervous system disorders	0 (0%)	1 (17%)	1 (17%)	0 (0%)	1 (17%)	1 (17%)	0 (0%)	4 (11%)	0 (0%)	1 (17%)
Dizziness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (17%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Presyncope	0 (0%)	1 (17%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
Renal and urinary disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Dysuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Micturition urgency	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	1 (8%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	2 (6%)	0 (0%)	0 (0%)
Cough	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)	0 (0%)	0 (0%)
Oropharyngeal pain	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (17%)	3 (8%)	0 (0%)	0 (0%)
Dermatitis contact	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Erythema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)	0 (0%)	0 (0%)
Hyperhidrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)	0 (0%)	0 (0%)

Nimbus Clinical Study 0976-101 Phase 1a SAD: General Conclusions

- Single doses (30 mg–1000 mg) of NDI-010976 were generally well tolerated
- Preliminary PK demonstrated dose-related increase in exposure by C_{max} and AUC
  - *Greater than dose-proportional exposure at 800 and 1000 mg; presumably due to saturation of hepatic uptake transporters*
- Food resulted in reduced C_{max} but similar AUC exposure (extended absorption period)
- There were no deaths, SAEs, or subject discontinuations due to AEs in this study. No clinically important treatment-related or dose-related trends in the TEAEs, clinical laboratories, vital signs, ECGs, or physical examination assessments were observed in this study

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