Clinical Breakthroughs: A plethora of new therapeutic targets
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Phase 1 Study of CAT-2054, a Novel Oral Modulator of Sterol Regulatory Element Binding Protein

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A return to health

Disclosure of Conflicts of Interest

- Joanne M. Donovan, MD PhD
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- Maria Mancini, MHP
  - Senior Director, Clinical Operations
- Michael Jirousek, PhD
  - Chief Scientific Officer

- All are employees of and hold stock in Catabasis Pharmaceuticals, Inc.

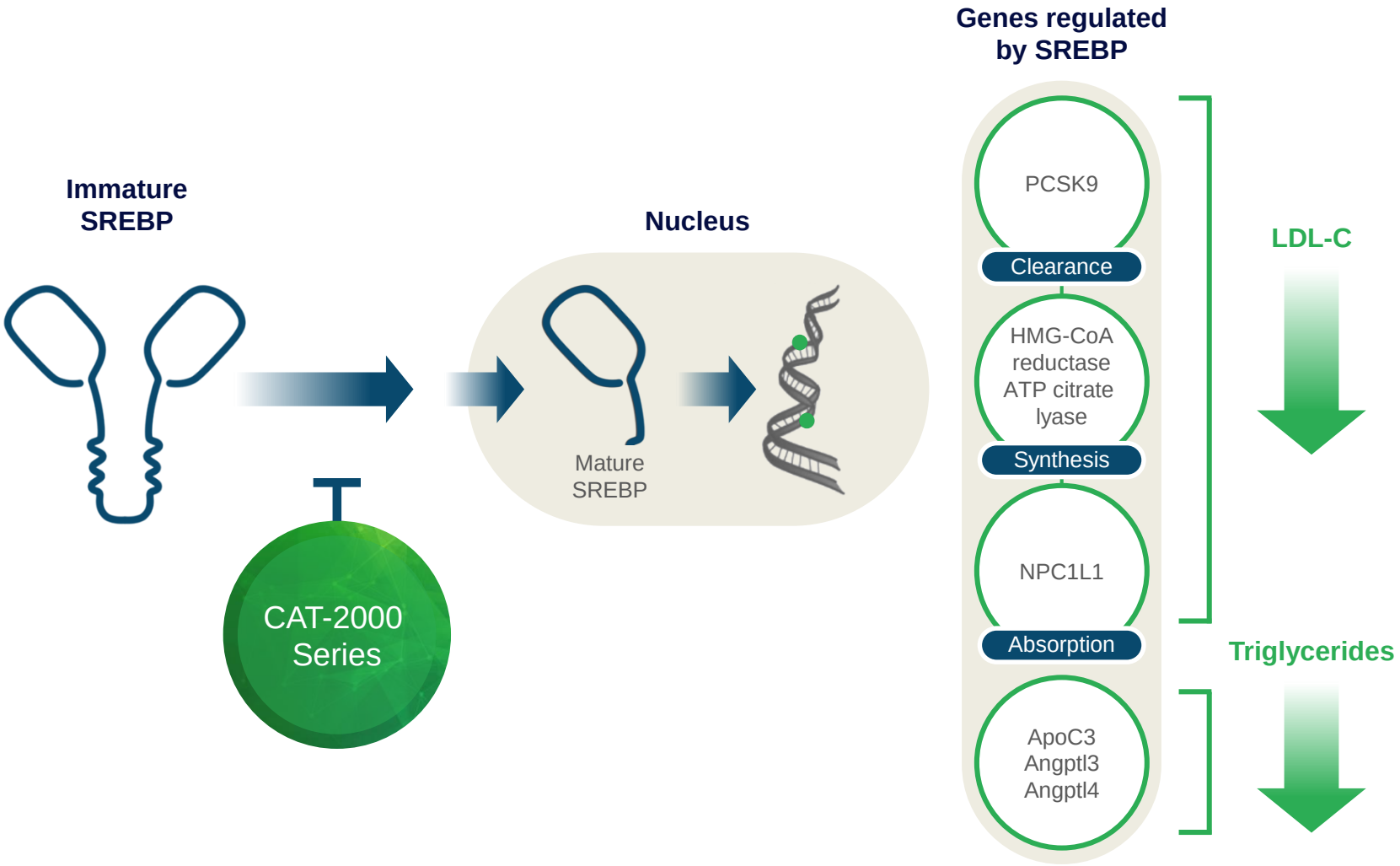
Background

- Sterol Regulatory Element Binding Protein (SREBP) is a master regulator of lipid metabolism and controls the metabolism of both LDL-C and triglycerides, through effects on multiple downstream proteins including PCSK9 and HMGCoA reductase.

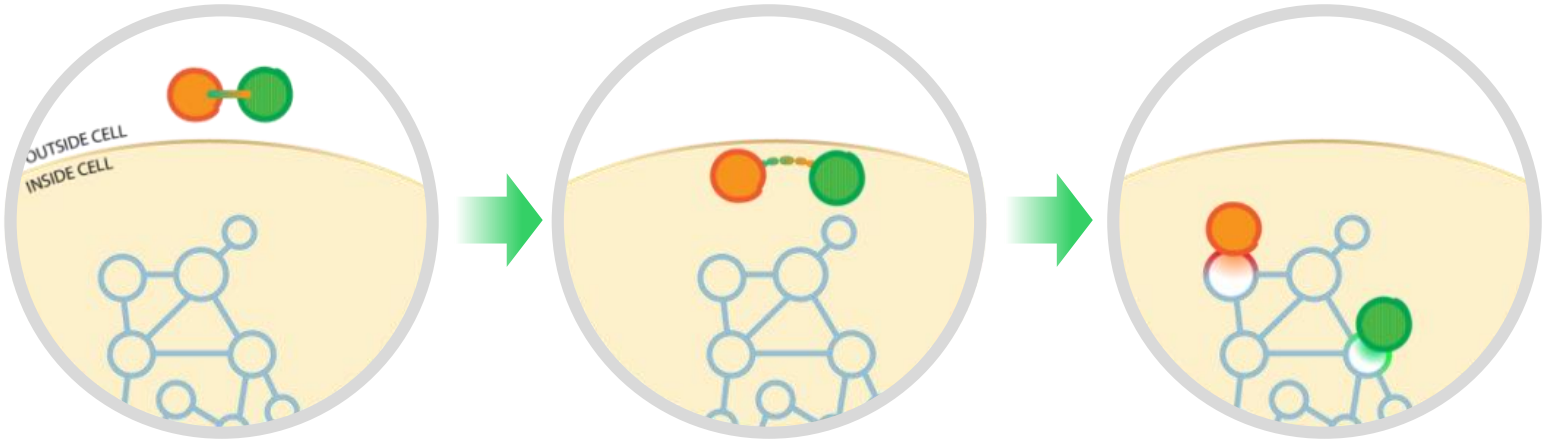
- CAT-2000 compounds are novel inhibitors of the SREBP transcription factor system. In this series of compounds eicosapentaenoic acid (EPA) and niacin are conjugated by proprietary linkers that can be cleaved by the intracellular enzyme fatty acid amide hydrolase (FAAH).
  - First generation compound, CAT-2003, targeting intestine and reduces in triglycerides, LDL-C and HbA1c

- CAT-2054 is a novel product candidate targeted to the liver in development for hypercholesterolemia in patients with uncontrolled LDL-C and other metabolic abnormalities

SREBP is a Master Regulator of Lipid Metabolism; the CAT-2000 Molecules Inhibit SREBP



SMART Linker Technology Platform Engineering Bi-Functional Product Candidates



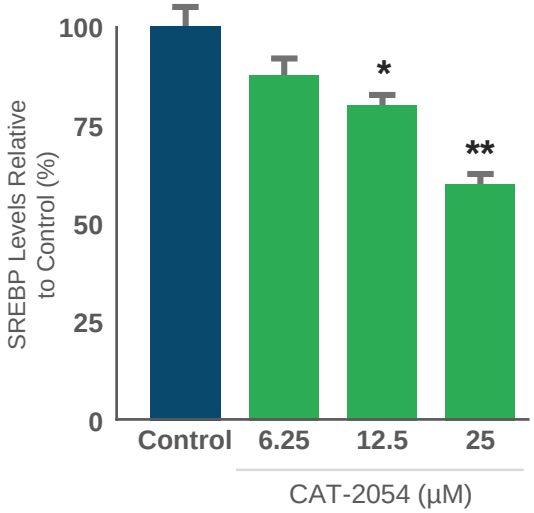
Designed for enhanced efficacy

- SMART Linker conjugate of two known bioactives – niacin and EPA
- Conjugates intact and inactive in systemic circulation
- Cleaved by fatty acid amide hydrolase, an intracellular enzyme
- Matched pharmacokinetics and biodistribution
- Simultaneous intra-cellular delivery of bioactives

CAT-2054 *in vitro* Studies: SREBP Inhibition, PCSK9 Reduction and Increased Cell Surface LDL Receptor

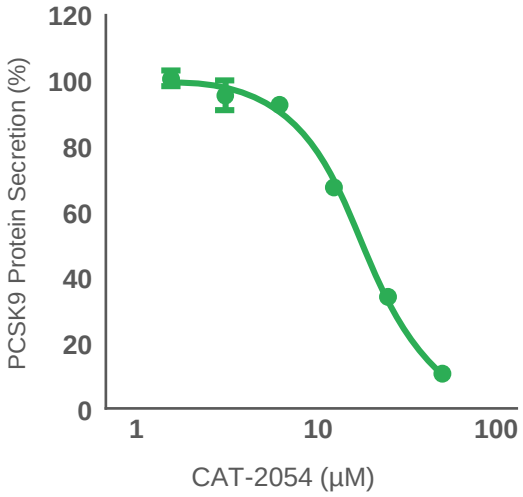
SREBP → PCSK9 → LDLR

Effect on Levels of the Mature SREBP Protein

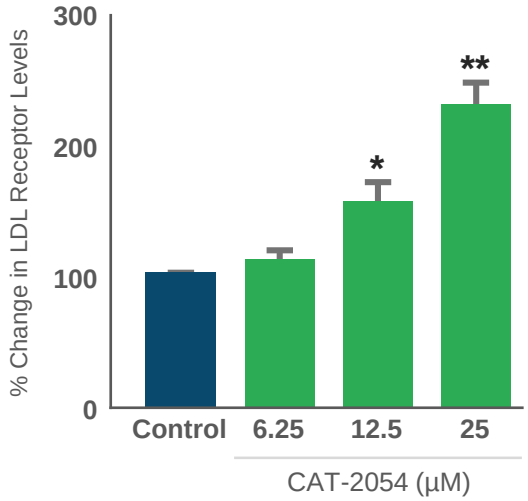


* p<0.05, ** p<0.01

Effect on Levels of PCSK9 Protein Secretion



Effect on Levels of the Cell Surface LDL Receptor



* p<0.05, ** p<0.01

- **CAT-2054 observed to:**
  - Reduce the amount of mature SREBP protein
  - Reduce the secretion of PCSK9 protein
  - Increase LDL-R protein levels

Human liver cell line

CAT-2054 *in vitro* Studies: Inhibition of Statin-Induced Increase in SREBP and PCSK9

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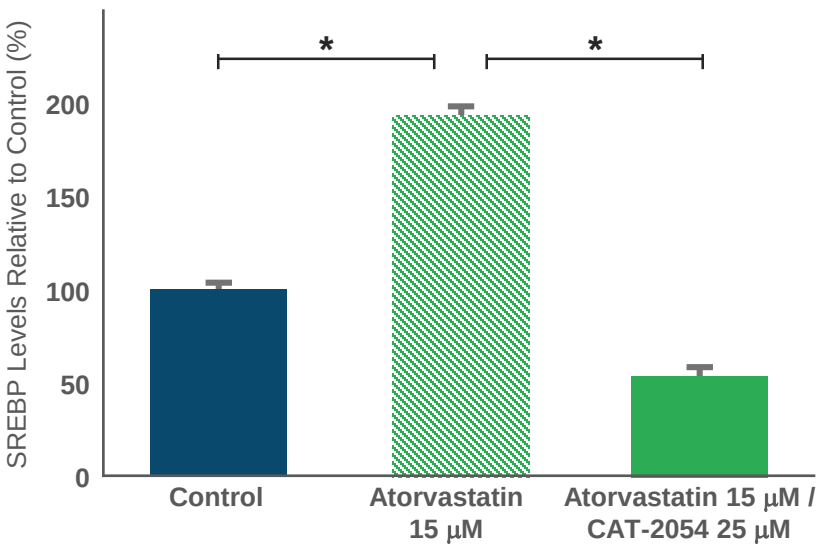
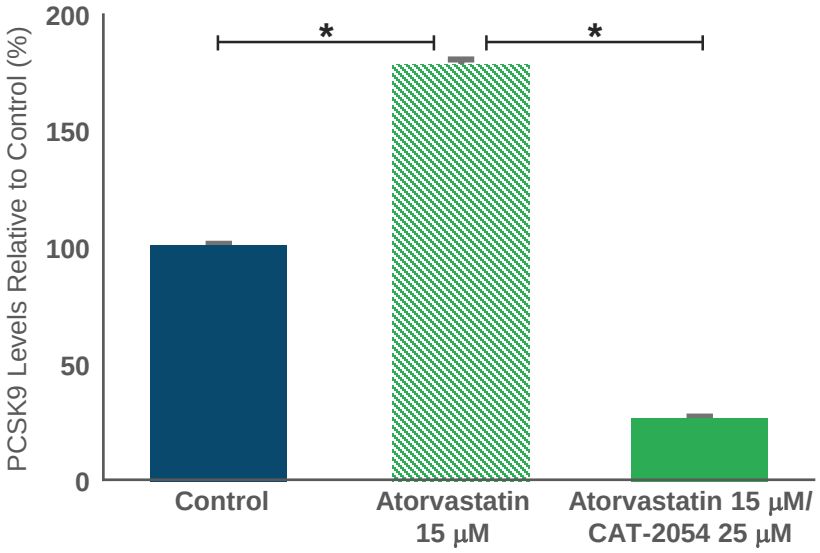
CAT-2054 Effect on SREBP Activation in the Presence of a Statin



* p < 0.01

CAT-2054 Effect on PCSK9 Levels in the Presence of a Statin

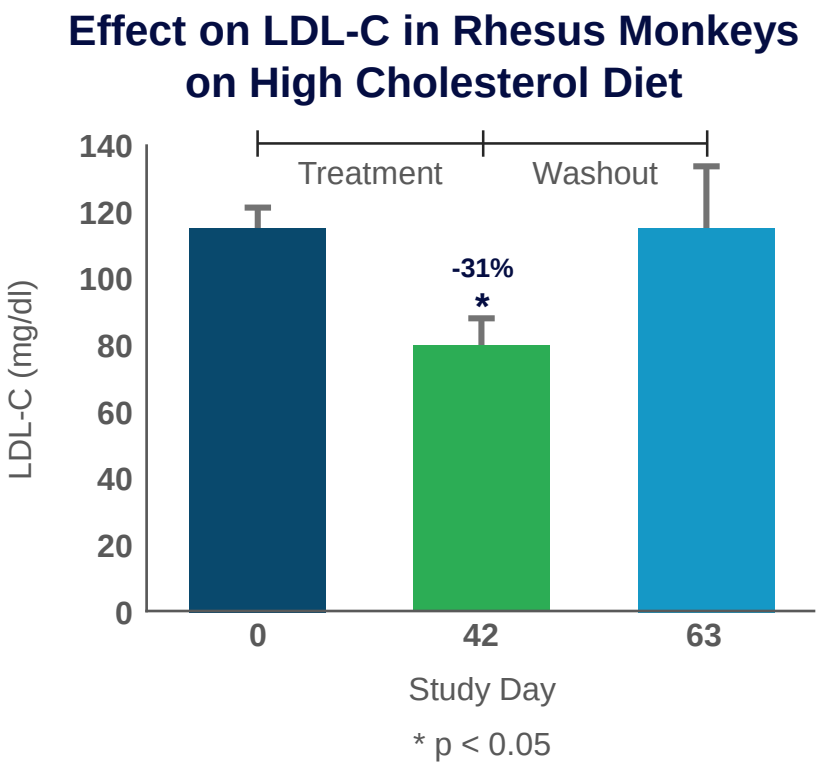


* p < 0.0001

- Statins activate SREBP and increase PCSK9, ultimately limiting their therapeutic effect
- CAT-2054 observed to abrogate the statin-induced increase in PCSK9, and may enhance efficacy

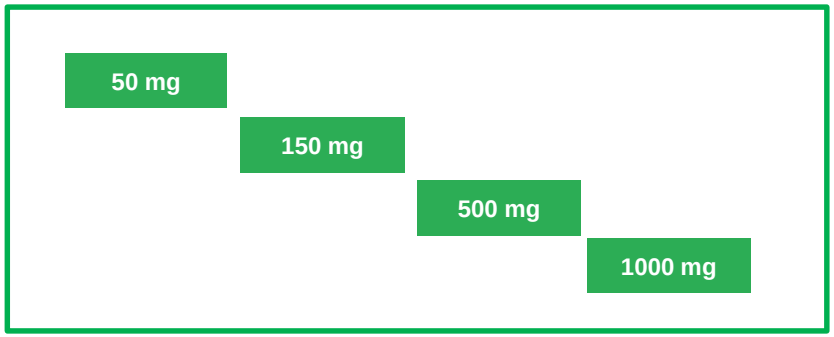
Human liver cell line

CAT-2054 Preclinical Studies: LDL-C Reductions in Non-Human Primate Model



- CAT-2054 reduced LDL-C by 31% in non-human primates (rhesus) at day 42
- Additionally, in cynomolgus macaque monkeys that had developed age-related spontaneous dyslipidemia on a normal diet, CAT-2054 also significantly reduced fasting plasma LDL-C by 21%, which was most pronounced in the monkeys with the highest baseline LDL-C levels.

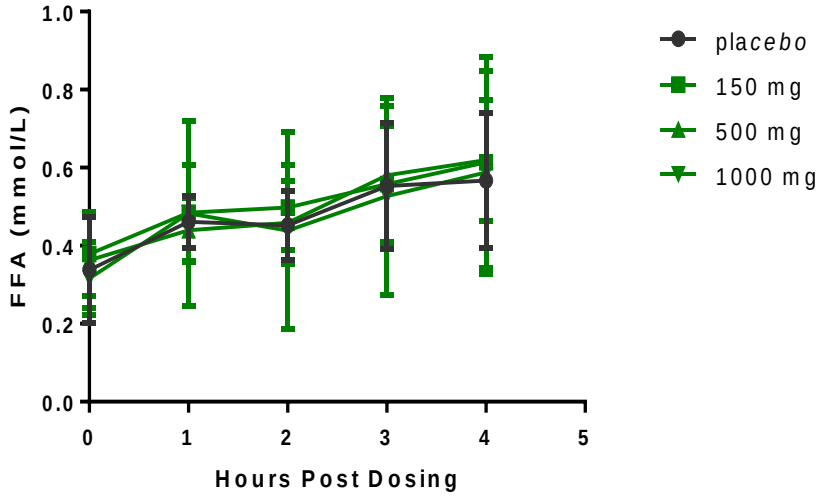
CAT-2054 Phase 1 Single Ascending Dose Trial



- **Study population**
  - Normal healthy volunteers, N of 8-10 per cohort with 2 placebo in each
- **Key Endpoints**
  - Safety
  - Pharmacokinetics
  - Pharmacodynamics
    - Effects on free fatty acids
    - Assessment of flushing

CAT-2054: No Evidence of Interaction with GPR109A Receptor

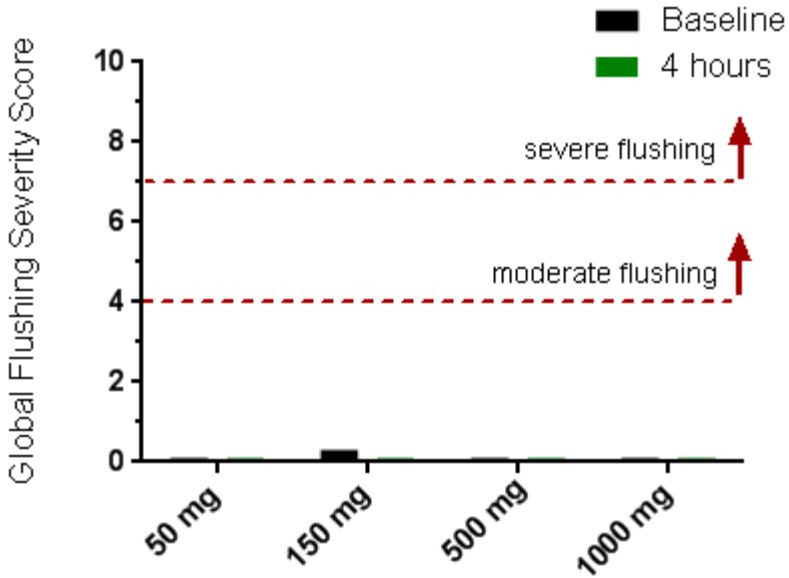
- Niacin reduces plasma free fatty acids by >50%, followed by rebound



- No post-dose suppression observed in free fatty acids at any CAT-2054 dose

Carlson, 1962

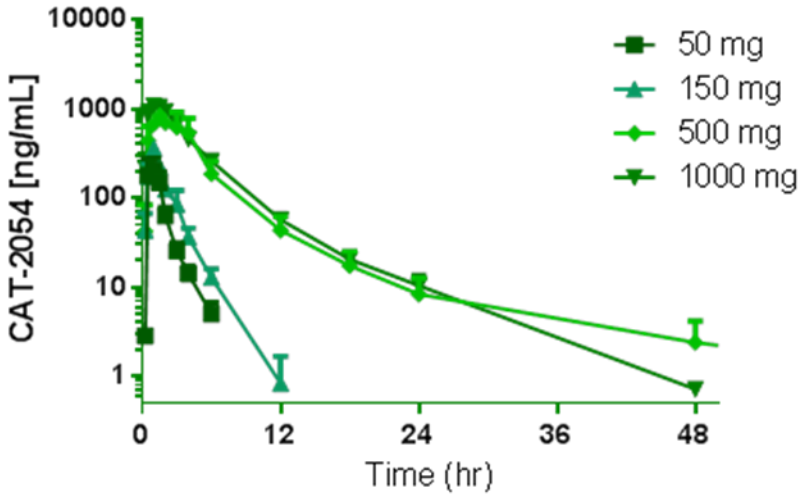
- Niacin causes moderate to severe flushing immediately after administration



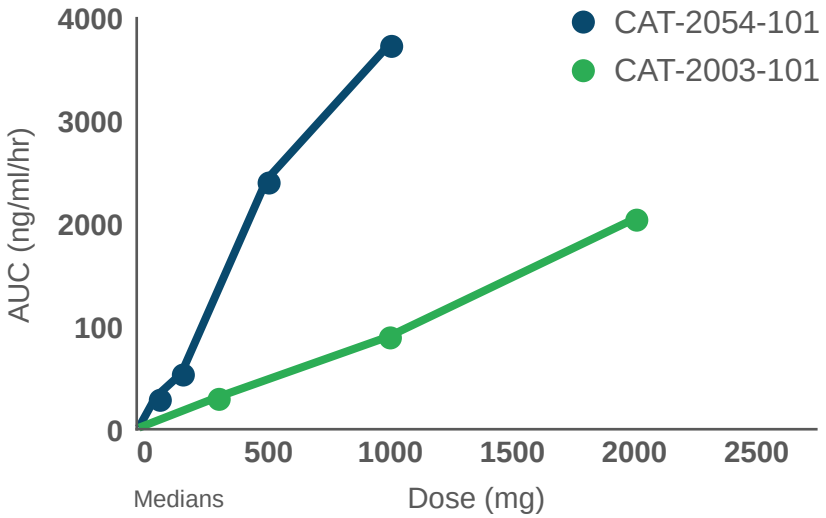
- No evidence of flushing, consistent with lack of extracellular nicotinic acid

CAT-2054 Phase 1 Clinical Trial : Evidence for SMART Linker Stability

Plasma Exposure of CAT-2054



Plasma Exposure of CAT-2054 and CAT-2003



CAT-2054 and CAT-2003 data from independent Single Ascending Dose trials

- Dose-proportional increase in exposure
- CAT-2054 exposure similar fed vs fasted
- Plasma exposure of CAT-2054 is greater than that of CAT-2003 reflecting more stable linker

CAT-2054 Phase 1 Clinical Trial: Safety

- Under fed and fasted conditions, CAT-2054 was well-tolerated
- No safety signals in laboratory, vital signs or electrocardiogram results
- Observed AEs occurring under fed and fasted conditions at doses up to 500 mg were similar for CAT-2054 and placebo.
  - most common AEs observed in fed and fasting conditions were mild nausea and diarrhea at highest dose.

Phase 1 Study of CAT-2054, a Novel Oral Modulator of Sterol Regulatory Element Binding

- CAT-2054 is a novel oral product candidate designed to modulate SREBP in the liver and to reduce LDL-C levels in patients with hypercholesterolemia.
- CAT-2054 was designed to be more stable to intracellular enzymatic cleavage, which is supported by pharmacokinetics of CAT-2054 in the single ascending dose Phase 1 study.
- We hypothesize that this slower rate of cleavage enables more intact CAT-2054 to pass through the portal vein and to the liver, where SREBP controls cholesterol levels.
- Based on a mechanism of inhibiting SREBP and reducing the expression of downstream target genes in the SREBP pathway, including HMG-CoA reductase, PCSK9 and ATP citrate lyase, we believe CAT-2054 may be effective in reducing elevated LDL-C and positively affect other metabolic parameters.