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

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Disclosure of Conflicts of Interest

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

CAT-2054 observed to:

- Reduce the amount of mature SREBP protein
- Reduce the secretion of PCSK9 protein
- Increase LDL-R protein levels

**CAT-2054 (µM)**

- Control
- 6.25
- 12.5
- 25

* p<0.05, ** p<0.01

**SREBP**

Effect on Levels of the Mature SREBP Protein

**PCSK9**

Effect on Levels of PCSK9 Protein Secretion

**LDLR**

Effect on Levels of the Cell Surface LDL Receptor

Human liver cell line
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 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.
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

- 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

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
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.
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.