Introduction: CAT-2054, an orally administered small molecule being developed for hypercholesterolemia, is a novel inhibitor of Sterol Response Element Binding Protein (SREBP), a master regulator of lipid metabolism, including cholesterol and triglycerides, and with impact on glucose and liver fat. In CAT-2054, eicosapentaenoic acid (EPA) and niacin are conjugated to a linker that is cleared intracellularly, producing novel pharmacology. The linker modulates the hydrolysis rate so that higher plasma concentrations and developed or lipid events, there are no higher concentrations and ultimately reduces LDL-C. In nonhuman primates, CAT-2054 was tolerated at a reduced LDL-C over a 6 week dosing period.

Purpose: To assess safety, pharmacokinetics (PK) and pharmacodynamics of CAT-2054 in a multiple ascending dose study.

Methods: Doses of 100-750 mg QD, and 250 mg BID of CAT-2054 or matching placebo were administered for 14 days to normal healthy volunteers (N=70) aged 18-55 with LDL-C<100 mg/dL. CAT-2054 and its metabolites in plasma were measured over 24 hours. Additionally, CAT-2054 500 mg QD with 40 mg atorvastatin was given to assess PK in combination. CAT-2054 over 14 days. Safety was evaluated by adverse events, laboratories (chemistry, hematology, coagulation), physical examination and EKG. Plasma lipids were assessed after 14 days of treatment.

Results: CAT-2054 was well-tolerated and there were no serious adverse events or discontinuations. Following CAT-2054 administration, no safety signals in laboratories, vital signs or electrocardiogram results were observed, and there was no evidence of flushing. At the highest doses, the most common adverse events were gastrointestinal. PK showed dose-proportional increases in plasma CAT-2054 concentrations and there was no evidence for impact on atorvastatin PK. At Day 14, median decreases in LDL-C of up to 11% were observed. At Day 21, there were decreases in LDL-C of up to 20% in all dosing groups.

Conclusions: In this initial clinical study, CAT-2054 lowered LDL-C and was well tolerated with no safety signals. Consistent with the intent to modulate the hydrolysis rate to deliver higher levels to the liver, CAT-2054 had greater systemic exposure than CAT-2003. CAT-2054 is being studied in a Phase 2 trial to inhibit SREBP, the master regulator of lipid metabolism, for patients with hypercholesterolemia.

Pharmacokinetics of Co-administration of CAT-2054 and Atorvastatin

Results: Phase 1

CAT-2054 are First in Class inhibitors of SREBP with Oral Administration

Inhibition of SREBP with CAT-2054 Analog (CAT-2003)

Reversed Steatohepatitis in ApoE/3 LDL-C Loading

Inhibition of SREBP with CAT-2054 Analog (CAT-2003) Decreased Liver Lipid Content When Administered Intraperitoneally

Multiple Dose Pharmacokinetics of CAT-2054

CAT-2054 and CAT-2003 are First in Class inhibitors of SREBP with Oral Administration

Inhibition of SREBP with CAT-2054 Analog (CAT-2003) Decreased Liver Lipid Content When Administered Intraperitoneally

Multiple Dose Pharmacokinetics of CAT-2054

CAT-2054 and CAT-2003 are First in Class inhibitors of SREBP with Oral Administration

Inhibition of SREBP with CAT-2054 Analog (CAT-2003) Decreased Liver Lipid Content When Administered Intraperitoneally

Multiple Dose Pharmacokinetics of CAT-2054

CAT-2054 and CAT-2003 are First in Class inhibitors of SREBP with Oral Administration