28AB-ISMS08 **Discovery of Potent, Liver-Selective Stearoyl-CoA Desaturase-1 (SCD1) Inhibitors, Thiazole-4-acetic Acid Derivatives for the Treatment of Diabetes, Hepatic Steatosis and Obesity**

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SCD1 is a rate-limiting enzyme on converting saturated fatty acids to monounsaturated fatty acids. It has been shown that SCD1 inhibitors have potential effects on obesity, diabetes, acne, and cancer. However, the adverse effects associated with the inhibition of SCD1 in skin and eyes are the impediments for the clinical development. To avoid the mechanism-based side effects, we embarked on identifying liver-selective SCD1 inhibitors by measuring the SCD1 activities in the liver and off-target tissues after oral dosing of the compounds to rodents. This effort led us to discover thiazole-4-acetic acid derivatives as potent and liver-selective SCD1 inhibitors. They showed significant effects in the rodent models of diabetes, hepatic steatosis and obesity, and sufficient safety margins in a toxicology study in rats with repeated dosing.