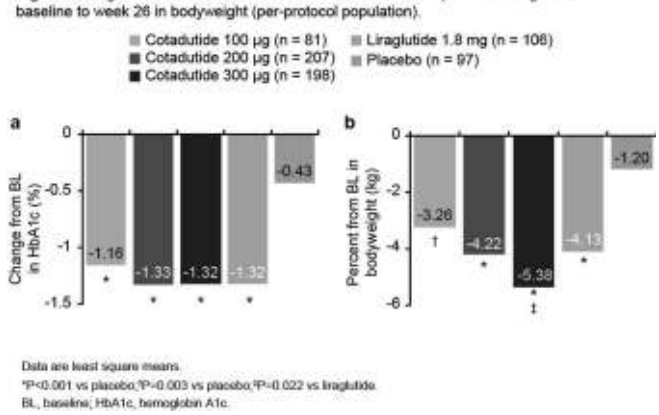
population). A multivariate model selection process was used to identify predictors for efficacy (exploratory analysis). Changes in AST and ALT levels, diastolic and systolic blood pressure (BP), and lipid profiles were exploratory end points. **Results:** Significant reductions from BL to W26 in HbA1c and bodyweight were observed with all doses of cotadutide vs placebo (**Figure**). Cotadutide 300 µg provided similar glycemic control, but superior weight loss vs liraglutide (**Figure**). Early discontinuations with cotadutide were primarily due to gastrointestinal TEAEs. Waist circumference and uric acid levels at BL were significant predictors of HbA1c response with cotadutide 300 µg vs liraglutide (both P≤0.020). Significantly greater reductions from BL to W26 were observed with cotadutide 300 µg vs liraglutide in ALT (-18.9% vs -9.0%; P=0.016), and vs placebo in triglycerides (-8.4% vs 6.3%; P=0.007) and cholesterol (-6.1% vs 0.7%; P=0.002). At all doses of cotadutide, a decrease from BL in systolic BP and an increase in pulse rate that was numerically similar to liraglutide was observed. **Conclusion:** Cotadutide improved metabolic and CV parameters in overweight or obese subjects with T2DM. Superior reductions in ALT levels with cotadutide vs liraglutide suggest a weight-independent effect on liver health, which may be glucagon driven. These data support development of cotadutide for NASH with potential impacts on liver health and cardiometabolic risk.

Figure. Change from baseline to week 26 in HbA1C levels and percent change from baseline to week 26 in bodyweight (per-protocol population).



Data are least square means.
*P<0.001 vs placebo; †P=0.003 vs placebo; ‡P=0.022 vs liraglutide.
BL, baseline; HbA1c, hemoglobin A1c.

Disclosures:

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Lutz Jermutus – Patent pending for glucagon and glp-1 co-agonists fro the treatment of obesity: Patent Held/Filed; AstraZeneca: Stock Shareholder

Boaz Hirshberg – AstraZeneca: Employment; AstraZeneca: Stock Shareholder

Philip Ambery – AstraZeneca: Employment; Patent for dosing for cotadutide: Patent Held/Filed

The following people have nothing to disclose: Michael Stumvoll

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ARAMCHOL, SCD1 INHIBITOR, IMPROVES LIVER GLUCOSE HOMEOSTASIS IN NASH

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Background: Aramchol, an arachidyl cholic acid adduct that targets stearoyl CoA desaturase 1, which catalyzes the first reaction committing fatty acids into triglyceride synthesis, targets both the metabolic alterations that characterize NASH (accumulation of lipids, lipotoxicity and oxidative stress) and fibrosis (collagen production). In a one year study in 247 NASH patients, Aramchol improved NASH resolution without worsening of fibrosis and fibrosis improvement without worsening of NASH as well as hepatic biochemistry. At week 52 placebo patients exhibited an increase in HbA1C, while those treated with Aramchol (400 or 600 mg/day) showed a reduction with a dose response pattern. The differences from placebo were statistically significant suggesting Aramchol also targets glucose metabolism. This study tries to elucidate the mechanism by which Aramchol regulates liver glucose metabolism. **Methods:** We collected liver samples from mice fed with 0.1% methionine MCD diet (0.1MCD) for four weeks, which developed steatohepatitis and fibrosis, as well as mice under control diet; and the liver metabolomes were determined. A group of 0.1MCD fed mice were given Aramchol (5mg/kg/day or 1 mg/kg/day, for the last 2 weeks). In addition, we treated murine primary hepatocytes with 20µM Aramchol for 48h, adding ^{13}C-labeled glucose and determining changes related with glucose metabolism, TCA cycle, lysophosphatidylcholine (LPC) and glycerophosphorylcholine (GPC). **Results:** 0.1MCD fed mice developed steatohepatitis and showed a statistically significant reduction 1.5 to 4 fold of liver glucose, glucose-6-phosphate, fructose-6-phosphate and fructose-1,6-bisphosphate as compared to control diet mice. As shown previously, Aramchol treatment improved NASH features reducing lipid accumulation, inflammation and fibrosis. Glycolysis/gluconeogenesis in 0.1MCD fed mice treated with Aramchol was improved in a dose dependent manner. In Aramchol treated hepatocytes, we found a reduction in the formation of LPC and GPC and in TCA-related metabolites, which may reflect a decrease in TCA activity. **Conclusion:** These results suggest that Aramchol targets not only the alterations in lipid metabolism that characterize NASH but additionally improves liver glucose homeostasis in patients and murine models. Also, in Aramchol-treated primary hepatocytes, there is an inhibition in LPC and GPC formation, which would improve VLDL-TG secretion, together with a reduction in TCA cycle metabolites.

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LIVER AND PANCREAS : 'CASTOR AND POLLUX' REGARDING STEATOSIS AND EXOCRINE INSUFFICIENCY

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