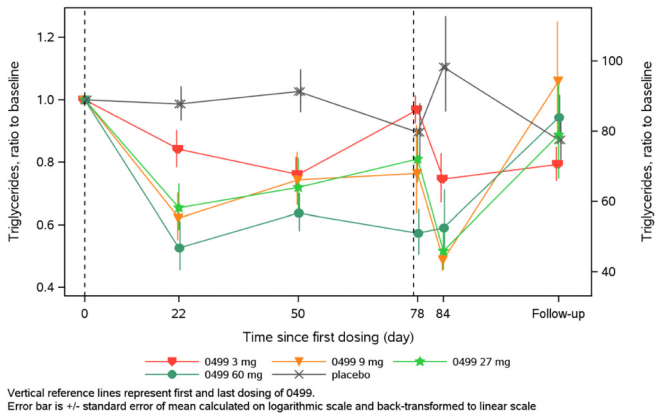

Vertical reference lines represent first and last dosing of 0499.
Error bar is +/- standard error of mean calculated on logarithmic scale and back-transformed to linear scale

Conclusion: The novel FGF21 analogue was well tolerated at doses up to 60 mg/week for 12 weeks. Treatment was associated with beneficial effects on lipid profile including lowering of TG and LDL levels. These results are encouraging for the further development of 0499 for treatment of NASH.

SAT103

Multimodality assessment of hepatic fibrosis: ranked paired reading and artificial intelligence identifies fibrosis improvement with aramchol missed by conventional staging

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Background and aims: Aramchol is a partial inhibitor of hepatic stearoyl-CoA desaturase with direct anti-fibrotic activity in pre-clinical models and histological improvement in a phase 2b trial. This open-label study explored the speed and extent of fibrosis reduction. We compared different methodologies of fibrosis scoring to optimize the design of a registrational placebo-controlled investigation.
Method: 46 Patients (pts) with NASH and fibrosis (28 F3, 11 F2, 7 F1) documented by biopsy were randomized 1:1:1 to receive Aramchol 300 mg BID and underwent a control biopsy at weeks 24, 48 or 72. Biopsies were read by 3 independent pathologists individually, followed by a consensus reading, which determined the final NASH CRN scoring. Three different assessments of the antifibrotic effect were studied on the same slides: 1) a ≥1 stage reduction by NASH CRN; 2) a ranked assessment (improvement/worsening/stable) of paired (pre and post baseline) biopsies, blinded to sequence; 3) an automated and continuous score of Fibrosis Composite Severity (FCS), using FibroNest™, a quantitative digital pathology image analysis and artificial intelligence (AI) Method: a 0.3 reduction in FCS (4 fold higher than the analytical variability) identified any reduction in fibrosis; a 25% relative decline in FCS, a strong reduction in fibrosis.
Results: Control biopsies were performed for 26, 15 and 5 pts at 24, 48, and 72 weeks, respectively. Mean (sd) baseline FCS was 5.05 (1.05). Table shows greater fibrosis improvement with longer duration of therapy for both conventional histology and digital pathology readings. Mean FCS reduction was −0.62 ($p = 0.017$) at Wk24 and −1.74 ($p < 0.0001$) at Wk≥48. AI evaluation was consistent with paired reading in 21/24 (87.5%) of the pts with fibrosis improvement. When analyzed by AI, 17/23 pts with unchanged NASH CRN stages had any fibrosis response, including 7 with a strong response. Similarly, 13/17 pts with stable ranking had a fibrosis response, including 5 with a strong reduction. No pts with worse CRN stages or worsening ranking had a strong AI fibrosis reduction.

Fibrosis reduction	Wk24, N = 26% (N)	Wk ≥ 48, N = 20% (N)
By NASH CRN ≥1 stage	27% (7)	40% (8)
By ranked assessment	42% (11)	65% (13)
By AI reading, any (delta FCS ≥0.3)	58% (15)	100% (20)
By AI reading, strong (-25% FCS)	27% (7)	65% (13)

Conclusion: Aramchol resulted in a high proportion of fibrosis improvement using three separate biopsy reading methodologies, with a larger treatment effect with longer duration of therapy. Both ranked assessments and AI evaluations identified more subjects with fibrosis improvement, indicating greater sensitivity to change vs categorical scoring. Digital pathology quantification by AI reveals a high level of fibrosis improvement that would have been missed by conventional histological measurements. AI technologies are promising for the detection of fibrosis changes in future clinical trials.

SAT104

The effect of glucagon on rates of hepatic mitochondrial oxidation and pyruvate carboxylase flux in man assessed by positional isotopomer tracer analysis (PINTA)

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Background and aims: Dual GLP-1/glucagon agonists are now in clinical trials for the treatment of T2D and NASH. In addition to promoting further reduction in food intake on top of GLP-1, the glucagon component of these dual agonists may also promote increased rates of hepatic mitochondrial fat oxidation.
Method: In order to investigate this possibility we assessed the glucagon-specific effects of a dual agonist on rates of hepatic mitochondrial oxidation (V_{CS}) and pyruvate carboxylase flux (V_{PC}) in humans by infusing glucagon to achieve a physiological increase in plasma glucagon concentrations in combination with a novel ^{13}C PINTA method to assess rates of hepatic V_{CS} and V_{PC} in 15 healthy volunteers using a paired study design. Following an overnight fast a 3-h IV infusion of [3-^{13}C]lactate (4.3 μmol/Kg-min) and [1, 2, 3, 4, 5, 6, 6-$^{2}H_7$]glucose (0.22 μmol/Kg-min) was begun and during the last 2 hours glucagon (GLG) was co-infused [6 ng/ (Kg-min)] or no GLG (CON).
Results: The GLG infusion resulted in a ~2.4 fold increase in plasma GLG conc. (from 75 ± 11 to 183 ± 20 pg/ml; *P < 0.0001*), which was associated with an ~20% increase in both plasma C-peptide (from 1.89 ± 0.17 to 2.30 ± 0.26 ng/ml; *P = 0.02*) and plasma insulin conc. (from 9.9 ± 2.0 to 12.0 ± 2.4 μU/ml; *P = 0.06*). Plasma glucose conc. increased from 4.90 ± 0.16 to 5.64 ± 0.19 mmol/L ($p = 0.0001$) which was associated with a tendency for increased rates of glucose production (CON:1042 ± 123 vs. GLG:1148 ± 122 μmol/min; *p = 0.086*) despite no change in rates of V_{PC} flux (CON: 403 ± 69 vs. GLG: 373 ± 55 μmol/min; *p = NS*). In contrast, this physiological increase in plasma GLG concentrations caused an 85% increase in rates of hepatic V_{CS} ($p < 0.05$).