Reduced triglycerides and LDL cholesterol from once-weekly administration of the well-tolerated novel FGF21 analogue 0499

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Aim

- To investigate the safety and tolerability of repeated administration of the new, long-acting fibroblast growth factor 21 (FGF21) analogue 0499 in healthy participants.

Introduction

- FGF21 is a metabolic regulator with pleiotropic effects on food preferences, energy and lipid metabolism.[1]
- Activation of the FGF21 receptor complex has been associated with several attractive effects in preclinical models, including weight loss and decreased hepatic fat content.[2,3]
- This has led to the pursuit of FGF21 as pharmacotherapy for patients with obesity and non-alcoholic steatohepatitis (NASH).
- In two single ascending dose studies in healthy participants (poster #SAT-116), the novel alkylated FGF21 analogue 0499 was found to have an acceptable safety profile with a plasma half-life of approximately 120 hours and promising improvements in plasma lipid profile.
- Here we report the investigation into the safety and tolerability of repeated administration of the novel FGF21 analogue 0499[4] in healthy female and male participants.

Methods

- In a randomised, blinded, placebo-controlled multiple ascending dose study in healthy male and female participants with a body mass index of approximately 30 kg/m^2, weekly subcutaneous injections of either placebo or 0499 were administered for 12 weeks.
- Dose levels were 3, 9, 27, 60 and 120 mg.
- In each dose cohort, nine participants were randomised to active treatment and three to placebo.
- Participants were followed for safety monitoring and pharmacokinetic sampling up until 36 days after the last dose.

Results

- A total of 57 participants were randomised (**Table 1**).

Safety and tolerability

- Weekly administrations of 0499 at dose levels from 3 to 60 mg/week were well tolerated. There were no serious adverse events related to treatment (**Table 2**).
- In the dose cohort receiving 0499 at 120 mg/week, all six participants who started on treatment experienced tolerability issues within the first 3 weeks of treatment, including moderate gastro-oesophageal reflux and moderate vomiting, nausea and diarrhoea. Further enrolment to this cohort was cancelled and treatment with the 120 mg dose was stopped.
- Adverse events observed at the dose levels from 3 to 60 mg/week included vomiting, increased appetite, nausea and diarrhoea (**Table 3**). Increased appetite and diarrhoea were also observed in the placebo group.
- Either mild or moderate increased appetite was reported at all doses, including the placebo group, with unclear dose-dependency.
- Mild injection-site reactions were seen irrespective of dose level. One participant experienced generalised urticaria at a dose of 9 mg/week.
- In total, 25 participants discontinued treatment due to adverse events (n=5) or for other reasons (**Table 2**).
- No effect was observed on menstrual cycle, bone biomarkers or other safety parameters (data not shown).

Other observations

- The plasma half-life of 0499 was confirmed to be approximately 120 hours across the dose levels. Pharmacokinetic properties support once-weekly dosing and dose proportionality.
- Low titres of anti-drug antibodies were detected with some neutralising effect on endogenous FGF21.

Table 1: Participant disposition and baseline characteristics

Treatment group and dose	0499 3 mg	0499 9 mg	0499 27 mg	0499 60 mg	0499 120 mg	Placebo	Total
Randomised[a] and exposed	10 (100)	9 (100)	9 (100)	9 (100)	6 (100)	14 (100)	57 (100)
Completed treatment	7 (70.0)	3 (33.3)[b]	6 (66.7)	6 (66.7)	0 (0.0)	10 (71.4)	32 (56.1)
Sex, male	3 (30.0)	3 (33.3)	5 (55.6)	6 (66.7)	6 (100)	8 (57.1)	31 (54.4)
Age (years)	37.2 (6.1)	36.2 (4.4)	39.2 (5.4)	34.1 (8.6)	41.5 (5.3)	39.4 (7.4)	37.9 (6.6)
Body weight (kg)	89.1 (10.8)	89.4 (17.8)	98.8 (13.6)	97.2 (19.9)	99.1 (9.5)	92.1 (10.9)	93.8 (14.1)
Body mass index (kg/m^2)	32.5 (2.5)	32.1 (4.0)	34.1 (2.7)	33.7 (4.1)	32.1 (3.7)	31.2 (2.5)	32.5 (3.2)
Triglycerides (mmol/L)	1.34 (0.46)	2.51 (1.24)	1.82 (0.63)	2.02 (1.65)	2.24 (0.43)	1.39 (0.66)	1.82 (1.00)

One participant was replaced in the 3 mg dose cohort, leading to 10 rather than the intended 9 participants. Recruitment to the 120 mg dose group was stopped early owing to adverse events.
[a]Only 14 patients were randomised to placebo due to termination of enrolment in the last cohort; [b]Six participants did not complete treatment in the 9 mg cohort, five participants due to adverse events and one participant due to protocol violation. Data are n (%) or mean (standard deviation).

Table 2: Adverse events

Treatment group and dose	0499 3 mg			0499 9 mg			0499 27 mg			0499 60 mg			0499 120 mg			Placebo			Total		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	10			9			9			9			6			14			57		
Adverse events	8	(80.0)	23	9	(100)	61	8	(88.9)	42	9	(100)	50	6	(100)	28	10	(71.4)	33	50	(87.7)	237
Serious	0			0			0			0			0			0			0		
Events leading to withdrawal[a]	0	(0.0)	0	2	(22.2)	2[c]	0	(0.0)	0	1	(11.1)	1	2	(33.3)	2	0	(0.0)	0	5	(8.8)	5
Events leading to treatment discontinuation[a]	0	(0.0)	0	3	(33.3)	3	0	(0.0)	0	2	(22.2)	2	0	(0.0)	0	0	(0.0)	0	5	(8.8)	5
Related to trial product																					
Probable	5	(50.0)	9	7	(77.8)	21	7	(77.8)	22	8	(88.9)	18	5	(83.3)	12	4	(28.6)	5	36	(63.2)	87
Possible	4	(40.0)	7	5	(55.6)	10	3	(33.3)	3	4	(44.4)	10	4	(66.7)	7	6	(42.9)	10	26	(45.6)	47
Unlikely	7	(70.0)	7	9	(100)	30	6	(66.7)	17	8	(88.9)	22	4	(66.7)	9	9	(64.3)	18	43	(75.4)	103
Injection-site reaction[b]	1	(10.0)	2	4	(44.4)	10	6	(66.7)	18	5	(55.6)	11	0	(0.0)	0	2	(14.3)	3	18	(31.6)	44

[a]Weight gain/increased appetite/vomiting led to discontinuation from treatment or withdrawal for four participants at the 9 mg dose level and two participants at the 60 mg dose level; [b]All injection-site reactions were mild and included mainly redness, ecchymosis and itching; [c]One case of generalised urticaria, possibly hypersensitivity, led to withdrawal.
N, number of participants with event; E, number of events.

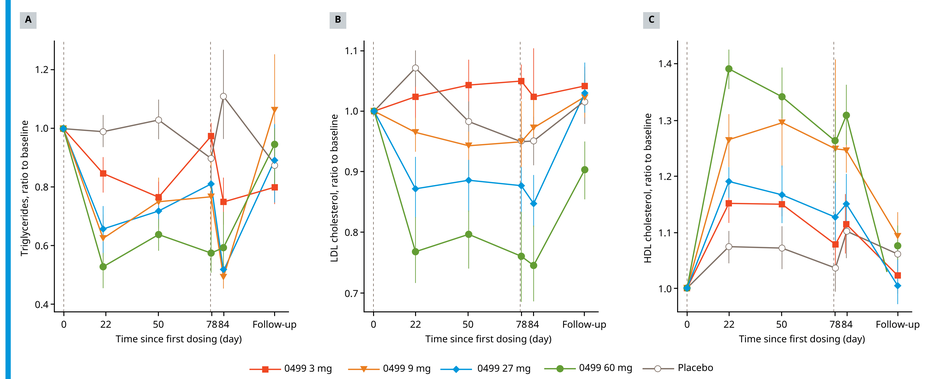
Table 3: Most frequently reported adverse events by preferred term

Treatment group and dose	0499 3 mg			0499 9 mg			0499 27 mg			0499 60 mg			0499 120 mg			Placebo			Total		
	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E	N	(%)	E
Number of participants	10			9			9			9			6			14			57		
Increased appetite	5	(50.0)	5	5	(55.6)	6	5	(55.6)	5	8	(88.9)	8	1	(16.7)	1	4	(28.6)	4	28	(49.1)	29
Hyperphagia	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(1.8)	1
Lack of satiety	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0	1	(1.8)	1
Vomiting	0	(0.0)	0	2	(22.2)	2	2	(22.2)	2	3	(33.3)	3	4	(66.7)	4	0	(0.0)	0	11	(19.3)	11
Nausea	0	(0.0)	0	3	(33.3)	3	1	(11.1)	1	1	(11.1)	2	5	(83.3)	6	0	(0.0)	0	10	(17.5)	12
Diarrhoea	1	(10.0)	1	1	(11.1)	1	0	(0.0)	0	2	(22.2)	2	2	(33.3)	2	1	(7.1)	1	7	(12.3)	7
Gastro-oesophageal reflux disease	0	(0.0)	0	1	(11.1)	1	0	(0.0)	0	0	(0.0)	0	2	(33.3)	2	0	(0.0)	0	3	(5.3)	3

N, number of participants with event; E, number of events.

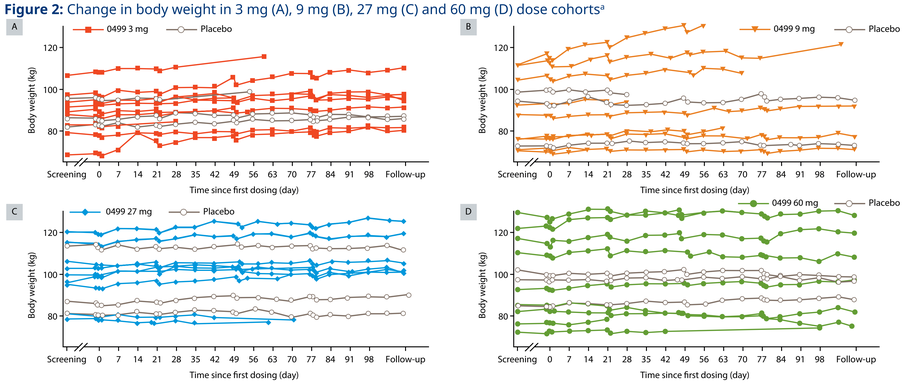
Key result

Figure 1: Change in ratio to baseline in triglycerides (A), LDL cholesterol (B) and HDL cholesterol (C)[a]



[a]Data not shown for the 120 mg cohort as treatment at this dose was discontinued early due to adverse events
Vertical reference lines represent first and last doses of 0499. Error bars are ± standard error of the mean calculated on logarithmic scale and back-transformed to linear scale
HDL, high-density lipoprotein; LDL, low-density lipoprotein

Figure 2: Change in body weight in 3 mg (A), 9 mg (B), 27 mg (C) and 60 mg (D) dose cohorts[a]



[a]Data not shown for the 120 mg cohort as treatment at this dose was discontinued early due to adverse events

Lipids

- Sustained improvements in triglyceride (TG) and high- and low-density lipoprotein (HDL/LDL) cholesterol levels were observed at the end of treatment. Furthermore, the improvements in LDL were dose-dependent (**Figure 1**).
  - Placebo-adjusted changes in the 3, 9, 27 and 60 mg dose cohorts were 33%*, 52%*, 61%* and 48%*, respectively, for TG and –7%, 1%, 13% and 20%*, respectively, for LDL. Placebo-adjusted changes in HDL were –1%, 11%, –1% and 20%*, respectively (*p<0.05).

Body weight

- A statistically significant weight gain of 4.5 %-points (placebo-adjusted) was observed in the 3 mg dose group. For the higher dose groups, weight changes of ±2 %-points were observed, although these were not statistically significant compared with placebo Changes in bodyweight in kilograms are shown in **Figure 2**.

Conclusions

- The novel FGF21 analogue 0499 was well tolerated at doses up to 60 mg/week for 12 weeks in healthy participants.
- The clinically relevant increase in body weight observed at the 3 mg dose was not observed at higher doses.
- Treatment was associated with beneficial effects on the lipid profile, including lowering of TG and LDL levels.
- This improvement in plasma lipid profile is encouraging for the further development of 0499 for the treatment of NASH.

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