Sustained reduction of triglycerides and LDL cholesterol from single administration of the novel long-acting FGF21 analogue 0499

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Aim

- To investigate the safety profile and pharmacokinetic (PK) and pharmacodynamic (PD) potential of the new, long-acting fibroblast growth factor 21 (FGF21) analogue, 0499.

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 for pharmacotherapy for obesity and non-alcoholic steatohepatitis.
- The novel FGF21 analogue 0499 has been akylated at position 180C with a C18 diacid, making it strongly albumin-bound and preventing proteolytic cleavage of the C-terminal.[4]
- Based on preclinical PK studies, the half-life of 0499 is predicted to make it suitable for once-weekly administration.[4]
- Here we report the exploration of 0499, with the purpose of investigating its safety profile as well as its PK and PD potential.

Methods

- In a randomised, blinded, placebo-controlled, first-in-human, single-dose study, healthy male participants with body mass index approximately 30 kg/m^2 received a single subcutaneous (s.c.) administration of either placebo or 0499 at dose levels of 2, 6, 12, 24, 48, 96 or 180 mg.
  - There was a 5–7 day in-clinic period immediately after dosing.
- In a separate study in Japanese and non-Asian healthy male participants, three dose levels of 12, 30 and 96 mg were tested to confirm a consistent safety profile and PK characteristics across ethnicity.
- In both studies, participants were followed for 36 days post-dose, during which blood samples were obtained for safety evaluation and PK and PD assessments.
- Exposure of 0499 was measured via an enzyme-linked immunosorbent assay using antibodies generated by Novo Nordisk.
- A total of 78 participants received a single dose of 0499.

Results

Pharmacokinetics

- The plasma half-life of 0499 was approximately 120 hours.
- In the healthy male participants in the two studies, maximum concentrations were dose proportional and were reached in the first 26–52 hours after dosing before dropping to 0 by approximately 672 hours (**Figure 1**; **Table 1**). Overall exposure to 0499 was similar between Japanese and non-Asian participants.

Body weight

- In the first study, a single s.c. administration of 0499 at doses of 2, 6, 12, 24, 48, 96 and 180 mg was not associated with a clinically relevant change in body weight in healthy male participants at the end of the study compared with baseline (**Table 2**).
- Weight loss was seen at day 5 (during the in-clinic period) but returned to ±2% of baseline by day 36 across dose groups.

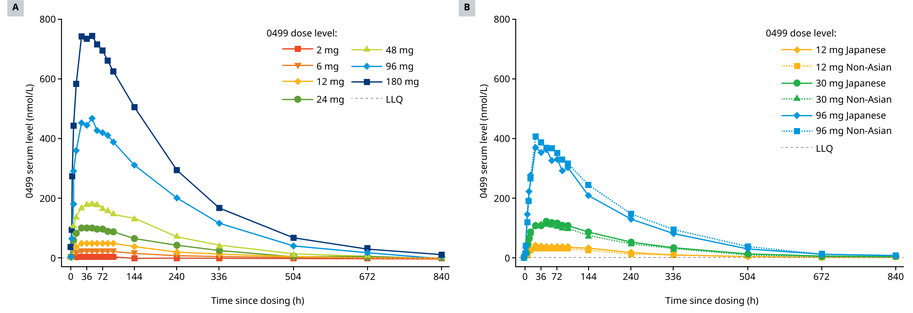
Lipids

- In both studies, single s.c. dosing of 0499 in healthy male participants resulted in a dose-dependent reduction of plasma triglycerides and low-density lipoprotein cholesterol levels, with an increase in high-density lipoprotein cholesterol levels (**Figure 2**).
- Changes in lipid parameters were sustained for up to 28 days after the single administration.

Other parameters

- Administration of 0499 was not associated with changes in heart rate, body temperature or clinical laboratory safety parameters (data not shown).

Figure 1: Pharmacokinetics of 0499 after a single dose in healthy male participants (A) and in healthy Japanese and non-Asian male participants (B)



Values below the LLQ are imputed. LLQ, lower limit of quantification

Table 1: Pharmacokinetics of 0499 after a single dose in healthy male participants (A) and in Japanese and non-Asian healthy male participants (B)

A **0499 dose level:**	2 mg (n=6)	6 mg (n=6)	12 mg (n=6)	24 mg (n=6)	48 mg (n=6)	96 mg (n=6)	180 mg (n=6)
C_{max} (nmol/L)	7.36 (33.0)	24.5 (12.8)	52.1 (23.9)	107 (16.4)	188 (24.6)	480 (25.3)	790 (22.3)
t_{max} (h)	38 (37.0)	43 (53.6)	44 (14.9)	38 (31.8)	51 (23.9)	39 (28.0)	45 (40.4)
$t_{1/2}$ (h)	118 (21.9)	123 (10.0)	128 (11.1)	116 (13.5)	115 (10.3)	124 (7.0)	123 (9.7)
CL/F (L/h)	0.0569 (27.6)	0.0505 (19.2)	0.0438 (25.7)	0.0468 (12.1)	0.0515 (19.7)	0.0401 (21.4)	0.0479 (20.3)
$AUC_{0-24\ h}$ (nmol*h/L)	126 (35.6)	358 (25.6)	821 (26.9)	1632 (17.8)	2781 (25.0)	7329 (27.2)	11,819 (27.5)
$AUC_{0-168\ h}$ (nmol*h/L)	983 (31.2)	3175 (15.1)	7190 (23.6)	13,960 (13.3)	24,985 (22.1)	62,432 (24.5)	101,458 (21.0)
AUC_{0-inf} (nmol*h/L)	1731 (27.6)	5842 (19.2)	13,484 (25.7)	25,215 (12.1)	45,897 (19.7)	117,710 (21.4)	184,967 (20.3)
AUC_{0-last} (nmol*h/L)	1482 (33.6)	5488 (21.1)	13,178 (25.8)	24,935 (12.2)	45,533 (19.7)	116,450 (21.4)	181,966 (20.3)

B	Japanese participants			Non-Asian participants		
0499 dose level:	12 mg (n=6)	30 mg (n=6)	96 mg (n=6)	12 mg (n=6)	30 mg (n=6)	96 mg (n=6)
C_{max} (nmol/L)	44.7 (22.3)	123 (18.0)	381 (15.5)	35.6 (22.4)	120 (21.3)	410 (10.6)
t_{max} (h)	39.0 (67.8)	49.8 (9.1)	35.2 (44.9)	52.2 (80.5)	43.1 (41.4)	25.7 (16.7)
$t_{1/2}$ (h)	134 (23.6)	125 (10.0)	121 (9.1)	135 (14.0)	117 (10.7)	126 (2.8)
CL/F (L/h)	0.0564 (19.6)	0.0468 (21.9)	0.0561 (14.0)	0.0643 (27.7)	0.0502 (18.0)	0.0504 (15.0)
$AUC_{0-168\ h}$ (nmol*h/L)	5774 (24.6)	16,615 (18.1)	46,973 (13.7)	4758 (24.1)	15,689 (19.9)	50,818 (11.9)
AUC_{0-inf} (nmol*h/L)	10,473 (19.6)	31,542 (21.9)	84,258 (14.0)	9183 (27.7)	29,412 (18.0)	93,694 (15.0)
AUC_{0-last} (nmol*h/L)	9837 (22.0)	30,992 (22.2)	83,449 (13.9)	8685 (28.4)	28,661 (18.4)	92,702 (14.9)

Data are geometric mean (coefficient of variation).
$AUC_{0-24\ h/168\ h/inf/last}$, area under the concentration–time curve from time zero to 24 h/168 h/infinity/last measurable plasma concentration; CL/F, apparent clearance; C_{max}, maximum plasma concentration; $t_{1/2}$, half-life; t_{max}, time to C_{max}.

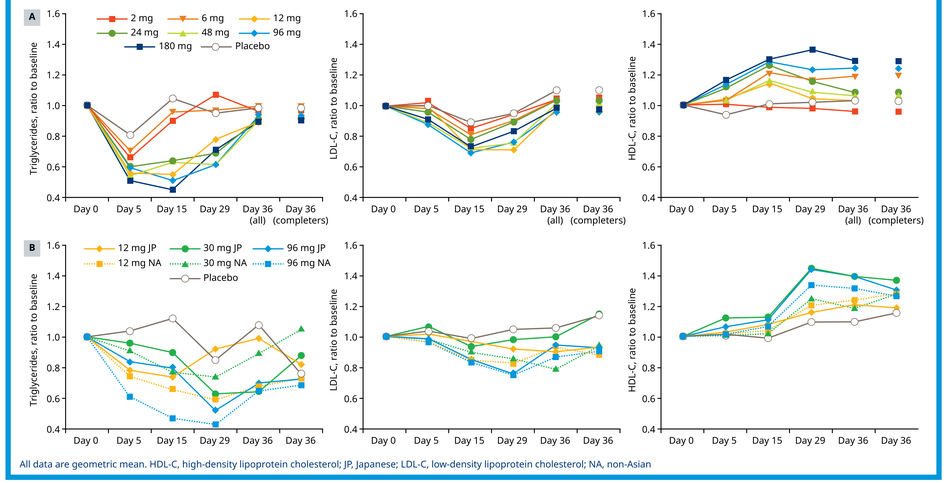
Table 2: Percentage change from baseline in body weight following a single dose of 0499

0499 dose level:	2 mg (n=6)	6 mg (n=6)	12 mg (n=6)	24 mg (n=6)	48 mg (n=6)	96 mg (n=6)	180 mg (n=6)	Placebo (n=14)
Day 5	−0.8 (0.5)	−1.3 (0.5)	−1.7 (1.0)	−1.6 (0.6)	−1.7 (0.6)	−1.9 (0.5)	−1.9 (0.3)	−1.2 (0.6)
Day 15	1.5 (0.6)	2.2 (1.4)	1.2 (1.9)	0.8 (1.3)	1.6 (1.8)	1.8 (0.9)	0.8 (2.5)	1.6 (0.9)
Day 29	2.4 (0.8)	3.5 (3.2)	1.8 (1.2)	1.1 (2.0)	1.1 (2.7)	2.0 (1.7)	−0.7 (2.1)	2.0 (2.0)
Day 36	0.8 (1.0)	1.4 (2.6)	0.6 (1.2)	−0.1 (1.7)	0.4 (3.1)	1.0 (2.0)	−2.0 (2.9)	−0.1 (1.7)

Data are mean (standard deviation).

Figure 2: Change from baseline in triglycerides, LDL-C and HDL-C after a single 0499 dose in healthy male participants (A) and in Japanese and non-Asian healthy male participants (B)

Key result



All data are geometric mean. HDL-C, high-density lipoprotein cholesterol; JP, Japanese; LDL-C, low-density lipoprotein cholesterol; NA, non-Asian

Safety

- Safety observations were similar in both studies (**Table 3**). No serious treatment-emergent adverse events (TEAEs) or deaths occurred.
- TEAEs were mainly related to the gastrointestinal tract and included nausea, diarrhoea, frequent bowel movements and vomiting, particularly at the higher doses tested; other observed events included increased appetite and early satiety (data not shown).
  - The highest numbers of TEAEs possibly or probably related to trial product were seen at the 48 and 180 mg dose levels in the first study of healthy male participants, for whom two events were reported in one participant and seven events were reported in two participants, respectively.
  - In the Japanese participants' dose groups, the highest number of TEAEs possibly or probably related to the trial product was eight, reported in three participants at a dose of 96 mg.
  - Although diarrhoea was the most common TEAE seen overall, the non-Asian group also had four events of increased appetite recorded in four participants.

Table 3: TEAEs after a single dose of 0499 in healthy male participants and in Japanese and non-Asian healthy male participants

		Healthy male participants								Japanese participants				Non-Asian participants		
0499 dose level: n (%) | E		2 mg (n=6)	6 mg (n=6)	12 mg (n=6)	24 mg (n=6)	48 mg (n=6)	96 mg (n=6)	180 mg (n=6)	Placebo (n=14)	12 mg (n=6)	30 mg (n=6)	96 mg (n=6)	Placebo (n=6)	12 mg (n=6)	30 mg (n=6)	96 mg (n=6)
Any TEAE		4 (66.7) | 4	0 | 0	1 (16.7) | 4	3 (50.0) | 4	2 (33.3) | 5	4 (66.7) | 4	4 (66.7) | 11	5 (35.7) | 5	3 (50.0) | 4	2 (33.3) | 2	3 (50.0) | 9	1 (16.7) | 2	3 (50.0) | 3	2 (33.3) | 6	4 (66.7) | 9
Events leading to withdrawal		0 | 0	0 | 0	1 (16.7)[a] | 1	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0
Severity:	Mild	2 (33.3) | 2	0 | 0	1 (16.7) | 1	3 (50.0) | 3	2 (33.3) | 4	4 (66.7) | 4	4 (66.7) | 7	2 (14.3) | 2	3 (50.0) | 3	2 (33.3) | 2	3 (50.0) | 9	1 (16.7) | 2	3 (50.0) | 3	2 (33.3) | 6	4 (66.7) | 9
	Moderate	2 (33.3) | 2	0 | 0	0 | 0	1 (16.7) | 1	1 (16.7) | 1	0 | 0	2 (33.3) | 4	3 (21.4) | 3	1 (16.7) | 1	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0
	Severe	0 | 0	0 | 0	1 (16.7) | 3	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0	0 | 0

[a]Unlikely that event was related to trial product.
E, number of events; TEAE, treatment-emergent adverse event.

Conclusions

- From the two single ascending dose studies in healthy participants, it was concluded that the novel FGF21 analogue 0499 has an acceptable safety profile at all dose levels tested and that the PK profile seems compatible with once-weekly dosing. The PK profile was similar in Japanese and non-Asian participants.
- The promising improvement in plasma lipid profile was encouraging for the further development of 0499.

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These trials were sponsored by Novo Nordisk and are registered with ClinicalTrials.gov (NCT03015207 and NCT04722653). The authors acknowledge the medical writing assistance of Claudia Venables-Stack of Aura, a division of Spirit Medical Communications Group Limited, and Sarah Stowell, a contract writer working on behalf of Aura.
Presented at the International Liver Conference, 22–26 June 2022, London, UK.

References:
(**1**) Xie T, Leung PS. Am J Physiol Endocrinol Metab 2017;313:E292–E302; (**2**) Keinicke H et al. Endocr Connect 2020;9:755–68; (**3**) Kliewer SA, Mangelsdorf DJ. Cell Metab 2019;29:246–53; (**4**) Rakipovski G et al. Hepatology 2021;74:1128A

DOI: 10.3252/pso.eu.ILC2022.2022
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ILC2022