Maintaining a threshold concentration of AKR-001, a long-acting, degradation-resistant FGF21 analog, elicits sustained improvements in markers of glycemic control and lipid metabolism in a 4-week MAD study

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Introduction

The rising worldwide prevalence of obesity in recent decades has created an epidemic of associated metabolic disorders including metabolic syndrome, type 2 diabetes (T2D), cardiovascular disease, and non-alcoholic liver diseases. Excessive caloric burdening of multiple organ systems underlies these comorbidities, resulting in insulin resistance manifest by chronically elevated fasting glucose and insulin. Strategies to treat disorders associated with metabolic syndrome therefore focus on reducing caloric intake (e.g. appetite suppression), inducing negative caloric balance (e.g. inhibition of glucose re-absorption by the kidney), and/or improving insulin sensitivity (e.g. by reducing body weight, or improving peripheral glucose uptake from circulation).

Non-alcoholic steatohepatitis (NASH) is a liver manifestation of this metabolic dysregulation. Accumulating hepatic lipids drive lipotoxic stress, ER stress, and oxidative stress, which if unmitigated may irreparably damage hepatocytes, driving apoptosis, inflammation, and fibrosis. NASH increases the incidence of both liver-related and non-liver related (including cardiovascular disease and cancer) morbidity and mortality (Figure 1). There are currently no approved therapies for NASH, though many therapeutic targets are currently under investigation. Because of the multifactorial nature of NASH, it will be critical to engage multiple underlying drivers of the disease to restore patient health.

Fibroblast growth factor 21 (FGF21) is an endocrine hormone secreted by the liver in response to nutritional stress that regulates whole-body metabolism. The tissues on which FGF21 directly acts, including muscle, adipose tissue, pancreas, and liver, are defined by their co-expression of the canonical FGF receptor through which FGF21 signals (FGFR1c, FGFR2c, FGFR3c) and the obligate co-receptor, β-klotho. In preclinical models of metabolic diseases, FGF21 administration reduces body weight, and improves markers of insulin sensitivity as well as lipid and lipoprotein profiles. In previously reported clinical trials of FGF21 analogs, improvements in lipid profiles were seen, but markers of insulin sensitivity were minimally affected. Insufficient pharmacological exposure in humans may underlie this difference. Insulin sensitization is likely to be an important element of a potential NASH therapy, as peripheral caloric uptake and reduced adipose lipolysis would reduce hepatic energy burden.

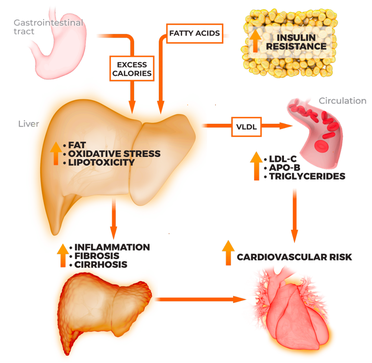


Figure 1. The complex pathophysiology of NASH contributes to both liver-related and cardiovascular morbidity and mortality

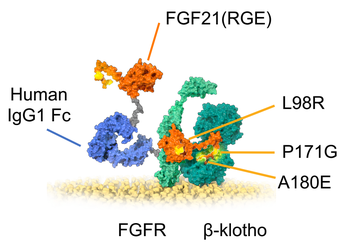
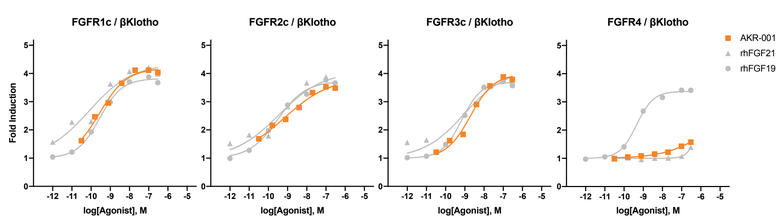


Figure 2. AKR-001, an Fc-fusion FGF21 variant, binds β-klotho and signals through a canonical FGFR

Here, we present results from a phase 1, multiple ascending dose study in subjects with type 2 diabetes of AKR-001, an Fc-FGF21 fusion protein (Figure 2) engineered for balanced agonism of FGF21's canonical receptors, enhanced stability, and sustained systemic exposure (Figure 3). AKR-001 also recapitulates native FGF21's inability to signal through FGFR4, which is associated with hepatocyte proliferation and elevation of LDL cholesterol (by suppressing bile acid synthesis).

Figure 3. AKR-001 maintains full, balanced agonism of FGFR1c/2c/3c without FGFR4 activity *in vitro*



EC50 (nM)	rhFGF19	rhFGF21	AKR-001
FGFR1c + βKlotho	0.2781	0.07813	0.2745
FGFR2c + βKlotho	0.3011	0.3558	0.6883
FGFR3c + βKlotho	0.678	0.9936	1.945
FGFR4 + βKlotho	0.4505	>8000	>1500

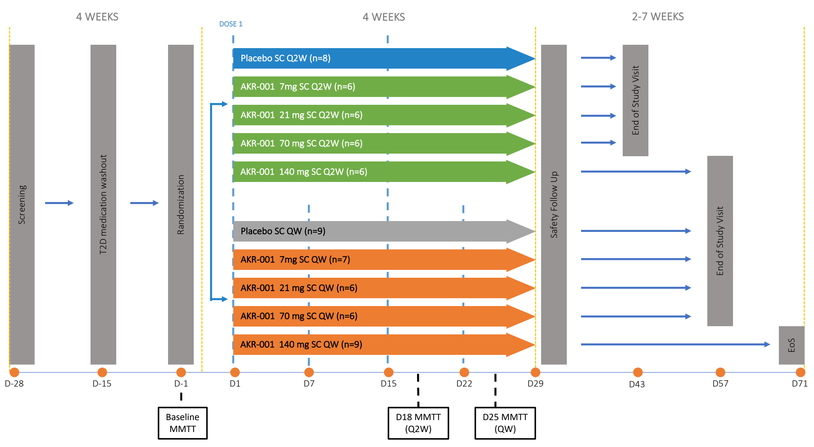
Key Takeaways:
- FGF21 functions through several key metabolic tissues to suppress adipose tissue lipolysis, enhance peripheral insulin sensitivity, and enhance protective cellular stress responses
- AKR-001, like FGF21, is a balanced agonist of FGFR1c/2c/3c
- AKR-001 is expected to maintain metabolic actions of FGF21 across metabolic tissues

Study Design and Methods

The trial (registered on www.clinicaltrials.gov as NCT01856881) was a multicenter, randomized, double-blind, placebo-controlled, ascending multiple-dose study in patients with T2D. 69 subjects were randomized to receive AKR-001 or placebo in a ratio of 3:1. AKR-001 was administered subcutaneously (SC) once every two weeks (Q2W) or once weekly (QW) for 4 weeks (See Figure 4).

The study population comprised adult females of non-reproductive potential and males aged 18–65, with a BMI of 25–40 kg/m², and a diagnosis of T2D. Eligible participants had elevated HbA1c between 6.5 and 10%, and a fasting C-peptide value of 0.8 ng/mL or greater at screening.

Figure 4. Study design of the AKR-001 multiple ascending dose trial.



A computer-generated randomization schedule was prepared prior to study start. Cohort size was based on practical considerations; however, calculations were performed to determine predictive power. 6 subjects per cohort received active, providing a 73% chance of detecting an AE with 20% true incidence. Analysis was performed on the safety analysis set (all subjects who received ≥1 dose of AKR-001). Safety data from the QW and Q2W placebo groups were combined.

PD endpoint data are reported as placebo-corrected % change from BL of least-square (LS) geo. means with 90% CI. CV safety endpoints are reported as LS-mean % change from BL. Assessments presented as LS-mean were fit on the log scale with a linear mixed effects model and back-transformed to the linear scale for reporting. The models had fixed effects for treatment, time, treatment by time, and a random effect on baseline by subject.

Baseline Characteristics

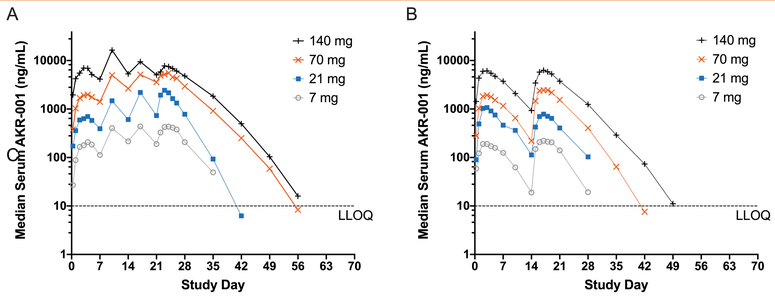
Figure 5. Patient demographics and baseline characteristics for enrolled subjects in all treatment groups

Geometric mean (% CV), unless otherwise noted	Placebo QW (N=8–9)	Placebo Q2W (N=6–8)	AKR-001 QW 7 mg (N=5–7)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=6–9)	AKR-001 Q2W 7 mg (N=5–7)	AKR-001 Q2W 21 mg (N=5–6)	AKR-001 Q2W 70 mg (N=5–6)	AKR-001 Q2W 140 mg (N=5–9)
Mean age, years (SD)	51 (8)	58 (6)	60 (3)	46 (10)	59 (5)	57 (6)	58 (4)	58 (4)	54 (9)	54 (7)
Male, N (%)	6 (67)	6 (75)	3 (43)	3 (50)	2 (33)	5 (56)	3 (50)	2 (33)	5 (83)	4 (67)
Mean weight, kg (SD)	84 (16)	81 (9)	98 (18)	83 (16)	89 (11)	93 (13)	98 (18)	73 (8)	92 (20)	88 (9)
Mean BMI, kg/m² (SD)	30 (3)	29 (3)	35 (3)	31 (3)	36 (3)	32 (5)	34 (3)	29 (2)	33 (6)	32 (3)
Fasting glucose, mmol/L	9.0 (28)	10.9 (16)	10.7 (32)	9.4 (26)	10.5 (16)	10.8 (20)	10.6 (15)	9.8 (15)	10.2 (18)	10.0 (31)
Fasting insulin, pmol/L	61 (84)	58 (45)	72 (44)	56 (27)	93 (47)	68 (68)	63 (87)	64 (36)	63 (42)	63 (88)
Fasting C-peptide, nmol/L	0.8 (36)	0.8 (25)	0.8 (25)	0.7 (31)	0.9 (18)	0.8 (37)	0.7 (60)	0.9 (13)	0.8 (53)	0.8 (36)
HOMA-IR	3.5 (70)	4.0 (43)	4.9 (40)	3.4 (44)	6.3 (42)	4.7 (76)	4.3 (97)	4.0 (46)	4.1 (59)	4.0 (81)
Fasting glucagon, ng/L	88 (19)	93 (18)	99 (35)	85 (32)	93 (30)	89 (38)	83 (26)	93 (22)	97 (12)	93 (27)
Fasting TG, mmol/L	1.6 (20)	1.7 (25)	1.4 (36)	2.1 (27)	2.0 (30)	1.5 (48)	2.1 (28)	1.9 (30)	1.7 (33)	1.6 (55)
Fasting TC, mmol/L	5.2 (17)	4.7 (19)	5.4 (20)	5.9 (13)	5.1 (20)	4.5 (25)	5.5 (23)	5.8 (19)	4.3 (18)	4.8 (19)
Fasting HDL-C, mmol/L	1.2 (21)	1.1 (30)	1.2 (18)	1.3 (16)	1.1 (32)	1.2 (24)	1.0 (18)	1.3 (17)	1.0 (30)	1.2 (28)
Fasting non-HDL-C, mmol/L	4.0 (25)	3.6 (23)	4.2 (28)	4.5 (21)	3.9 (27)	3.2 (38)	4.5 (25)	4.5 (22)	3.3 (20)	3.5 (29)
Fasting FFA, µmol/L	440 (35)	468 (39)	645 (21)	432 (24)	541 (40)	703 (25)	865 (17)	360 (23)	539 (41)	430 (34)
Fasting apoA-1, mg/dL	130 (18)	120 (25)	130 (11)	139 (7)	136 (28)	138 (16)	118 (9)	135 (14)	130 (18)	120 (25)
Fasting apoB, mg/dL	100 (24)	91 (19)	99 (24)	108 (20)	101 (20)	84 (34)	103 (28)	106 (20)	100 (24)	91 (19)
Fasting apoC-2, mg/dL	4.5 (69)	5.1 (31)	4.0 (62)	5.8 (29)	5.2 (36)	3.8 (52)	ND	ND	ND	ND
Fasting apoC-3, mg/dL	10.4 (42)	10.1 (25)	11.2 (78)	12.5 (17)	10.9 (45)	8.1 (42)	ND	ND	ND	ND
Lp(a), mg/dL	42 (196)	44 (139)	35 (71)	75 (113)	51 (134)	18 (236)	ND	ND	ND	ND
ANGPTL4, ng/mL	153 (44)	147 (33)	197 (35)	137 (16)	156 (25)	155 (24)	ND	ND	ND	ND
Fasting C4, ng/mL	36 (89)	30 (86)	29 (162)	59 (88)	51 (52)	22 (112)	19 (323)	52 (51)	18 (96)	22 (232)
HbA_{1C}, %	8.0 (10)	7.8 (10)	8.0 (12)	8.4 (13)	8.1 (10)	7.4 (11)	7.6 (10)	8.2 (9)	7.7 (7)	8.1 (14)
Mean HR, bpm (SD)	66 (6)	62 (12)	65 (10)	70 (10)	69 (7)	63 (7)	65 (7)	62 (6)	67 (9)	63 (16)
Mean SBP, mm Hg (SD)	125 (12)	118 (11)	126 (16)	119 (14)	125 (13)	121 (18)	129 (12)	120 (17)	132 (19)	126 (18)
Mean DBP, mm Hg (SD)	77 (5)	74 (8)	74 (6)	77 (6)	80 (7)	73 (8)	75 (5)	72 (10)	81 (6)	75 (12)

SD, standard deviation; BMI, body mass index; CV, coefficient of variation; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; FFA, free fatty acids; apoA-1, apolipoprotein A-1; apoB, apolipoprotein B; apoC-2, apolipoprotein C-2; apoC-3, apolipoprotein C-3; Lp(a), lipoprotein(a); ANGPTL4, angiopoietin-like 4; C4, 7α-hydroxy-4-cholesten-3-one; HOMA-IR, homeostatic model assessment of insulin resistance; HbA_{1c}, Glycated hemoglobin; HR, heart rate, SBP, systolic blood pressure; DBP, diastolic blood pressure; ND, not determined.

Pharmacokinetics of AKR-001

Figure 6. Pharmacokinetic properties of AKR-001. **A**, Median serum concentration of AKR-001 administered weekly. **B**, Median serum concentration of AKR-001 administered every-other-week. **C**, Descriptive statistics of PK parameter estimates upon first dose (d1), and final dose (d15 for Q2W, day 22 for QW) of AKR-001.



PK Parameter		AKR-001 QW 7 mg	AKR-001 QW 21 mg	AKR-001 QW 70 mg	AKR-001 QW 140mg	AKR-001 Q2W 7 mg	AKR-001 Q2W 21 mg	AKR-001 Q2W 70 mg	AKR-001 Q2W 140 mg
Day 1	N	7	6	6	9	6	6	6	6
	Mean C_{max}, ng/mL (%CV)	297 (71.6)	806 (76.8)	2600 (67.4)	7590 (43.7)	193 (16.6)	1010 (37.1)	2110 (76.6)	6810 (33.4)
	Mean $AUC_{0-\tau}$, day•ng/mL (%CV)	1450 (72.5)	4060 (73.6)	13300 (67.8)	36700 (36.2)	1490 (17.4)	7170 (21.4)	17500 (80.1)	50600 (35.4)
Day 15 (Q2W) or Day 22 (QW)	N	6	6	6	5	6	6	6	6
	Mean C_{max}, ng/mL (%CV)	440 (47.1)	2290 (51.3)	6260 (48.3)	11900 (83.1)	236 (50.2)	881 (47.0)	3140 (69.5)	7530 (49.5)
	Mean $AUC_{0-\tau}$, day•ng/mL (%CV)	2260 (43.6)	10700 (48.4)	31900 (48.5)	57500 (70.4)	1750 (44.5)	6110 (35.4)	27800 (78.5)	55600 (44.4)
	$t_{1/2,z}$, days (%CV)	3.24 (23.5)	2.56 (12.0)	3.30 (12.7)	3.54 (13.8)	2.81[a] (30.2)	3.27[b] (13.2)	3.29 (7.1)	3.44 (11.3)

QW, once weekly; Q2W, once every two weeks; N, number of subjects per group; %CV, coefficient of variation expressed as a percent; C_{max}, maximum observed concentration; $AUC_{0-\tau}$, area under the concentration-time curve during the inter-dose interval, post-dose; τ – inter-dose interval (QW = 7 days, Q2W = 14 days); $t_{1/2,z}$ – terminal half-life. [a] N = 4, [b] N = 5.

Key Takeaways:
- Full-length, intact C-terminus AKR-001 has a half-life of 3-3.5 days in humans
- Approximately 2-3-fold accumulation was observed after four weekly doses of AKR-001
- Median AKR-001 peak:trough ratio with QW dosing was 2; with Q2W dosing, 6-11

Tolerability of AKR-001

Figure 7. Treatment-emergent, investigational product-related AEs with ≥2 observations[#] in all cohorts

	Placebo QW/Q2W (N=17)	AKR-001 QW 7 mg (N=7)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=9)	AKR-001 Q2W 7 mg (N=6)	AKR-001 Q2W 21 mg (N=6)	AKR-001 Q2W 70 mg (N=6)	AKR-001 Q2W 140 mg (N=6)
Subjects reporting all-grade IP-related TEAEs (n)	3	2	4	5	8	3	3	2	3
Grade 2-4*	0	0	1	0	2	0	1	0	1
Adverse events with two or more observations									
Nausea (all grade)	0	1	3	0	6	0	2	1	2
Grade 2-4	0	0	0	0	0	0	0	0	2
Diarrhea (all grade)	1	1	0	2	2	0	1	1	1
Grade 2-4	0	0	0	0	0	0	1	0	0
Change in appetite† (all grade)	0	1	0	2	5	0	1	0	0
Grade 2-4	0	0	0	0	0	0	0	0	0
Vomiting (all grade)	0	0	0	0	3	0	1	0	2
Grade 2-4	0	0	0	0	1	0	0	0	1
Gastrointestinal, other‡ (all grade)	1	0	1	0	5	2	1	1	0
Grade 2-4	0	0	0	0	0	0	0	0	0
Tremor (all grade)	0	0	0	0	4	0	0	0	0
Grade 2-4	0	0	0	0	1	0	0	0	0
Headache (all grade)	1	0	0	0	1	1	1	0	0
Grade 2-4	0	0	0	0	0	0	0	0	0
Injection-site rash or erythema (all grade)	0	0	1	2	1	0	0	0	1
Grade 2-4	0	0	1	0	0	0	0	0	0
Withdrawals	0	0	0	0	4§	0	0	0	0

* - CTCAE toxicity grades
# - a single event of the following AEs was observed in the trial: dizziness (140 mg QW), dysgeusia (140 mg QW), musculoskeletal pain (7 mg Q2W), muscle spasms (140 mg QW), ventricular extrasystoles (140 mg QW), hyperhidrosis (140 mg QW), flushing (21 mg Q2W); all events Grade 1
† - includes increased appetite, decreased appetite, and hunger
‡ - includes constipation, dyspepsia, abdominal distension, abdominal pain, abdominal tenderness, and epigastric discomfort
§ - reason for withdrawals: nausea and tremor (1 subject), diarrhea (1 subject), nausea (1 subject), tremor (1 subject)

Figure 8. Least-squares mean (90% CI) change from baseline in BP and pulse rate, 3 days post-final dose

Parameter	QW (day 25) Placebo (N=8)	QW (day 25) 7 mg (N=6)	QW (day 25) 21 mg (N=6)	QW (day 25) 70 mg (N=6)	QW (day 25) 140mg (N=5)	Q2W (day 18) Placebo (N=8)	Q2W (day 18) 7 mg (N=6)	Q2W (day 18) 21 mg (N=6)	Q2W (day 18) 70 mg (N=6)	Q2W (day 18) 140 mg (N=6)
Systolic BP, mm Hg	-7 (-14, -1)	-3 (-10, 5)	4 (-4, 12)	-8 (-16, -1)	3 (-5, 11)	0 (-7, 7)	0 (-8, 8)	-2 (-9, 6)	-4 (-12, 4)	0 (-8, 8)
Diastolic BP, mm Hg	-2 (-6, 1)	-1 (-5, 4)	-2 (-6, 3)	-6 (-11, -2)	1 (3, 6)	0 (-4, 4)	0 (-5, 4)	4 (-1, 9)	-2 (-6, 3)	3 (-2, 8)
Heart rate, bpm	5 (1, 9)	4 (0, 9)	5 (1, 10)	1 (-3, 6)	7 (3, 12)	-1 (-5, 3)	5 (0, 10)	1 (-3, 6)	5 (0, 9)	13 (7, 18)

Key Takeaways:
- There were no serious AEs at any dose during or after treatment, and no deaths
- AKR-001 appeared generally well-tolerated at doses up to and including 70 mg, with no treatment-related withdrawals at these doses
- Most frequently reported AEs with AKR-001 were gastrointestinal (all mild or moderate)
- No trends were observed in electrocardiography measurements, including cQT interval
- 7/52 subjects who received AKR-001 developed ADAs, with no NAb or effect on PK

AKR-001 Improved Lipid Markers

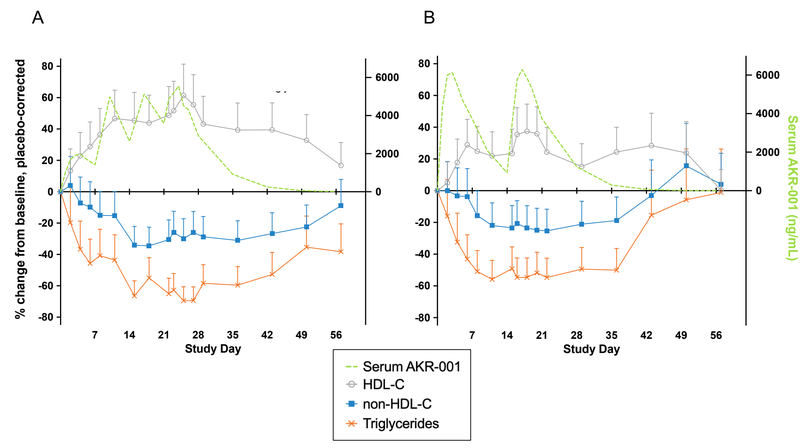
Figure 9. LS-mean (90% CI) placebo-corrected percent change from baseline of lipid markers in the fasted state on day 25 (QW cohorts) or day 18 (Q2W cohorts).

Treatment group	AKR-001 QW 7 mg (N=6)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=5)	AKR-001 Q2W 7 mg (N=6)	AKR-001 Q2W 21 mg (N=6)	AKR-001 Q2W 70 mg (N=6)	AKR-001 Q2W 140 mg (N=6)
Total Cholesterol	1 (-13, 16)	1 (-12, 17)	-8 (-21, 6)	-11 (-23, 3)	-7 (-20, 8)	3 (-11, 19)	-1 (-15, 14)	-7 (-20, 8)
HDL-C	28 (13, 46)	38 (21, 57)	61 (41, 84)	37 (20, 56)	2 (-11, 16)	23 (8, 41)	26 (10, 44)	37 (20, 57)
Non-HDL-C	-12 (-27, 8)	-11 (-27, 8)	-30 (-43, -14)	-34 (-46, -19)	-10 (-26, 10)	-4 (-21, 18)	-9 (-26, 11)	-23 (-37, -6)
Triglycerides	-37 (-55, -11)	-60 (-71, -43)	-69 (-78, -57)	-60 (-71, -45)	-19 (-41, 12)	-29 (-48, -2)	-42 (-58, -20)	-55 (-67, -38)
FFA	-16 (-46, 30)	15 (-27, 80)	-4 (-38, 51)	-12 (-43, 37)	-31 (-56, 9)	30 (-17, 104)	25 (-21, 96)	23 (-22, 93)
3-hydroxybutyrate	11 (-40, 106)	53 (-18, 187)	69 (-10, 217)	30 (-30, 142)	-9 (-52, 72)	-13 (-54, 64)	68 (-11, 218)	60 (-15, 203)

QW, once weekly; Q2W, once every two weeks; N, number of subjects per group; HDL-C, high-density lipoprotein cholesterol; FFA, free fatty acids

AKR-001 Rapidly and Durably Improved Lipid and Lipoprotein Markers

Figure 10. Time course plots of lipid and lipoproteins over the study duration with 70 mg QW (**A**) or 140 mg Q2W (**B**) AKR-001. Data presented as LS-mean + 90% CI.



AKR-001 Improved Markers of Glycemic Control with Weekly Dosing

Figure 11. LS-mean (90% CI) placebo-corrected percent change from baseline of markers of glycemic control in the fasted state on day 25 (QW cohorts) or day 18 (Q2W cohorts). Adiponectin is day 29 for both cohorts

Treatment group	AKR-001 QW 7 mg (N=6)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=5)	AKR-001 Q2W 7 mg (N=6)	AKR-001 Q2W 21 mg (N=6)	AKR-001 Q2W 70 mg (N=6)	AKR-001 Q2W 140 mg (N=6)
Glucose	4 (-12, 22)	5 (-11, 24)	-23, (-35, -9)	-20 (-32, -6)	-3 (-18, 15)	3 (-13, 22)	-6 (-20, 12)	-1 (-16, 18)
Insulin	-20 (-47, 23)	-28 (-53, 12)	-49 (-67, -22)	-50 (-68, -24)	-8 (-40, 43)	-23 (-50, 19)	-15 (-45, 31)	-28 (-54, 11)
C-peptide	-22 (-40, 1)	-29 (-46, -7)	-39 (-54, -20)	-45 (-58, -29)	4 (-20, 37)	-13 (-34, 14)	-4 (-27, 26)	-26 (-43, -2)
HOMA-IR	-18 (-49, 32)	-24 (-53, 24)	-60 (-75, -35)	-60 (-75, -36)	-12 (-46, 43)	-22 (-52, 28)	-21 (-52, 28)	-29 (-56, 16)
Glucagon	36 (8, 72)	13 (-11, 43)	13 (-11, 43)	24 (-2, 57)	7 (-16, 36)	0 (-21, 28)	46 (15, 86)	31 (3, 67)
Adiponectin	42 (-13, 131)	62 (-3, 172)	94 (18, 220)	143 (48, 300)	60 (-3, 165)	73 (5, 187)	65 (0, 174)	141 (45, 298)

QW, once weekly; Q2W, once every two weeks; N, number of subjects per group; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance;

Figure 12. Time course plots of fasting serum markers of glycemic control over the study duration with 70 mg QW (**A**) or 140 mg Q2W (**B**) AKR-001. Data presented as LS-mean + 90% CI.

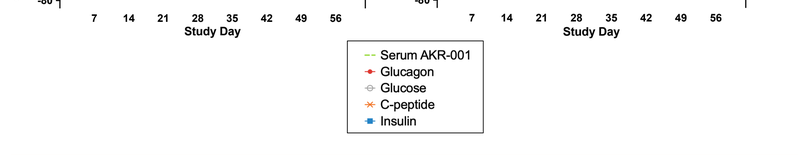


Figure 13. LS-mean (90% CI) placebo-corrected percent change from baseline AUC_{0-4hr} of metabolic markers following a mixed meal tolerance test on day 25 (QW cohorts) or day 18 (Q2W cohorts).

Treatment group	AKR-001 QW 7 mg (N=7)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=5)	AKR-001 Q2W 7 mg (N=6)	AKR-001 Q2W 21 mg (N=6)	AKR-001 Q2W 70 mg (N=6)	AKR-001 Q2W 140 mg (N=6)
Glucose	-3 (-20, 18)	6 (-13, 28)	-29 (-42, -14)	-30 (-42, -15)	-6 (-23, 15)	14 (-7, 39)	-10 (-26, 10)	-6 (-23, 14)
Insulin	-28 (-44, -8)	-26 (-43, -6)	-24 (-41, -3)	-49 (-60, -35)	-14 (-33, 11)	0 (-22, 29)	-23 (-40, -1)	-28 (-44, -7)
C-peptide	-14 (-27, 1)	-17 (-30, -3)	-15 (-28, 0)	-37 (-46, -26)	2 (-13, 21)	6 (-11, 25)	-7.4 (-22, 9)	-17 (-30, -2)
Glucagon	34 (14, 58)	3 (-13, 22)	11 (-6, 32)	22 (3, 44)	12 (-6, 32)	-10 (-24, 7)	32 (11, 57)	4 (-13, 23)
FFA	2 (-23, 36)	-10 (-33, 20)	-31 (-49, -8)	-19 (-39, 7)	-18 (-39, 10)	21 (-10, 62)	-4 (-28, 29)	31 (-3, 75)

AUC_{0-4hr}, area under the concentration-time curve in the four hours post-mixed meal tolerance test; QW, once weekly; Q2W, once every two weeks; N, number of subjects per group; FFA, free fatty acids

Figure 14. LS-mean (90% CI) placebo-corrected percent change from baseline for *post hoc* analysis of fasting serum biomarkers collected on day 25 after four QW doses.

	AKR-001 QW 7 mg (N=6)	AKR-001 QW 21 mg (N=6)	AKR-001 QW 70 mg (N=6)	AKR-001 QW 140mg (N=5)
apoA-1	21 (5, 39)	15 (0, 33)	-7 (-20, 7)	16 (0, 33)
apoB	0 (-19, 23)	-16 (-32, 4)	-42 (-53, -28)	-18 (-34, 1)
apoC-2	-48 (-70, -12)	-54 (-73, -22)	-55 (-74, -22)	-56 (-74, -25)
apoC-3	-24 (-45, 7)	-24 (-46, 6)	-46 (-62, -24)	-46 (-61, -24)
Lp(a)	-4 (-26, 26)	-1 (-25, 30)	9 (-17, 43)	11 (-16, 46)
C4	276 (69, 737)	54 (-32, 248)	36 (-40, 206)	47 (-34, 230)
ANGPTL4	-18 (-33, 0)	-30 (-43, -14)	-13 (-29, 7)	-9 (-26, 12)

apoA-1, apolipoprotein A-1; apoB, apolipoprotein B; apoC-2, apolipoprotein C-2; apoC-3, apolipoprotein C-3; Lp(a), lipoprotein(a); C4, 7α-hydroxy-4-cholesten-3-one; ANGPTL4, angiopoietin-like 4

Figure 15. Model-predicted effect of AKR-001 on markers of glycemic control and lipid metabolism, after overnight fast, **A**. insulin, **B**. C-peptide, **C**. glucose, **D**. HDL-C, **E**. non-HDL-C, **F**. triglycerides, over the range of AKR-001 concentrations at all timepoints measured following administration of 7-140 mg QW or Q2W doses. Shading represents 90% confidence interval.

Key Takeaways:
- Delivering total exposure of AKR-001 by Q2W dosing equivalent to QW dosing improved lipoprotein profiles but failed to improve markers of glycemic control
- QW dosing of AKR-001 improved post-prandial glucose metabolism and reduced adipose tissue lipolysis
- QW dosing of AKR-001 reduced serum triglyceride, apoB, and apoC-3, independent risk factors for cardiovascular disease—the leading cause of mortality for NASH patients

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