TAS2R Agonist ARD-101 Attenuates Weight Gain in Mice and Reduces Hunger in Adults with Obesity

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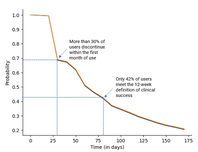
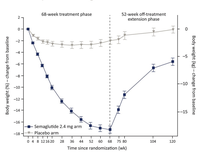
Introduction

GLP-1 based drugs are effective therapies for obesity but >50% of patients stop taking them within 3 months. Moreover, discontinuation can result in rapid weight regain and loss of metabolic benefits.

High Discontinuation Rates[1]



Rapid Weight Rebound[2]

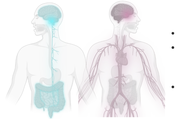


Aardvark is targeting the gut-brain axis to control both hunger and appetite. ARD-101 is >99% gut-restricted and modulates the local secretion of gut hormones, including CCK.

Hunger vs Appetite: Distinct Neural Pathways

HUNGER

- Penalty avoidance
- Mediated by local gut hormones like CCK
- Signaling through the Gut-Brain Axis



APPETITE

- Reward-based
- Mediated by circulating hormones like GLP-1
- Targeted systemically through the bloodstream

Taste receptors 2 (TAS2Rs) belong to the G protein-coupled receptor family and detect compounds in the oral cavity. TAS2Rs are also expressed on gastrointestinal enteroendocrine cells, where activation modulates the release of gut-derived peptide hormones involved in the satiation of both hunger and appetite.

We developed a novel oral formulation of the TAS2R agonist **denatonium acetate monohydrate (DA)**, called **ARD-101**, designed to deliver DA directly to the gastrointestinal tract while avoiding oral TAS2Rs.

We are investigating the synergistic effect of ARD-101 combined with a dipeptidyl-peptidase-4 (DPP-4) inhibitor, sitagliptin.

Study 1: ARD-101 Attenuates Weight Gain in Mice on HFD Compared to Vehicle

Table 1. Study 1 Animal Grouping and Dosing

Group	N	Treatment	Administration	Dose
1	12	Vehicle	PO, BID	-
2	12	ARD-101	PO, BID	20 mg/kg
3	12	ARD-101	PO, BID	40 mg/kg
4	12	ARD-101	PO, BID	80 mg/kg

PO: Oral, BID: Twice Daily

Figure 1. Study 1 Schema[3]

Body weight, food, and water consumption were evaluated three times weekly starting at Day 0.

Figure 2. Body Weight Changes in Mice Given HFD, Treated with ARD-101 or Vehicle Over 8 Weeks[4]

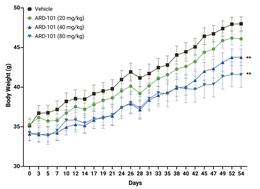


Figure 3. Percent Weight Gain Normalized to Vehicle[5]

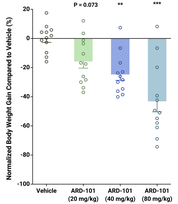


Table 2. Change in Metabolic Biomarker Levels from Baseline

	Glucose	Insulin	LDL	TG	TC
Vehicle	52.2	12.3	72.3	-0.5	122.4
ARD-101 (20 mg/kg)	25.8	4.2	85.8	1.1	84
ARD-101 (40 mg/kg)	7.8	3.7	99.1	6.9	20.1
ARD-101 (80 mg/kg)	23.6	3.1	66.9	-19.6	57.2

Glucose (mg/dL); Insulin (ng/mL); LDL (Low-density lipoprotein, mg/dL); TG (Triglyceride, mM); (Total cholesterol, µg/µL)

Study 2: Combination of ARD-101 & DPP-4 Inhibitor Augments Weight Loss in DIO Mice

Table 3. Study 2 Animal Grouping and Dosing

Group	N	Treatment	Administration	Dose
1	9	Vehicle	PO, QD	-
2	9	ARD-101	PO, QD	75 mg/kg
3	9	ARD-101	PO, QD	75 mg/kg
		Sitagliptin Diet	Ad libitum	6 g/kg diet
4	7	Sitagliptin Diet	Ad libitum	6 g/kg diet

PO: Oral, QD: Once Daily

Figure 4. Study 1 Schema[7]

Body weight, food, and water consumption were evaluated 2-3 times weekly, starting at Day 0.

Figure 5. Weight Changes in DIO Mice Treated with Vehicle, Mono- and Combo- ARD-101 and Sitagliptin over 30 Days[6]

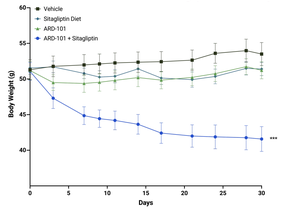
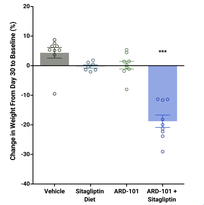


Figure 6. Percent Body Weight Change from Day 30 to Baseline[8]



Study 3: Combination of ARD-101 & DPP-4 Inhibitor Mitigates Weight Regain After GLP-1RA Discontinuation

Table 4. Phase 2 Animal Grouping and Dosing Regimen

Group	N	Treatment	Administration	Dose
1	8	Vehicle	PO, QD	-
2	8	Tirzepatide	SQ, QD	1 nmol/kg
3	8	Tirzepatide	SQ, QD	10 nmol/kg
4	8	ARD-101	PO, QD	75 mg/kg
5	8	ARD-101	PO, QD	75 mg/kg
		Sitagliptin Diet	Ad libitum	6 g/kg diet
6	8	ARD-101	PO, QD	75 mg/kg
		Tirzepatide	SQ, QD	1 nmol/kg
7	8	ARD-101	PO, QD	75 mg/kg
		Sitagliptin Diet	Ad libitum	6 g/kg diet
		Tirzepatide	SQ, QD	1 nmol/kg

PO: Oral, SQ: Subcutaneous, QD: Once Daily

Figure 7. Study 3 Schema[7]

Body weight, food, and water consumption were evaluated 2-3 times weekly, starting at Day 0.

Figure 8. Body Weight Changes in DIO Mice Treated with Tirzepatide and Post-tirzepatide Dosing Paradigm[9]

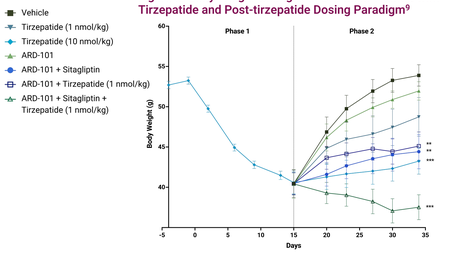


Figure 9. Percent Body Weight Change in Phase 2[10]

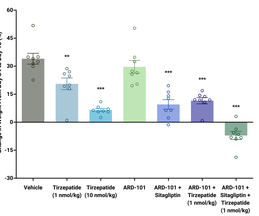


Figure 10. Terminal Values of Fat and Lean Mass in Dosing Paradigms[11]

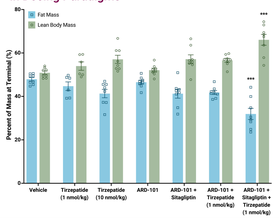


Figure 11. Intraperitoneal Glucose Tolerance Test (IPGTT)

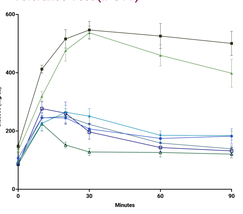
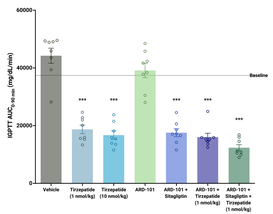
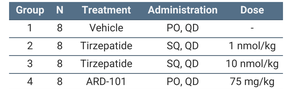


Figure 12. IPGTT: Total Area Under the Curve[12]



Phase 2 Study: Multi-dimensional Benefits Independent of Weight Loss

Figure 13. Phase 2 Clinical Study



A Phase 2, Placebo-Controlled, Randomized, Blinded Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of ARD-101 in Adults With Obesity (NCT05121441).

Table 6. Demographic and Baseline Characteristics of Pilot Phase 2 Clinical Study of ARD-101 in Adults with Obesity

Parameter	ARD-101 N=14[18] (%)	Placebo N=6[18] (%)	Overall N=20[15] (%)
Age	57 (12) [38, 75]	49 (9) 35, 59]	55 (12) [35, 75]
Sex			
Female	10 (71)	3 (50)	13 (65)
Male	4 (29)	3 (50)	7 (35)
Race			
Asian	2 (14)	2 (33)	4 (20)
Black or African American	3 (21)	0 (0)	3 (15)
White	9 (64)	4 (67)	13 (65)
Ethnicity			
Hispanic or Latino	1 (7.1)	1 (17)	2 (10)
Non-Hispanic or Latino	13 (93)	5 (83)	18 (90)
Height at Baseline (cm)	167 (9) [157, 187]	169 (11) [159, 188]	168 (10) [157, 188]
Weight at Baseline (kg)	95.4 (12.4) [80.4, 126.0]	101.6 (23.8) [76.8, 137.4]	97.3 (16.2) [76.8, 137.4]
BMI at Baseline (kg/m^2)	34.1 (3.6) [28.5, 38.4]	35.2 (5.5) [29.6, 44.9]	34.5 (4.1) [28.5, 44.9]

BMI: Body mass index

Table 5. Adverse Events Considered Related to ARD-101 (N=14)[13]

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	All Grades[14]
Acid Reflux	1	--	--	2 (14%)
Transient Nausea	1	--	--	

Figure 14. Effect of ARD-101 on Body Weight in Adults with Obesity

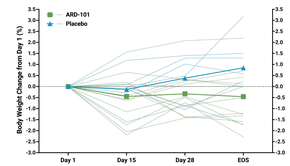
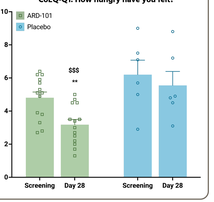


Figure 15. Effect of ARD-101 on Hunger-related Score in Adults with Obesity[16]



Conclusions

- In the weight prevention mouse model, ARD-101 demonstrated **a significant attenuation of weight gain over an eight-week period.**
- In DIO mice, **ARD-101 + sitagliptin reduced BW by ~19%**, comparable to high-dose tirzepatide.
- In DIO mice, **ARD-101 + sitagliptin achieved weight maintenance** post tirzepatide, and **~30% weight loss when combined with micro-dose tirzepatide.**
- Well tolerated with **no serious adverse events in Phase II clinical study in adults with obesity.**
- ARD-101 led to a trend of **weight control and metabolic improvements in participants** with elevated baseline metabolic parameters and **significantly reduced self-reported hunger and food craving** as assessed by the CoEQ.

Future Human Studies

Weight Maintenance

Potential maintenance-phase solution as an **off-ramp for GLP-1RA therapy responders** → **POWER Trial**

Weight Loss

Potential **oral alternative or adjunct** for patients who are hesitant, intolerant, and/or unresponsive to GLP-1RA therapy → **STENGTH Trial**

References & Footnotes

1. Real-World Trends in GLP-1 Treatment Persistence and Prescribing for Weight Management Blue Health Intelligence, Issue Brief May 2024
2. Withdrawal of Semaglutide: The STEP 1 Trial Extension. Diabetes Obes Metab. 2022;24:1553– 1564.
3. Mice arrived on a Standard Diet (2018 Teklad Global 18% Protein, Inotiv, Inc., West Lafayette, IN) and then were switched to a High-fat Diet (HFD, 60% kcal from fat; Research Diets No. D12492, Research Diets, Inc., New Brunswick, NJ.)
4. ** $P < 0.01$, vs the vehicle group at Day 54
5. ** $P < 0.01$ and *** $P < 0.001$, vs the vehicle group
6. *** $P < 0.001$, vs the vehicle group at Day 30
7. IPGTT: Intraperitoneal Glucose Tolerance Test
8. *** $P < 0.001$, vs the vehicle group
9. ** $P < 0.01$, *** $P < 0.001$, and **** $P < 0.0001$, vs the vehicle group at Day 34
10. ** $P < 0.01$ and *** $P < 0.001$, vs the vehicle group
11. *** $P < 0.001$, vs the vehicle group
12. *** $P < 0.001$, vs the vehicle group
13. AARD-201 clinical trial data. Company internal data on file.
14. Denominator: N=14 subjects dosed with ARD-101 for 28 days
15. Mean (SD), [min, max] for continuous variables; n (%) for categorical variables are presented.
16. ** $P < 0.01$, vs placebo at Day 28. $$$ $P < 0.001$ vs Screening within the ARD-101 group

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ObesityWeek, November 4-7, 2025