Obesity Drug Market Update

July 9, 2025

STIFEL | Healthcare

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ADA Clinical Update: Emerging Obesity Data

Oral GLP-1 Agonists
(monotherapy)

ACHIEVE-1 Study: Lilly's Orforglipron in Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

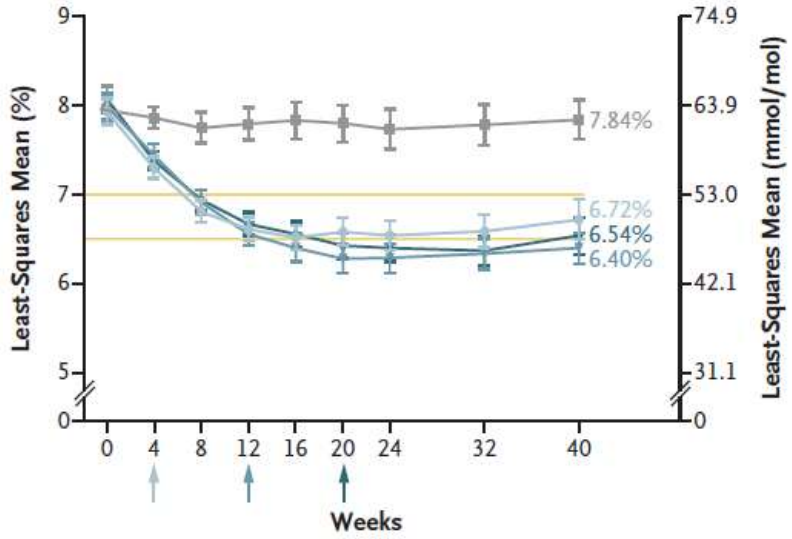
June 21, 2025

ORIGINAL ARTICLE

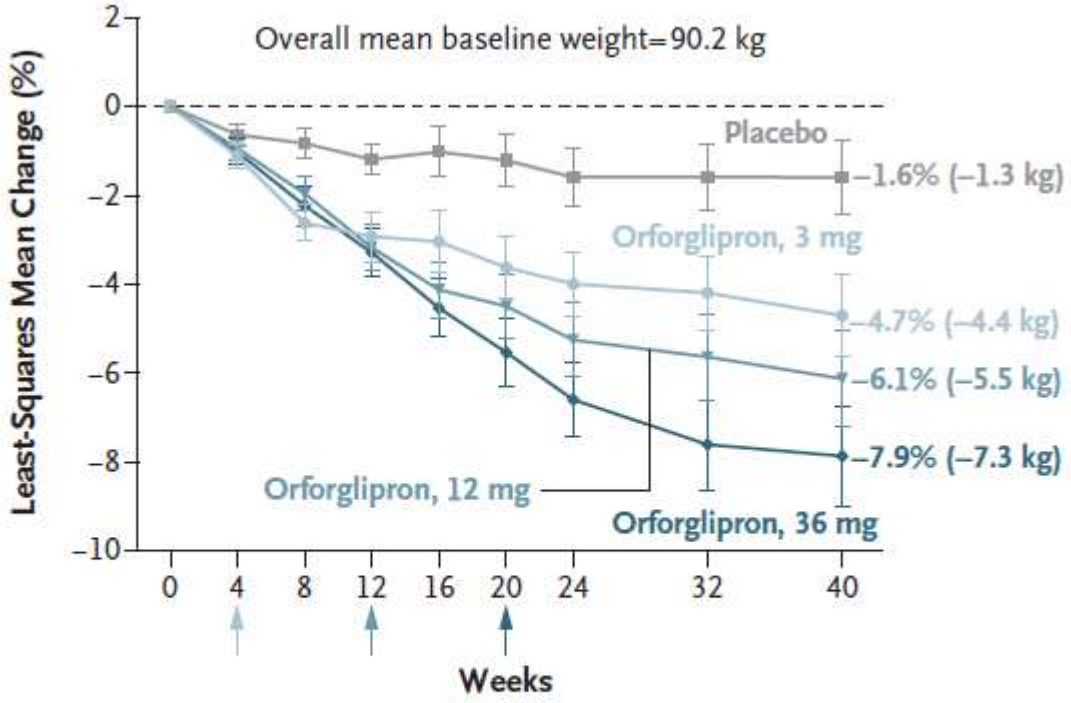
Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

J. Rosenstock,[1] S. Hsia,[2] L. Nevarez Ruiz,[3] S. Eyde,[4] D. Cox,[4] W.-S. Wu,[4] R. Liu,[4] J. Li,[4] L. Fernández Landó,[4] M. Denning,[4] L. Ludwig,[4] and Y. Chen,[4] for the ACHIEVE-1 Trial Investigators*

B Glycated Hemoglobin Level over Time (MMRM analysis)



B Percent Change in Body Weight over Time (MMRM analysis — efficacy estimand)



No. of Participants

Placebo	138	134	130	128	124	115	108	100	96
Orforglipron, 3 mg	143	141	139	133	133	132	133	123	119
Orforglipron, 12 mg	137	133	131	130	126	122	123	120	111
Orforglipron, 36 mg	141	138	137	135	134	130	128	121	119

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2505669

Orforglipron: Manageable Side Effects / Low Dropout Rate

Event	Orforglipron, 3 mg (N=143)	Orforglipron, 12 mg (N=137)	Orforglipron, 36 mg (N=141)	Placebo (N=138)	Overall (N=559)
	number of participants (percent)				
Any adverse event emerging during treatment	102 (71.3)	111 (81.0)	119 (84.4)	102 (73.9)	434 (77.6)
Any serious adverse event	8 (5.6)	7 (5.1)	4 (2.8)	5 (3.6)	24 (4.3)
Death†	2 (1.4)	1 (0.7)	0	1 (0.7)	4 (0.7)
Adverse event leading to discontinuation of orforglipron or placebo	8 (5.6)	6 (4.4)	11 (7.8)	2 (1.4)	27 (4.8)
Gastrointestinal adverse event leading to discontinuation of orforglipron or placebo	4 (2.8)	3 (2.2)	8 (5.7)	0	15 (2.7)
Adverse events that emerged during treatment and occurred in ≥5% of participants in any trial group					
Diarrhea	27 (18.9)	29 (21.2)	36 (25.5)	12 (8.7)	104 (18.6)
Dyspepsia	15 (10.5)	28 (20.4)	21 (14.9)	9 (6.5)	73 (13.1)
Nausea	18 (12.6)	25 (18.2)	23 (16.3)	3 (2.2)	69 (12.3)
Hyperglycemia	10 (7.0)	6 (4.4)	9 (6.4)	37 (26.8)	62 (11.1)
Constipation	12 (8.4)	23 (16.8)	19 (13.5)	5 (3.6)	59 (10.6)
Abdominal distention	6 (4.2)	7 (5.1)	16 (11.3)	11 (8.0)	40 (7.2)
Decreased appetite	5 (3.5)	14 (10.2)	16 (11.3)	3 (2.2)	38 (6.8)
Vomiting	7 (4.9)	9 (6.6)	20 (14.2)	2 (1.4)	38 (6.8)
Headache	8 (5.6)	5 (3.6)	10 (7.1)	6 (4.3)	29 (5.2)

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2505669

Orforglipron side effects appear reasonably benign with a vomiting rate under 15%.

Impressive for an oral treatment (and considering other orals).

Given the benefit of this drug for the patients tested in the study, the adverse events appear well worth bearing.

Importantly, whispers that orfo might be associated with potential serious risks such as causing liver damage or cardiac risk were not supported in any way by this study. The rate of SAE's was higher in placebo than the highest dose arm.

Lilly Pitch: Orforglipron Has Potential to Make Significant Impact on Public Health

Broad Development Plan		Scalable Supply	Commercial Potential
Obesity *2 Studies*	Type 2 Diabetes *5 Studies*	Separate Small Molecule Manufacturing Footprint	Once-Daily Pill
Obstructive Sleep Apnea	Hypertension	Investment At-Risk to Support Global Launch	No Food or Water Restrictions
Maintenance	Other	No Cold-Chain Storage Requirement	International Reach and Scale

Source: https://investor.lilly.com/static-files/36604492-7d65-4649-bc20-f7b4372c2b2b

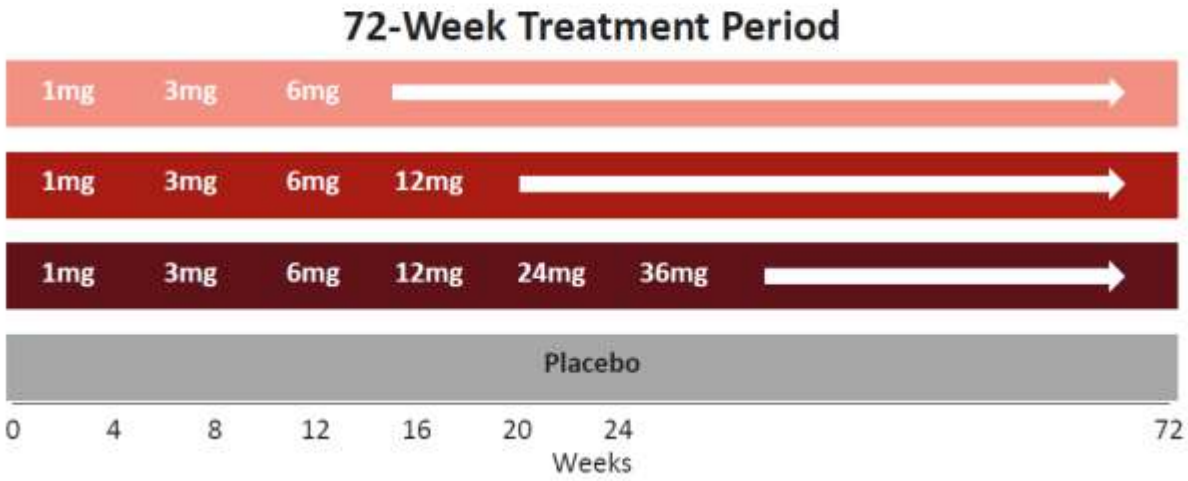
Investigator Comment

“There is always room for innovation. This is a small-molecule nonpeptide that has potential to open access to more people because it is easier to take and is simpler to produce, and in theory should be less expensive.”

Julio Rosenstock, M.D., FACE

Topline Phase 3 Orforglipron Data for Obese Patients Scheduled for Q3 2025

Trial Design



- Dose escalation every 4 weeks until reaching target dose of 6mg, 12 mg or 36 mg
- Topline results Q3 2025

Key Considerations

Baseline Characteristics

Weight (kg)	103.2
BMI (kg/m^2)	37.0
Age (years)	45.1
Female (%)	64.2%

- Orforglipron could provide an easy-to-use option leveraged across a range of care settings
- Potential to demonstrate efficacy and tolerability within the range of injectable GLP-1 medicines

Source: https://investor.lilly.com/static-files/36604492-7d65-4649-bc20-f7b4372c2b2b

Hengrui (Kailera) Data at ADA on 204 pt Oral GLP-1 Study (HRS-7535)

RESULTS

Patients

- 204 patients (86.8%, range: 79.2%-93.5%) completed the 36-week treatment period **(Figure 2)**.
- At baseline, the mean BMI was 32.5 kg/m² and the mean body weight was 91.6 kg; 48.5% of the patients were female **(Table 1)**.

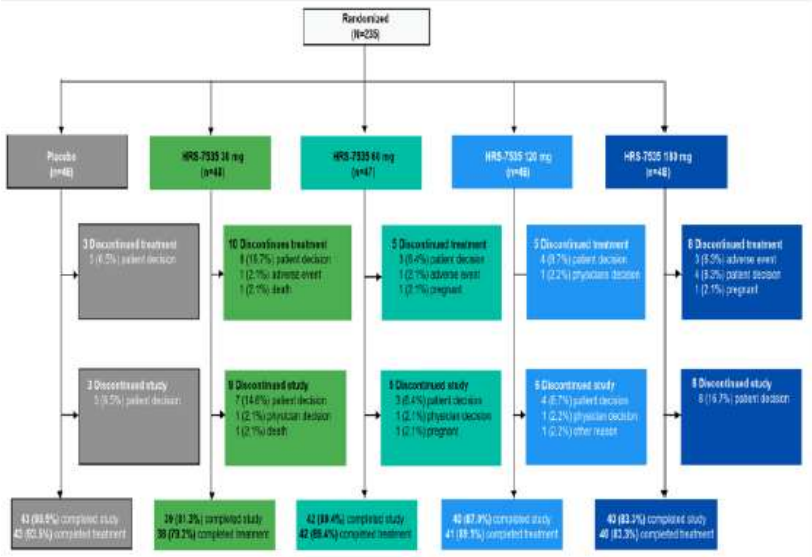


Figure 2. Trial profile

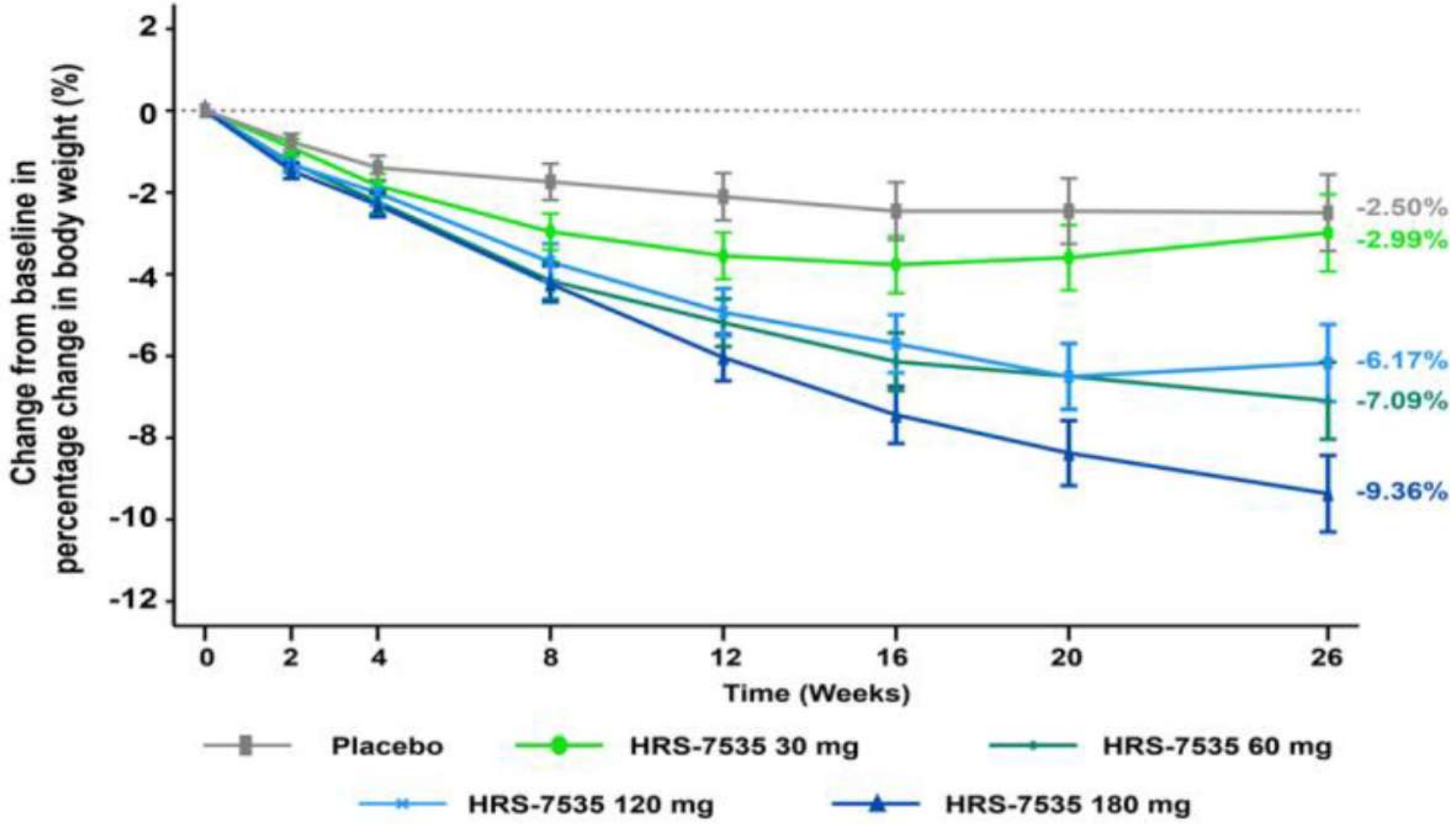
Table 1. Demographics and baseline characteristics.

Characteristics	Placebo (n=46)	HRS-7535 once daily 30 mg (n=48)	60 mg (n=47)	120 mg (n=46)	180 mg (n=48)
Age (years)	35.1 ± 8.2	34.1 ± 8.3	31.5 ± 7.3	33.2 ± 6.6	33.5 ± 10.2
Female sex, n (%)	22 (47.8)	23 (47.9)	23 (48.9)	22 (47.8)	24 (50.0)
Body weight (kg)	90.4 ± 13.1	91.7 ± 14.6	93.9 ± 13.9	90.2 ± 13.7	91.7 ± 14.3
BMI (kg/m²), n (%)	32.4 ± 2.6	32.7 ± 3.4	32.8 ± 3.2	32.3 ± 3.2	32.3 ± 2.5
≥32.5	20 (43.5)	20 (41.7)	22 (46.8)	20 (43.5)	21 (43.8)
<32.5	26 (56.5)	28 (58.3)	25 (53.2)	26 (56.5)	27 (56.3)
Waist circumference (cm)	104.3 ± 9.5	103.9 ± 10.8	104.9 ± 9.5	103.2 ± 9.6	103.7 ± 8.5
HbA_{1c} (%) [a]	5.3 ± 0.3	5.3 ± 0.3	5.2 ± 0.3	5.3 ± 0.3	5.3 ± 0.3
FPG (mmol/L) [a]	5.6 ± 0.4	5.6 ± 0.5	5.5 ± 0.5	5.7 ± 0.5	5.6 ± 0.5
Fasting serum insulin (μIU/ml) [a]	144.48 ± 79.99	138.01 ± 70.07	146.74 ± 93.73	152.45 ± 90.62	131.16 ± 73.80
Total cholesterol (mmol/L)	4.92 ± 1.00	4.78 ± 0.85	5.03 ± 0.95	4.93 ± 0.94	4.88 ± 0.80
non-HDL-C (mmol/L)	3.78 ± 0.99	3.62 ± 0.87	3.89 ± 0.88	3.77± 0.91	3.72 ± 0.76
Triglycerides (mmol/L)	1.93 ± 0.99	1.69 ± 1.06	2.02 ± 2.31	1.94 ± 1.14	1.81 ± 0.91
SBP (mmHg)	120.5 ± 12.3	118.9 ± 11.2	118.3 ± 10.8	119.5 ± 11.6	118.3 ± 11.3
DBP (mmHg)	82.0 ± 9.6	81.4 ± 7.1	81.4 ± 8.0	81.1 ± 8.2	79.3 ± 8.5
Pulse rate (beats/min)	75.9 ± 8.4	78.7 ± 8.5	79.9 ± 9.6	79.5 ± 8.8	77.3 ± 8.8
eGFR (mL/min/1.73m²) [b]	112.1 ± 13.3	110.7 ± 13.2	112.9 ± 13.8	112.0 ± 14.0	113.5 ± 14.9

Note: Data are presented as n (%), mean ± standard deviation, or as otherwise indicated.
[a] Measurements in this table were obtained using local laboratory testing. [b] The estimated glomerular filtration rate (eGFR) was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.
non-HDL-C, non-high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate.

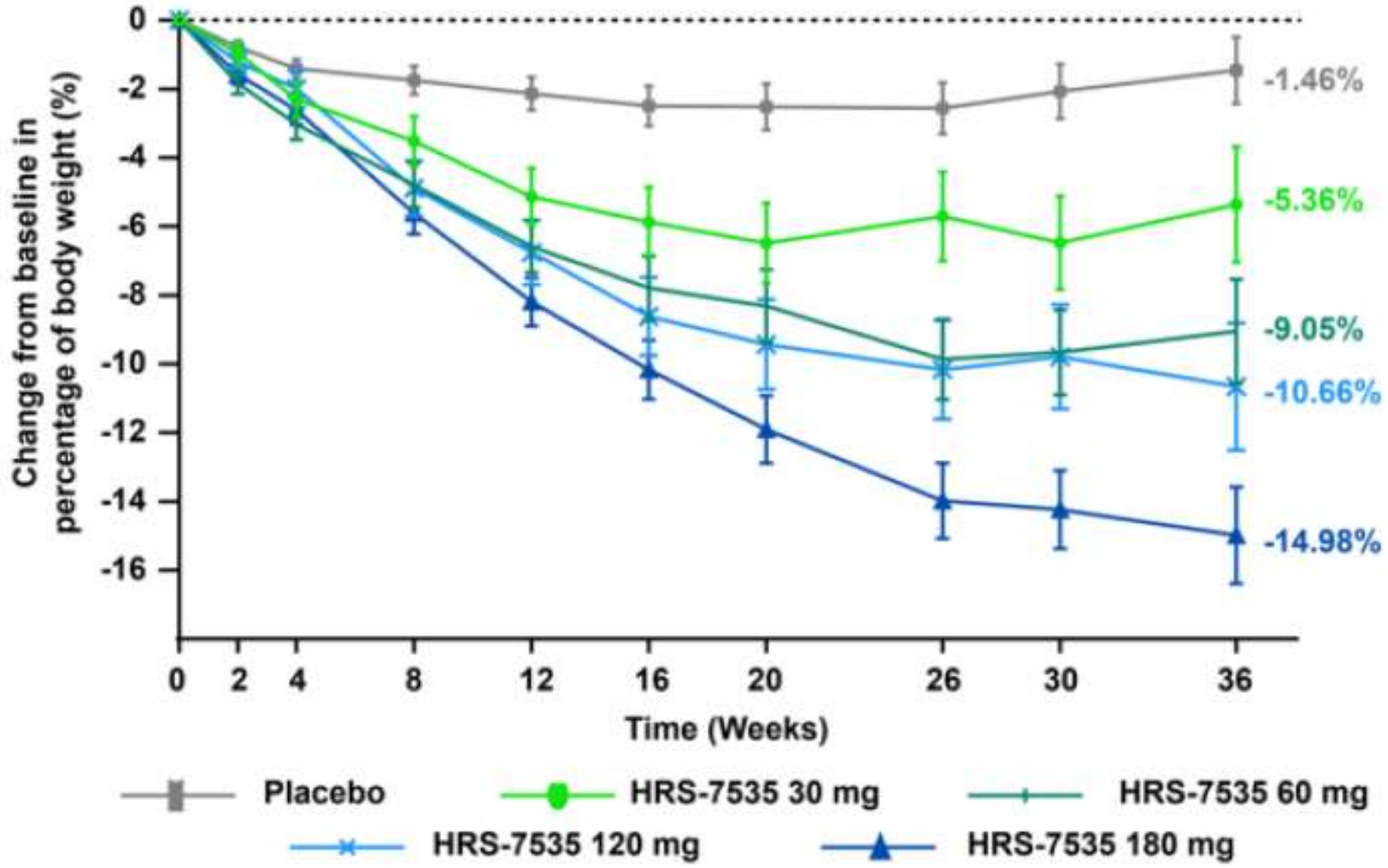
Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/837-P/159533/837-P-Efficacy-and-Safety-of-a-Novel-Oral-Small

6.8% Weight Loss with Hengrui/Kailera Oral HRS-7535 at 26 Weeks



Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/837-P/159533/837-P-Efficacy-and-Safety-of-a-Novel-Oral-Small

Much Higher Weight Loss on HRS-7535 Drug if Only Patients that Got Exposure to Drug are Included



This is an interesting post-hoc analysis which implies that not all patients get the same exposure to an oral GLP-1 but that those that do respond very well.

This seems to suggest that the drug could ultimately do much better than one sees in early datasets.

This analysis also makes one wonder how much exposure other drugs are getting.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/837-P/159533/837-P-Efficacy-and-Safety-of-a-Novel-Oral-Small

Regor's RGT-075 (Oral GLP-1 Agonist)

First Report on the Small-Molecule, Oral GLP-1 Receptor Agonist RGT-075 in Obesity: A Randomized, Placebo-Controlled Phase 2a POC 12-Week Study

785-P

Regor Therapeutics Group

Rosenstock J[1], Lender D[1], Crawford K[1], Guzman D[2], Raiser F[3], Sun F[4], Cai Q[4], Lin J[4], Liu F[5], Grimm M[5]

1.Velocity Research at Medical City Dallas. TX,USA; 2. Velocity Clinical Research at Los Angeles (Westlake), CA, USA; 3. Velocity Clinical Research at Omaha, NE, USA; 4. QL Regor Therapeutics Inc. Shanghai, China; 5. Regor Pharmaceutical Inc. MA, USA

Abstract

Background and Aims: GLP-1 RAs are highly effective peptides increasingly used for type 2 diabetes (T2D) and obesity management. However, mainly injectable options are available except for oral semaglutide. RGT-075 is a new, non-peptide, small molecule oral GLP-1 RA being developed as a treatment for adults with obesity.

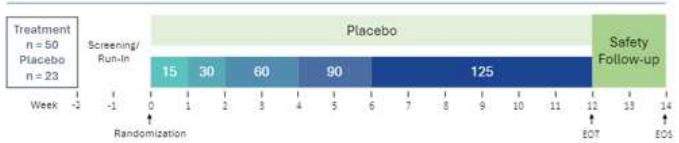
Materials and Methods: This phase 2a, randomized, double-blind trial (NCT06277934) involved adults with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with at least one comorbidity and no T2D (HbA1c < 6.5%). Participants (N=73) were randomly assigned to either 125 mg of RGT-075 or placebo once daily for 12 weeks, with a 6-week dose titration (from 15 to 125 mg QD) followed by a 6-week dose maintenance period (125 mg QD).

Results: Baseline characteristics were generally comparable between the groups (median age 50.0 yrs, Weight 103.9 kg, BMI 36.6 kg/m^2). Out of the total participants, 50 received RGT-075, and 23 received placebo. At week 12, the LS mean percentage change in body weight was -5.4% with RGT-075 compared to -0.45% with placebo ($p < 0.0001$). In addition, a significant and clinical meaningful reduction of systolic (-10.8 mmHg (placebo adjusted), $p = 0.0022$) and diastolic (-4.9 mmHg (placebo adjusted), $p = 0.0371$) blood pressure was observed. There was no pulse rate increases. The most frequently reported adverse events in the RGT-075 group were nausea (40%) and vomiting (24%), which were mild or moderate. No liver abnormalities or other serious adverse events related to RGT-075 were observed. The discontinuation rate due to adverse events (AEs) was 4% for both RGT-075 and placebo. The pharmacokinetic profile supported once-daily (QD) oral dosing. **Conclusion:** RGT-075, a small molecule oral GLP-1 RA, demonstrated a significant weight reduction with robust blood pressure changes and a safety profile consisted with the GLP-1 RA class. These findings support further clinical development of RGT-075.

Conclusion: RGT-075, a small molecule oral GLP-1 RA, demonstrated a significant weight reduction with robust blood pressure changes and a safety profile consisted with the GLP-1 RA class. These findings support further clinical development of RGT-075.

Study Design

Study Population: Obesity or Overweight without Type-2 Diabetes



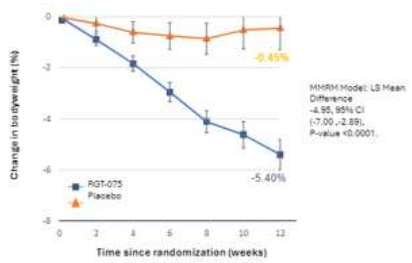
Demographics and Baseline Characteristics

	RGT-075 (N = 50)	Placebo (N = 23)
• Age (Years), Mean (SD)	50.0 (13.09)	50.8 (13.30)
• Sex, female (%)	82	74
• Race, white (%)	72	87
• Baseline Weight (Kg), mean (SD)	101.9 (16.4)	103.7 (17.0)
• BMI (Kg/m2), mean (SD)	37.1 (4.1)	37.1 (4.0)
• Baseline HbA1C (%), mean (SD)	5.68 (0.40)	5.61 (0.46)
• Patients (%) with baseline HbA1c (5.7-6.4%)	38	35

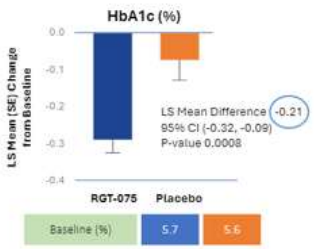
- **Key Inclusion Criteria:** Age ≥18 and ≤75, BMI ≥27 kg/m^2 and ≤45 kg/m^2, Stable body weight
- **Key Exclusion Criteria:** Diabetes

Efficacy

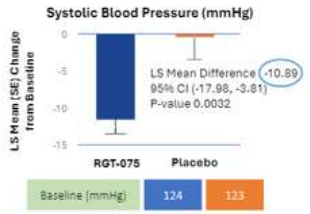
Body Weight Loss without Plateau

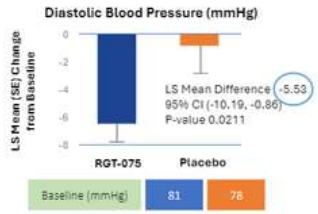


HbA1c Change



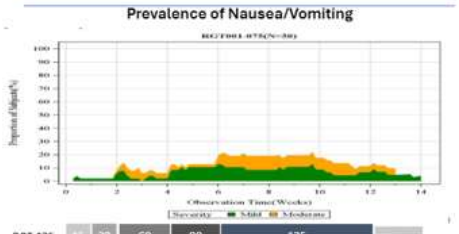
Blood Pressure Reduction





GI Adverse Events

Prevalence of Nausea/Vomiting



- Overall low prevalence of nausea and vomiting
- No drug-related drop-outs due to AEs (same rate as placebo)
- Tolerability improves within 4 weeks on target dose

Adverse Events that Occurred in ≥5% of Patients

Patients with Drug-related GI TEAEs	RGT-075 (N = 50)	Placebo (N = 23)
Nausea	40%	4%
Vomiting	24%	0%
Constipation	10%	9%

Well acceptable even with the relatively short titration (6 vs. 12 weeks)

Safety and Tolerability

Treatment Discontinuations

	RGT-075 (N = 50)	Placebo (N = 23)
Total Number of Patients		
Completed Treatment	84%	87%
Discontinued Treatment	16%	13%
Reason for Treatment Discontinuation		
Adverse Event	4%*	4%*
Death	0	0
Non-compliance with Study Drug	0	0
Non-compliance with Protocol	2%	0
Withdrawal by Subject	6%	9%
Lost to follow-up	4%	0

*All were due to GI AEs

Treatment-Emergent Adverse Events Were Mild or Moderate – No Serious AE

Percentage of Patients with TEAEs	RGT-075 (N = 50)	Placebo (N = 23)
Any TEAEs	68%	52%
Mild	66%	44%
Moderate	30%	30%
Severe	2%*	0%
Serious (SAE)	0%	0%
Leading to Dose Reduction	2%	0%
Leading to Withdrawal from Treatment	4%	4%

*Investigations: asymptomatic 42yo male with self-limited, nonspecific elevation of AST and CPK after heavy exercise. Not related to study drug.

Conclusions

RGT-075, a small molecule oral once daily dosing GLP-1R agonist

- Significant weight loss without reaching a plateau
- Meaningful blood pressure reduction within 12 weeks of treatment
- Tolerability and GI adverse event profile consistent with GLP-1 RA class
- These proof-of-concept findings support further clinical development of RGT-075, an oral small molecule, non-peptide GLP-1 RA

Clinical Trial Registration Number: NCT06277934

DISCLOSURES: 1-J. Rosenstock: Advisory Panel; Amgen Inc, Applied Therapeutics, Bayer Pharmaceuticals, Inc, Biomea Fusion, Corcept Therapeutics, Eli Lilly and Company, Hanmi Pharm. Co., Ltd., Novo Nordisk, Regeneron Pharmaceuticals, Regor Therapeutics, Roche Pharmaceuticals, Sanofi, Structure Therapeutics, Inc. and Zealand Pharma A/S. Research Support; Amgen Inc., Applied Therapeutics, AstraZeneca, Eli Lilly and Company, Merck & Co., Inc, Novartis AG, Novo Nordisk, Pfizer Inc, Regeneron Pharmaceuticals, and Sanofi.

FUNDING: The study was sponsored by Regor Pharmaceutical

Source: https://ada.apprisor.org/

MindRank MD001 Shows Solid Weight Loss with Oral GLP-1

HANGZHOU, China and LONDON, June 24, 2025 (GLOBE NEWSWIRE) -- MindRank, a clinical stage artificial intelligence (AI)-empowered drug discovery company, today announced positive topline results from a Phase 2b clinical trial of its proprietary AI-designed oral GLP-1 receptor agonist (GLP-1RA), MDR-001, in adults with obesity or overweight in China.

In this 24-week, randomized, placebo-controlled study, MDR-001 demonstrated clinically meaningful, dose-dependent weight reduction. Participants receiving MDR-001 achieved mean body weight reductions ranging from 8.2% to 10.3% (7.4-9.2 kg) compared to 2.5% (2.4 kg) in the placebo group ($p<0.00001$). Placebo-adjusted weight loss ranged from 7.1% to 7.8%, with 70.9% to 85.4% of participants achieving at least 5% weight loss and 34.5% to 48.1% achieving at least 10% weight loss.

In addition to weight reduction, MDR-001 delivered significant improvements in key cardiometabolic markers, including waist circumference, blood pressure, and lipid profiles, underscoring its potential as a comprehensive metabolic therapy.

MDR-001 was well tolerated, with no treatment-related serious adverse events (SAEs) reported. The most common treatment-emergent adverse events (TEAEs) were mild to moderate gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, which were predominantly observed during the initial 6-week dose-escalation period and resolved within 1 to 5 days.

Importantly, hepatic safety analyses showed no evidence of transaminase elevation, even among approximately 20% of participants with pre-existing liver impairment. In fact, ALT and AST levels were significantly reduced in the MDR-001 treatment groups compared to placebo. Additionally, no clinically relevant increases in heart rate were observed. The overall discontinuation rate due to TEAEs was only 0.8%.

Professor Linong Ji, Leading Principal Investigator of the study, Director of Endocrinology and Metabolism at Peking University People's Hospital, remarked: “MDR-001 has demonstrated compelling efficacy, tolerability, and metabolic benefit in this trial. Its oral formulation and favorable safety profile make it a highly attractive candidate for long-term obesity management, supports its progression to Phase 3 trials.”

Source: https://www.globenewswire.com/news-release/2025/06/24/3104170/0/en/MindRank-Announces-Positive-Phase-2b-Results-for-AI-Designed-Oral-GLP-1-Receptor-Agonist-MDR-001-in-Adults-with-Obesity-or-Overweight.html

Ascletis SAD Data Shows Reasonable Safety and Good PK

Poster number: 750-P

ASC30, an Oral GLP-1R Biased Small Molecule Agonist in Participants with Obesity—A First-in-Human Single Ascending Dose Study

Jinzi Jason Wu and Vanessa Wang. Ascletis Pharma (China) Co., Limited, Hong Kong

① Introduction

ASC30 is a fully biased oral GLP-1R small-molecule agonist that does not recruit β-arrestin and is more potent than orforglipron (Table 1.). It is designed as one small molecule for both once-daily oral and once-monthly subcutaneous administration to treat obesity and related metabolic disorders.

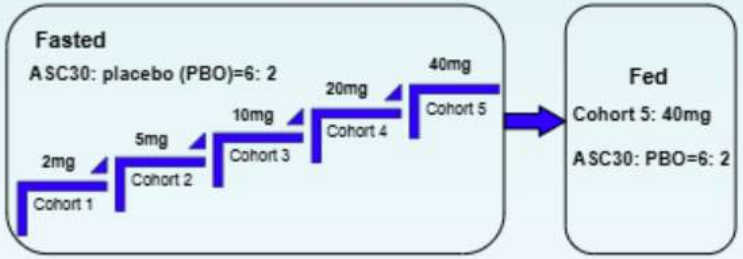
Table 1. cAMP activation in Flp-In-293-GLP1R cells expressing human GLP-1R (Head-to-head study)

Compound	cAMP activation EC_{50}, nM (mean±SD)	β-arrestin 2 EC_{50}, nM (mean±SD)
Orforglipron	0.0180 ± 0.0043	>30,000
ASC30	0.0088 ± 0.0017	>30,000

② Methods

This was a randomized, double-blind, placebo-controlled single ascending dose FIH study of ASC30 tablet (NCT06680440, Figure 1.).

Figure 1. FIH SAD Study Design



American Diabetes Association. 85TH SCIENTIFIC SESSIONS CHICAGO, IL | JUNE 20-23, 2025

Scan QR code for an interactive mobile-friendly copy of the poster

③ Results

Key findings in ASC30 tablet SAD PK

- Mean half-lives (T1/2) support once-daily oral dosing (Table 2.).
- ASC30 pharmacokinetics show dose proportional across the range of 2 mg to 40 mg tested. (Table 2. and Figure 2.). No statistically significant difference between fasted and fed cohorts.

Table 2. ASC30 tablet SAD PK profile in humans

	Cohort 1 OB (n=6)	Cohort 2 OB (n=6)	Cohort 3 OB (n=6)	Cohort 4 OB (n=6)	Cohort 5 OB (n=6)
Fasted Condition	Fasted	Fasted	Fasted	Fasted	Fasted
Dose level (mg)	2	5	10	20	40
$T_{1/2}$ (hr)	11.1±1.1	56.4±36.1	43.7±4.5	33.9±9.3	39.3±15.5
T_{max} (hr) Median (Min, Max)	7.0 (4.0,8.0)	5.0(4.0,6.0)	5.0(4.0,6.0)	6.0(4.0,8.0)	6.0(6.0,8.0)
C_{max} (ng/mL)	8.5±2.3	48.8±20.5	73.4±27.3	209.3±56.1	409.0±161.9
AUC_{0-24} (hr*ng/mL)	88.2±20.4	450.0±142.6	746.9±360.9	2,250.9±648.8	4,251.7±1,246.5
AUC_{last}* (hr*ng/mL)	109.0±24.1	691.1±319.4	1,110.5±561.9	3,058.3±787.8	6,776.5±1,969.0
AUC_{inf} (hr*ng/mL)	131.3±24.8	889.6±674.7	1,175.9±742.8	3,098.6±891.1	7,283.9±2,874.9

Note: *AUC_{last}: Cohort 1: calculated from 0 to 36 or 48 hours; Cohort 2: calculated from 0 to 96 or 120 hours; Cohort 3-5: calculated from 0 to 120 hours. OB = obesity.

Figure 2. ASC30 oral daily tablet PK curves

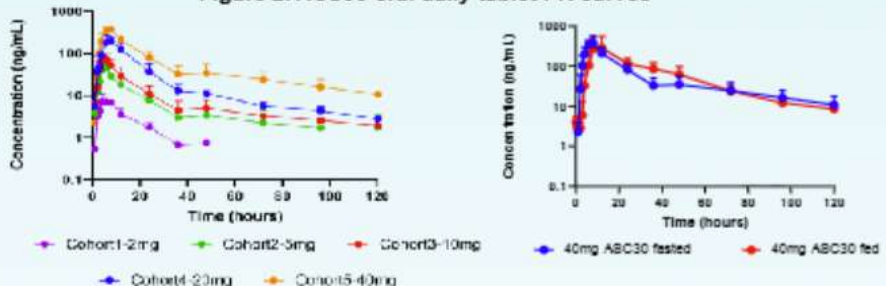
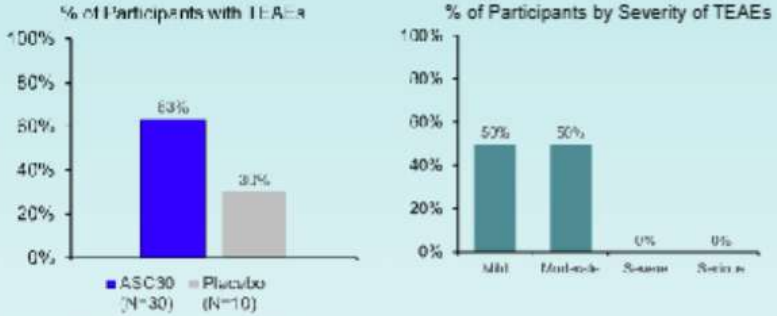


Figure 3. ASC30 tablet SAD Safety Profile



Key findings in safety profile

- TEAEs were higher than placebo, with all mild/moderate in severity (Figure 3.).
- No SAEs, deaths, or discontinuations.
- No liver enzyme elevations, QTc prolongation, or other clinically significant ECG/lab changes.
- GI TEAEs were mild or moderate, consistent with other incretin therapies. No vomiting at 2 mg and 5 mg doses.

④ Conclusions

- ASC30 tablet was well tolerated, with low GI TEAEs and no vomiting at 2 or 5 mg.
- ASC30 demonstrated high potency and a superior, dose-proportional PK profile supporting once-daily oral dosing.
- In MAD study, ASC30 tablet achieved up to 6.3% weight loss in 4 weeks in participants with obesity*.
- In participants with obesity, ASC30 SQ injection exhibited a half-life of 36 days, supporting once-monthly dosing*.

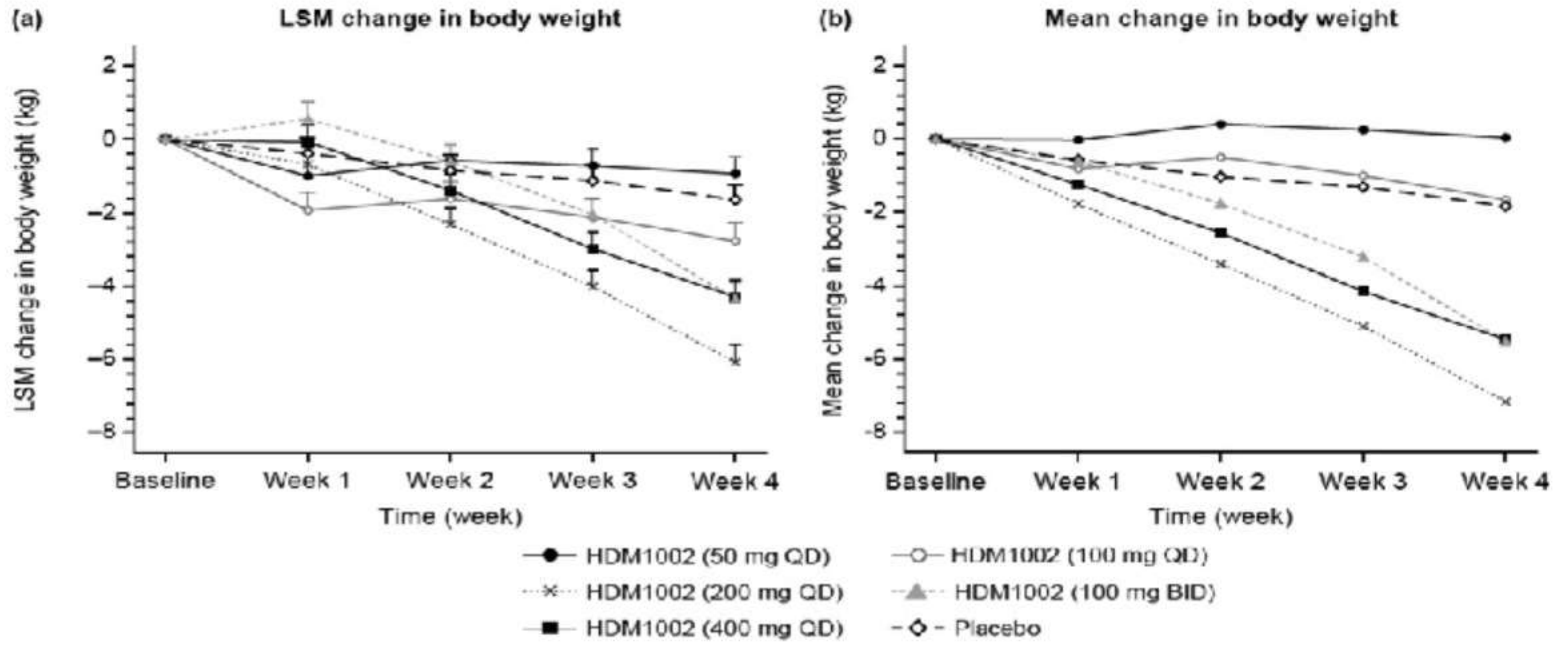
* Detailed results will be presented at future conferences.

Source: https://www.ascletis.com/data/upload/ueditor/20250618/ASC30_poster_@_ADA_2025.pdf

ADA: Huadong Medicine HDM1002 Small Molecule GLP-1 Agonist

Preliminary Effect on Body-Weight Reduction

Figure. LSM change from baseline in bodyweight during treatment (a) and absolute mean change from baseline in bodyweight during treatment (b)



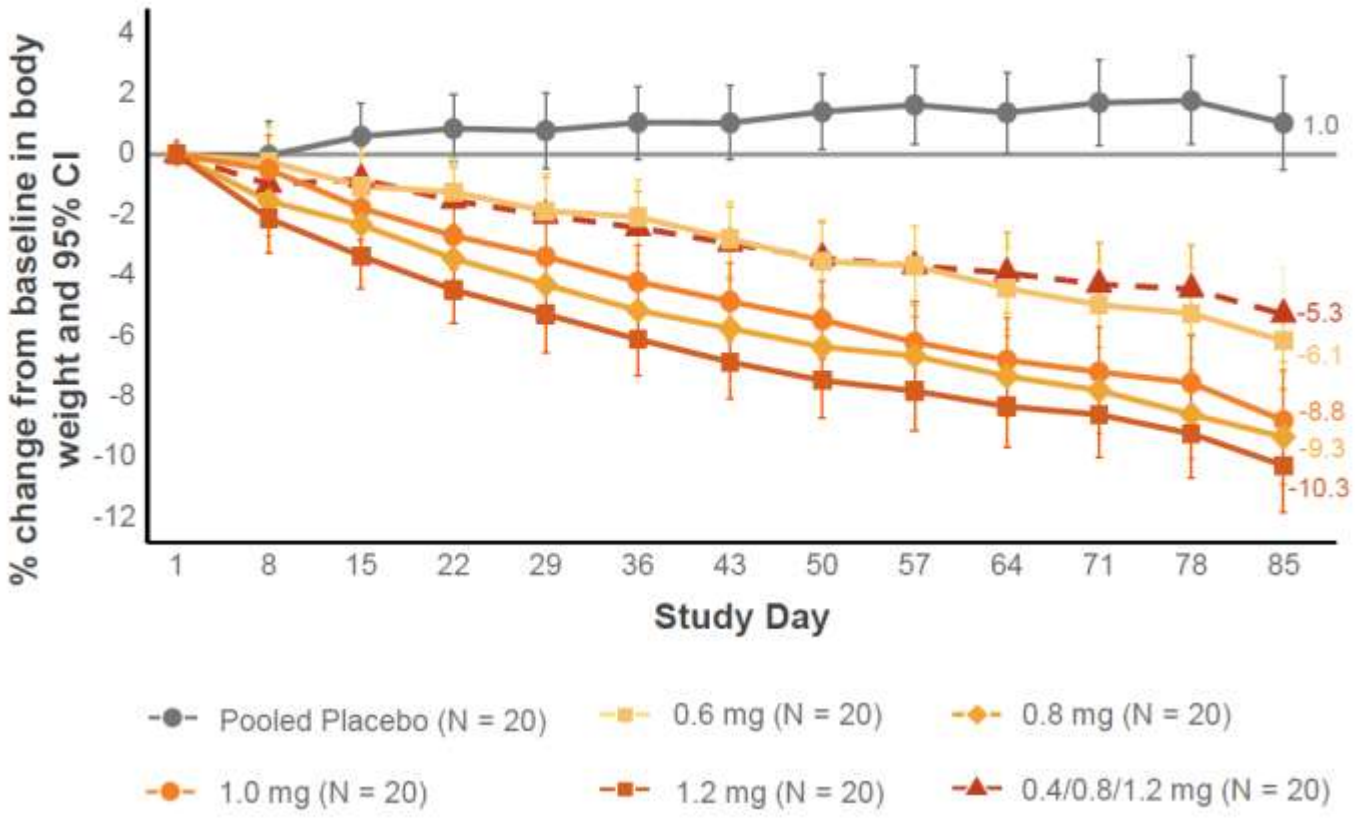
- Dose-dependent body weight reduction was observed on Day 29.
- Dose groups of 200 mg QD, 100 mg BID and 400 mg QD showed greater absolute and percent decreases in body weight compared to placebo group ($p<0.001$). The LSMean (95% CI) percentage changes from baseline were -6.843% (-8.023, -5.662), -5.076% (-6.213, -3.939) and -4.902% (-6.039, -3.764), respectively.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/737-P/160213/737-P-HDM1002-in-Chinese-Adults-with-Overweight-or

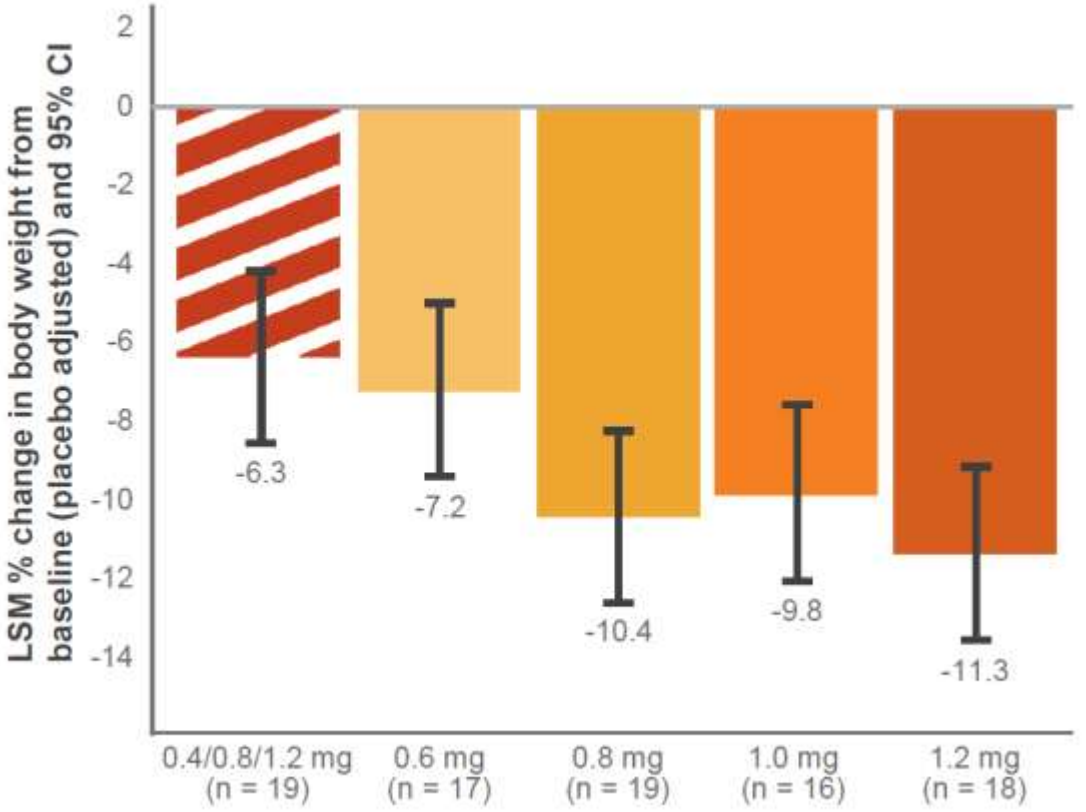
SubQ GLP-1 Agonists (monotherapy)

Weight Loss at ADA from Metsera's MET-097i Fully Biased, Ultra-long Acting GLP-1 Receptor Agonist

MEAN % CHANGE FROM BASELINE IN BODY WEIGHT ACROSS COHORTS



MEAN PLACEBO-ADJUSTED % CHANGE IN BODY WEIGHT AT DAY 85



Results are based on a mixed effects repeated measures (MMRM) model where treatment group, visit, treatment – by visit interaction, and baseline body weight are fixed effects .

Source: https://investors.metsera.com/static-files/3c3a57f8-8fe9-46f1-9fb2-d174833fea8e

Metsera GLP-1 Poster at ADA

A 12-Week Trial of MET-097: A Potent and Ultra-Long Acting GLP-1 Receptor Agonist

Robert Stoekenbroek, Jenna Bisch, Sheela Kolluri, Mustafa Noor, Jason Mallory, Rory Cunningham, Brian Hubbard, and Steven P. Marso

Metsera, Inc. New York, NY and London, UK

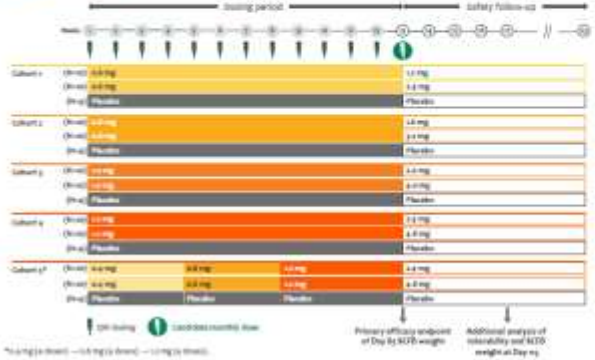
BACKGROUND

- Nutrient-stimulated hormone (NuSH) analogs are highly effective and have the potential to improve population health
- Yet, their utilization is limited relative to the addressable patient population due to the need for weekly injections, complex and prolonged titration regimens, tolerability issues, and access limitations[1]
- MET-097 is a fully biased, ultra-long acting glucagon-like peptide-1 receptor (GLP-1R) agonist, with the potential for monthly dosing and weekly dosing with simplified or no titration
- This study evaluated the efficacy, safety, tolerability, and pharmacokinetics (PK) of 12 once-weekly (QW) MET-097 doses with and without dose titration
- We also evaluated the safety, tolerability, and efficacy of a single candidate monthly dose

METHODS

- This was a randomized, double-blind, placebo-controlled Phase 2a clinical trial conducted at 3 sites and in adult participants with obesity or overweight but otherwise healthy (NCT06857617)
  - Key inclusion criteria included body mass index (BMI) of 27 to 38 kg/m² and estimated glomerular filtration rate (eGFR) of ≥90 mL/min
  - Key exclusion criteria included diabetes, pregnant/lactating, seated blood pressure of >160/95 mmHg, and elevated resting pulse of >100 bpm
- A total of 120 participants were assigned to 5 cohorts (randomization within each cohort) with 20 MET-097 and 4 placebo participants per cohort receiving 12 QW doses and a single candidate monthly 13th dose (2x or 4x the weekly dose)
- The primary efficacy endpoint was percent change from baseline (%CFB) body weight at Day 85 (1 week after the 12th QW dose)
- Additionally, we explored safety, tolerability, and body weight loss after the single candidate monthly 13th dose
- The primary efficacy analysis compared each MET-097 dose group to the pooled placebo group at Day 85 without multiplicity adjustment using a mixed model for repeated measures (MMRM) with treatment group, visit, treatment-by-visit interaction, and baseline body weight as fixed effects

Figure 1. Study design



RESULTS WITH 12 WEEKLY DOSES

PRIMARY EFFICACY ENDPOINT: %CFB BODY WEIGHT

Figure 2. LS Mean (±95% CI) %CFB Weight

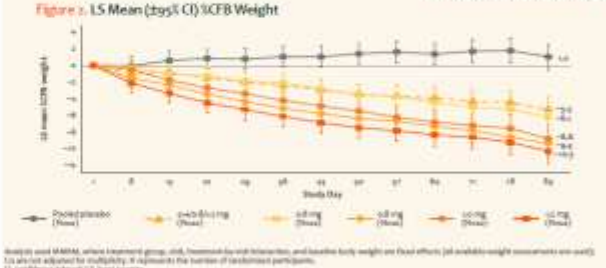
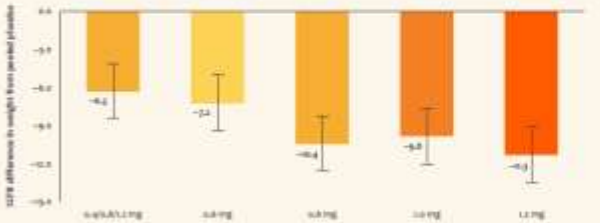


Figure 3. LS Mean Difference (±95% CI) From Placebo %CFB Weight at Day 85



BASELINE CHARACTERISTICS AND DISPOSITION

- All 120 randomized participants were treated
- Overall, 11.7% of participants discontinued treatment (5% to 20% for MET-097, 5% for placebo)
- Reasons for discontinuation included withdrawal by subject (6 participants), lost to follow-up (4), protocol deviation, physician decision, noncompliance with study drug, and pregnancy (1 each); no discontinuations were attributed to adverse events (AEs) by investigator

Table 1. Demographics and baseline characteristics

	Pooled placebo	MET-097				
	N=20	0.4/0.8/1.2 mg N=20	0.8 mg N=20	1.6 mg N=20	2.4 mg N=20	3.2 mg N=20
Age, years, mean (SD)	38.8 (9.79)	42.9 (11.05)	40.6 (10.81)	38.3 (11.85)	40.6 (14.02)	41.1 (9.68)
Sex, n (%)						
Female	8 (40.0)	8 (40.0)	11 (55.0)	8 (40.0)	12 (60.0)	10 (50.0)
Male	11 (55.0)	12 (60.0)	8 (40.0)	11 (55.0)	8 (40.0)	9 (45.0)
Ethnicity, n (%)						
Hispanic or Latino	10 (50.0)	9 (45.0)	10 (50.0)	9 (45.0)	8 (40.0)	9 (45.0)
Not Hispanic or Latino	10 (50.0)	11 (55.0)	10 (50.0)	11 (55.0)	12 (60.0)	11 (55.0)
Race, n (%)						
White	15 (75.0)	13 (65.0)	15 (75.0)	13 (65.0)	14 (70.0)	15 (75.0)
Black or African American	3 (15.0)	8 (40.0)	3 (15.0)	5 (25.0)	5 (25.0)	3 (15.0)
Asian	0	0	1 (5.0)	1 (5.0)	0	0
Multiple	0	1 (5.0)	1 (5.0)	1 (5.0)	1 (5.0)	2 (10.0)
Weight, kg, mean (SD)	96.4 (11.58)	96.7 (14.04)	85.9 (10.54)	87.4 (10.80)	89.4 (15.32)	89.8 (11.58)
BMI, kg/m², mean (SD)	30.9 (3.48)	31.2 (3.80)	28.8 (2.92)	30.1 (3.24)	32.0 (5.85)	31.9 (3.48)
Waist circumference, inches, mean (SD)	38.5 (3.81)	38.3 (3.83)	34.7 (3.52)	37.0 (3.90)	38.5 (4.84)	39.4 (3.24)

n represents the number of randomized participants.

METABOLIC PARAMETERS AFTER WEEKLY DOSING

Table 2. Metabolic parameters after 12 weeks of treatment

Parameters		Pooled placebo	MET-097				
		N=20 Mean (SD)	0.4/0.8/1.2 mg N=20 Mean (SD)	0.8 mg N=20 Mean (SD)	1.6 mg N=20 Mean (SD)	2.4 mg N=20 Mean (SD)	3.2 mg N=20 Mean (SD)
Systolic BP (mmHg)	Baseline	122.1 (8.07)	125.5 (15.02)	117.7 (14.34)	120.8 (14.86)	116.8 (13.32)	122.5 (13.87)
	CFB	-1.2 (9.47)	0.0 (11.75)	-3.2 (9.93)	-8.8 (13.98)	-13.5 (8.98)	-11.8 (10.17)
Diastolic BP (mmHg)	Baseline	76.8 (9.94)	71.3 (10.78)	72.0 (7.08)	78.4 (11.77)	71.3 (8.89)	83.9 (5.74)
	CFB	-0.9 (7.84)	4.3 (10.01)	-1.2 (8.84)	-5.2 (8.35)	-6.1 (8.91)	-8.3 (8.47)
Total cholesterol (mg/dL)	Baseline	184.5 (26.95)	198.0 (30.89)	193.8 (31.09)	178.0 (32.74)	188.0 (44.08)	210.9 (28.84)
	CFB	-5.7 (21.51)	-5.5 (26.32)	-14.1 (17.68)	-17.2 (24.24)	-15.7 (23.00)	-21.5 (36.08)
LDL cholesterol (mg/dL)	Baseline	117.1 (23.46)	126.1 (23.31)	115.0 (26.91)	109.3 (24.78)	117.3 (31.84)	131.4 (25.81)
	CFB	-0.3 (19.84)	5.4 (17.88)	-1.8 (15.58)	-8.5 (16.05)	-8.2 (22.32)	-15.0 (30.65)
Triglycerides (mg/dL)	Baseline	105.7 (39.84)	88.4 (31.62)	94.1 (33.48)	85.4 (28.71)	79.4 (21.14)	108.4 (40.05)
	CFB	4.1 (38.12)	-3.8 (47.28)	-25.3 (31.04)	-19.3 (38.87)	-18.8 (31.71)	-0.8 (30.00)

Arithmetic means are shown. n represents the number of treated participants. Total cholesterol, LDL cholesterol, and triglycerides were measured at Day 85; systolic and diastolic BP were measured at Day 85.
BP, blood pressure.

SAFETY AND TOLERABILITY OF WEEKLY DOSING

- All gastrointestinal (GI) TEAEs were mild or moderate; none were severe
- The safety profile was in line with GLP-1R agonist class, with no unexpected findings

Table 3. Overall TEAEs and GI AEs during weekly dosing

	Pooled placebo	MET-097				
	N=20 n (%)	0.4/0.8/1.2 mg N=20 n (%)	0.8 mg N=20 n (%)	1.6 mg N=20 n (%)	2.4 mg N=20 n (%)	3.2 mg N=20 n (%)
Overall TEAEs	13 (65.0)	8 (40.0)	15 (75.0)	14 (70.0)	13 (65.0)	20 (100.0)
Serious TEAEs	0	0	0	0	0	1 (5.0)*
At least 1 GI TEAE	8 (40.0)	3 (15.0)	11 (55.0)	11 (55.0)	14 (70.0)	17 (85.0)
Nausea	3 (15.0)	1 (5.0)	8 (40.0)	8 (40.0)	10 (50.0)	12 (60.0)
Mild	3 (15.0)	1 (5.0)	8 (40.0)	7 (35.0)	8 (40.0)	10 (50.0)
Moderate	0	0	0	1 (5.0)	2 (10.0)	2 (10.0)
Severe	0	0	0	0	0	0
Vomiting	1 (5.0)	2 (10.0)	8 (40.0)	4 (20.0)	8 (40.0)	11 (55.0)
Mild	0	2 (10.0)	8 (40.0)	3 (15.0)	7 (35.0)	7 (35.0)
Moderate	1 (5.0)	0	0	1 (5.0)	1 (5.0)	3 (15.0)
Severe	0	0	0	0	0	0
Diarrhea	2 (10.0)	0	0 (20.0)	1 (5.0)	5 (25.0)	2 (10.0)

*Serious TEAE was due to a spontaneous miscarriage in a woman with a prior history of miscarriages, unrelated to treatment. Participants are summarized under their maximum severity for each event. n represents the number of treated participants.
TEAE, treatment-emergent AE.

Table 4. Onset of nausea by week

Week	Pooled placebo N=20 n (%)	MET-097 0.4/0.8/1.2 mg N=20 n (%)	MET-097 0.8 mg N=20 n (%)	MET-097 1.6 mg N=20 n (%)	MET-097 2.4 mg N=20 n (%)	MET-097 3.2 mg N=20 n (%)
1	0	1 (5.0)	3 (15.0)	8 (40.0)	9 (45.0)	11 (55.0)
2	1 (5.0)	0	2 (10.0)	1 (5.0)	1 (5.0)	0
3	0	0	0	1 (5.0)	0	1 (5.0)
4	0	0	1 (5.0)	0	0	0
5	0	0	0	0	1 (5.0)	1 (5.0)
6	0	0	0	0	1 (5.0)	0
7	0	0	0	1 (5.0)	1 (5.0)	0
8	0	0	0	0	0	0
9	0	0	0	1 (5.0)	0	0
10	1 (5.0)	0	1 (5.0)	0	0	0
11	0	0	0	0	0	0
12	1 (5.0)	0	0	0	0	0
TEAE	3 (15.0)	1 (5.0)	6 (30.0)	8 (40.0)	9 (45.0)	11 (55.0)

n represents the number of treated participants; n is the number of participants with onset of an AE during the given week. Percentages (%) are based on the sample size for the given week, not the total treated. Numbers of unique participants reporting nausea or vomiting are shown in the total row of their respective tables. This demonstrates for the total row are the number of treated participants.

Table 5. Onset of vomiting by week

Week	Pooled placebo N=20 n (%)	MET-097 0.4/0.8/1.2 mg N=20 n (%)	MET-097 0.8 mg N=20 n (%)	MET-097 1.6 mg N=20 n (%)	MET-097 2.4 mg N=20 n (%)	MET-097 3.2 mg N=20 n (%)
1	0	0	2 (10.0)	3 (15.0)	4 (20.0)	5 (25.0)
2	0	0	0	0	2 (10.0)	4 (20.0)
3	0	0	2 (10.0)	1 (5.0)	3 (15.0)	3 (15.0)
4	0	1 (5.0)	0	0	0	0
5	0	0	0	0	0	1 (5.0)
6	0	0	0	2 (10.0)	0	2 (10.0)
7	0	0	0	0	2 (10.0)	2 (10.0)
8	0	0	0	1 (5.0)	1 (5.0)	0
9	0	0	0	0	1 (5.0)	1 (5.0)
10	1 (5.0)	0	1 (5.0)	0	0	0
11	0	0	0	1 (5.0)	0	1 (5.0)
12	0	0	0	1 (5.0)	0	2 (10.0)
TEAE	1 (5.0)	1 (5.0)	3 (15.0)	8 (40.0)	8 (40.0)	11 (55.0)

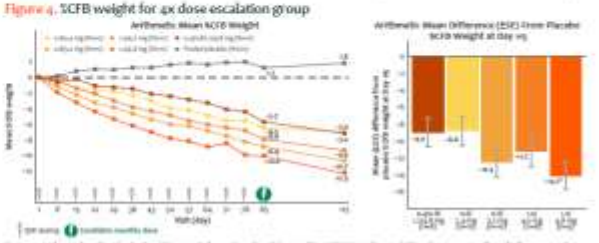
n represents the number of participants; n is the number of participants with onset of an AE during the given week. Percentages (%) are based on the sample size for the given week, not the total treated. Numbers of unique participants reporting nausea or vomiting are shown in the total row of their respective tables. This demonstrates for the total row are the number of treated participants.

RESULTS AFTER SINGLE CANDIDATE MONTHLY DOSE

EFFICACY OF CANDIDATE MONTHLY DOSE

- Weight loss trajectory continued from Day 85 to Day 115 after a single 4x QM dose
- In the 2x dose groups, body weight was maintained between Day 85 and Day 115 (difference in mean placebo-subtracted %CFB body weight of ≤1% or less; data not shown)

Figure 4. %CFB weight for 4x dose escalation group



SAFETY AND TOLERABILITY OF CANDIDATE MONTHLY DOSE

- GI TEAEs were uncommon, and all were mild; none were moderate or severe
- One participant experienced calculous cholecystitis (classified as a serious AE) 49 days after the last dose of MET-097, considered related to treatment by investigator

Table 6. Onset of vomiting after 2x or 4x dose titration

Week	Pooled placebo N=20 n (%)	MET-097 0.4/0.8/1.2 mg N=20 n (%)	MET-097 0.4/0.8/2.0 mg N=20 n (%)	MET-097 0.8/1.6 mg N=20 n (%)	MET-097 1.6/3.2 mg N=20 n (%)	MET-097 2.4/4.8 mg N=20 n (%)	MET-097 3.2/6.4 mg N=20 n (%)	MET-097 4.0/8.0 mg N=20 n (%)
1	0	0	1 (5.0)	1 (5.0)	0	0	0	1 (5.0)
2	0	0	0	1 (5.0)	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0

n represents the number of treated participants.
n (%) is the number and percentage of participants with onset of an AE during the given week. Percentages are based on the sample size for the given week, not the total treated.

CONCLUSIONS

- Twelve weeks of QW MET-097 resulted in up to 11.3% weight loss from baseline (placebo subtracted) without plateau
- The overall safety profile was consistent with GLP-1 class
- GI TEAEs were mostly mild, none were severe, and tolerability in the cohort that received dose titration was similar to placebo
- A 4x single candidate monthly dose was well tolerated and continued the weight loss trajectory of QW dosing
- Ongoing Phase 2b MET-097 trials are studying weekly dosing with simplified or no titration and monthly dosing

Reference: 1. Gleason PP, et al. J Manag Care Spec Pharm. 2019;25(8):880-887.

Data statement: Data used to generate outputs are pre-database lock and subject to change following completion of database lock processes.

Disclosures: This study was funded by Metsera, Inc. All authors are employees of Metsera, Inc.

Acknowledgments: The authors thank Natasha Sahr and Sophie Shapcott of Metsera, Inc. for statistical support.

Contact Robert Stoekenbroek at robert.stoekenbroek@metsera.com for additional information.

For more info

Presented at: American Diabetes Association 85th Scientific Sessions; June 20-23, 2025; Chicago, IL.

788-P

Source: https://metsera.com/ada/

Safety, Tolerability, PK, and Efficacy of MET-097: A Next-Generation Nutrient-Stimulated Hormone Peptide Analog for Chronic Weight Management

Mark Stroh, James Minnion, Stephanie Ranck, Sheela Kolluri, Ali Seddighzadeh, Robert Stoekenbroek, Jason Mallory, and Steven P. Marso

Metsera, Inc., New York, NY and London, UK

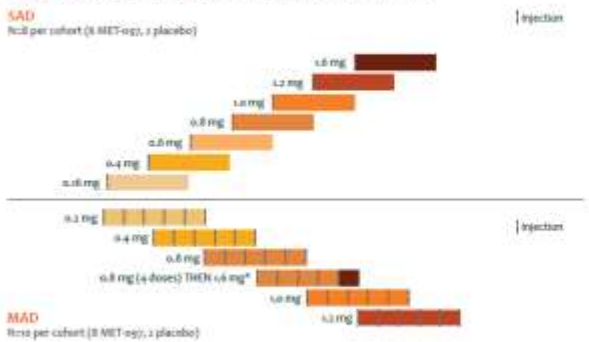
INTRODUCTION

- Nutrient-stimulated hormone (NuSH) analogs are highly effective and have the potential to improve population health
- Yet, their utilization is limited relative to the addressable patient population due to the need for weekly injections, complex and prolonged titration regimens, tolerability issues, and access limitations[1]
- MET-097 is a fully biased, ultra-long acting glucagon-like peptide-1 receptor (GLP-1R) agonist designed for weekly dosing with simplified or no titration and for monthly dosing
- This study evaluated the safety, tolerability, pharmacokinetics (PK), and efficacy of MET-097 in adults with overweight or obesity

METHODS

- This was a randomized, double-blind, placebo-controlled Phase 1 clinical trial conducted at 1 site (NCT06857617)
  - Key inclusion criteria included body mass index (BMI) 27 to 38 kg/m² and estimated glomerular filtration rate (eGFR) ≥90 mL/min
  - Key exclusion criteria included diabetes, seated blood pressure >160/95 mmHg, and elevated resting pulse >100 bpm
- In the single ascending dose (SAD) part, participants were assigned to 7 dose cohorts and randomized within each cohort 6:2 to MET-097 or placebo (Figure 1)
- In the multiple ascending dose (MAD) part, participants were assigned to 6 dose cohorts and randomized within each cohort 8:2 to MET-097 or placebo (Figure 1)
- The primary assessment explored safety and tolerability, and additional evaluations were performed on PK and efficacy

Figure 1. MET-097 SAD and MAD dosing regimens and schedules



Disclosures: This study was funded by Metsera, Inc. All authors are employees of Metsera, Inc.

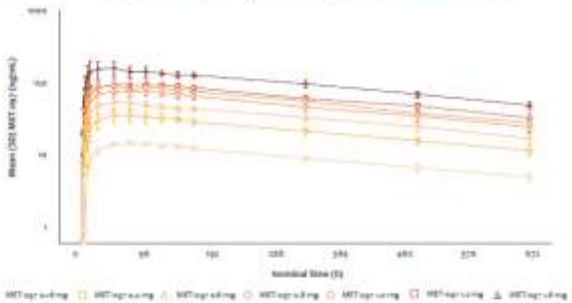
Acknowledgments: The authors thank Raj Bhardwaj and Craig Comtaar of Certara.

RESULTS

MET-097 SAD PK PROFILE

- MET-097 shows a dose-dependent concentration profile with low variability and a monophasic fall from peak (Figure 2)
- The MET-097 single-dose PK profile is further characterized with a clearance of 13.4 to 16.1 mL/h and time to half maximum (peak) concentration (C_{max}) of 18 days (observed half-life)

Figure 2. Preliminary PK profile up to Day 29 following a single dose of MET-097



MET-097 SAD SAFETY AND TOLERABILITY

- Overall, treatment-emergent adverse events (TEAEs) were reported in 66.7% of participants (ranges of 33.3% to 100% in MET-097 and 60.0% in the pooled placebo groups)
- Most gastrointestinal (GI) TEAEs were mild; none were severe

MET-097 MAD PARTICIPANT CHARACTERISTICS

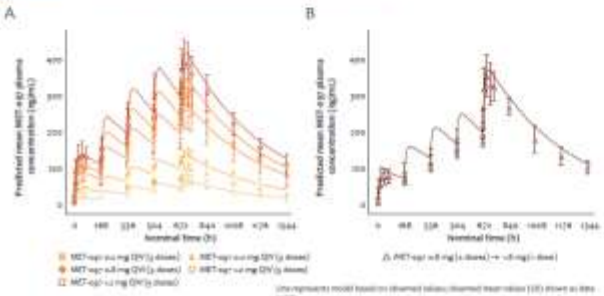
Table 1. Demographics and baseline characteristics

	Pooled placebo	MET-097					
	N=13	0.2 mg N=8	0.4 mg N=8	0.8 mg N=8	1.0 mg N=8	1.2 mg N=9	0.8 mg/1.6 mg N=8
Age, years, mean ± SD	33.9 ± 13.44	42.1 ± 17.51	43.8 ± 18.28	36.1 ± 14.54	36.4 ± 7.85	33.6 ± 11.24	38.9 ± 13.16
Female, n (%)	7 (53.8)	6 (75.0)	4 (50.0)	4 (50.0)	5 (62.5)	3 (33.3)	1 (12.5)
Race, n (%)							
White	6 (46.2)	5 (62.5)	6 (75.0)	4 (50.0)	3 (37.5)	2 (22.2)	2 (25.0)
Black	7 (53.8)	3 (37.5)	0	4 (50.0)	5 (62.5)	7 (77.8)	6 (75.0)
Other	0	0	2 (25.0)	0	0	0	0
Weight, kg, mean ± SD	94.8 ± 14.43	85.9 ± 15.91	84.4 ± 13.21	91.8 ± 12.74	93.9 ± 11.00	94.2 ± 11.58	101.7 ± 16.36
BMI, kg/m², mean ± SD	32.7 ± 3.77	31.8 ± 3.48	29.8 ± 1.75	32.1 ± 2.13	32.3 ± 2.74	31.0 ± 2.48	35.5 ± 3.28

MET-097 MAD PK PROFILE

- MET-097 plasma exposure accumulated gradually with an accumulation ratio of ~3 after 5 doses (Figure 3A)
- After 4 weekly doses (0.8 mg), a 2-fold dose increase (1.6 mg) led to a predictable increase in exposure (Figure 3B)

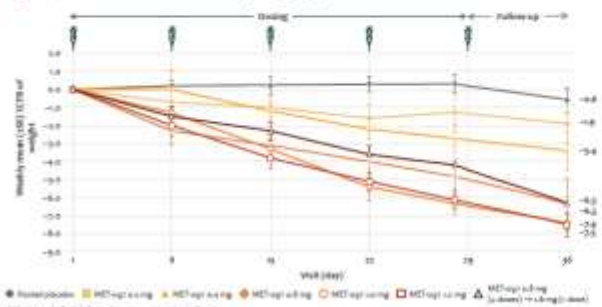
Figure 3. Preliminary PK profile following MAD of MET-097



BODY WEIGHT LOSS

- Weight loss was dose dependent, up to a mean change from baseline (%CFB) of 7.5% (SD, 1.56) at Day 36 in the 1.2 mg dose group (Figure 4)
- Weight loss was persistent after the dosing period, with a mean %CFB of 8.1% (SD, 2.15) at Day 57 and 7.5% (SD, 2.05) at Day 85 in the 1.2 mg group

Figure 4. Arithmetic mean %CFB body weight by week



MET-097 MAD SAFETY AND TOLERABILITY

- There were no serious TEAEs (Table 2)
- GI TEAEs were all mild among active MET-097 participants, except for 1 moderate vomiting in the 1.0 mg; none were severe

Table 2. Overall and GI TEAEs

	Pooled placebo	MET-097					
	N=13 n (%)	0.2 mg N=8 n (%)	0.4 mg N=8 n (%)	0.8 mg N=8 n (%)	1.0 mg N=8 n (%)	1.2 mg N=9 n (%)	0.8 mg/1.6 mg N=8 n (%)
TEAEs	8 (61.5)	4 (50.0)	6 (75.0)	7 (87.5)	8 (100.0)	8 (88.9)	6 (75.0)
Serious TEAEs	0	0	0	0	0	0	0
At least 1 GI TEAE	4 (30.8)	2 (25.0)	3 (37.5)	3 (37.5)	8 (100.0)	8 (88.9)	4 (50.0)
Nausea	3 (23.1)	0	2 (25.0)	3 (37.5)	8 (100.0)	7 (77.8)	4 (50.0)
Mild	3 (23.1)	0	2 (25.0)	3 (37.5)	8 (100.0)	7 (77.8)	4 (50.0)
Moderate	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0
Vomiting	0	0	2 (25.0)	1 (12.5)	4 (50.0)	3 (33.3)	2 (25.0)
Mild	0	0	2 (25.0)	1 (12.5)	3 (37.5)	3 (33.3)	2 (25.0)
Moderate	0	0	0	0	1 (12.5)	0	0
Severe	0	0	0	0	0	0	0
Diarrhea	0	1 (12.5)	0	0	2 (25.0)	0	0

- Vomiting was generally confined to the first week of treatment, suggesting a rapid onset of tolerance (Table 3)
- The 2× dose escalation in Week 5 was well tolerated with a single case of vomiting

Table 3. Onset of vomiting

	Pooled placebo	MET-097					
Week	N=13 n (%)	0.2 mg N=8 n (%)	0.4 mg N=8 n (%)	0.8 mg N=8 n (%)	1.0 mg N=8 n (%)	1.2 mg N=9 n (%)	0.8 mg/1.6 mg N=8 n (%)
1	0	0	1 (12.5)	1 (12.5)	3 (37.5)	3 (33.3)	1 (12.5)
2	0	0	0	0	2 (25.0)	0	0
3	0	0	0	0	1 (12.5)	0	0
4	0	0	1 (12.5)	0	1 (12.5)	0	0
5	0	0	0	0	0	1 (12.5)	1 (12.5)*
6	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0

CONCLUSIONS

- Five weekly doses of MET-097 1.2 mg provided 7.5% weight loss from baseline
- AEs were consistent with the GLP-1R agonist class
- The 2× dose titration was well tolerated
- MET-097's ultra-long half-life enables simplified weekly dosing regimens and monthly dosing

References: 1. Gleason PP, et al. J Manag Care Spec Pharm. 2024;30(8):860-867.

Data statement: Data used to generate outputs are pre-database lock and subject to change following completion of database lock processes.

Contact Mark Stroh at Mark.Stroh@Metsera.com for additional information.

For more info

Presented at: American Diabetes Association 85th Scientific Sessions; June 20-23, 2025; Chicago, IL.

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Source: https://metsera.com/ada/

Reduction of the 10-year ASCVD Risk in Patients with Overweight or Obesity Treated with Semaglutide 2.4 mg in Routine Clinical Care: A Real-World Study

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https://www.novonordisk.co.uk/

Introduction

- Individuals living with obesity face elevated risk for atherosclerotic cardiovascular disease (ASCVD) compared with those with a healthy weight[1,2]
- Semaglutide 2.4 mg (Wegovy®), approved on June 4, 2021, for chronic weight management, has been shown to improve cardiometabolic risk factors and reduce CV events in clinical trials, including the SELECT, STEP 1, and STEP 4 trials.[3,4,5] However, real-world evidence on the impact of semaglutide 2.4 mg on ASCVD risk is limited.
- This study compared the change in the 10-year ASCVD risk score (based on the AHA/ACC criteria) over one year among adults with overweight or obesity treated with once-weekly subcutaneous semaglutide 2.4 mg and those not treated with semaglutide 2.4 mg.

Methods

Study population and selection criteria

- Adult patients with obesity (BMI ≥30 kg/m²) or overweight (25 kg/m²≤BMI <30 kg/m²) and ≥1 obesity-related comorbidity (ORC) were identified in the Komodo Research Database, a database of administrative claims and clinical/lab data, from January 1, 2016 to June 30, 2024
- **Semaglutide 2.4 mg users:** patients treated with once-weekly subcutaneous semaglutide 2.4 mg who had ≥ 12 months of continuous days of supply (≤ 30-day gap allowed) (index date: initiation of any dose of the brand of semaglutide approved for chronic weight management [i.e., Wegovy®])
  Non-users: patients treated with other anti-obesity medications (AOMs) (index date: first claim for other AOMs) OR not treated with any AOMs (index date: random pharmacy claim date) on or after June 4, 2021
- Without use of AOMs or GLP-1 agonists during the 3-month washout period before the index date
- With 12-month continuous insurance enrollment before the index date and 12-month follow-up, defined as time from the index date to the earliest of: end of insurance eligibility, end of data availability, first evidence of bariatric surgery, death, or initiation of a new GLP-1, or AOMs
- With data available to calculate the 10-year AHA/ACC ASCVD risk score at baseline and at 12 months
- **Exclusion:** Type 1 diabetes, chronic or acute pancreatitis, multiple endocrine neoplasia type 2, medullary thyroid carcinoma, end-stage kidney disease, pregnancy, bariatric surgery 12 months before the index date

Study design and outcomes

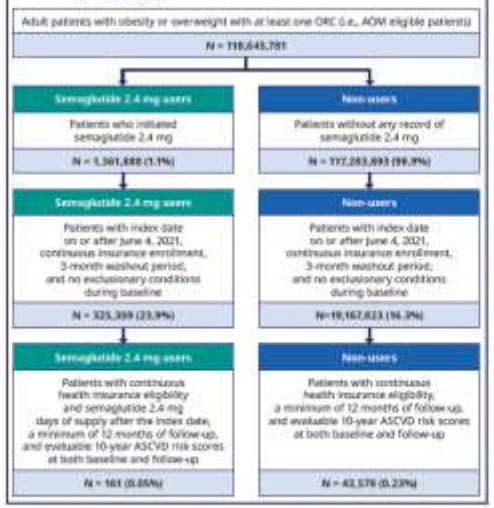
- **Baseline period:** 12 months prior to index date
- **Follow-up period:** 12 months post index date
- **Study outcome:**
  - The 10-year AHA/ACC ASCVD risk score at baseline, follow-up, and change from baseline to follow-up – calculated using age, sex, and race (baseline: as of index date; follow-up: as of end of follow-up); cholesterol levels, blood pressure, and antihypertensive treatment status (baseline: measured within 12 weeks prior to index; follow-up: within 12 weeks before/after the end of follow-up); diabetes status (baseline: assessed during the baseline period; follow-up: from baseline start through 12 weeks after the end of follow-up); and smoking status (baseline: recorded any time prior to index; follow-up: any time prior to 12 weeks after the end of follow-up)
  - BMI at baseline and follow-up – measured within 4 weeks prior to index at baseline and within 4 weeks before/after the end of follow-up at follow-up
- **Statistical analysis:**
  - **Propensity score (PS) weighting:** The standardized mortality ratio (SMR) weighting method was applied to balance baseline characteristics between semaglutide 2.4 mg users and non-users. PS weights were generated using demographics, BMI, comorbidities, and medication use at baseline.
  - **10-year AHA/ACC ASCVD risk score:** A weighted logistic regression model was used to compare the proportion of patients in the *intermediate-high-risk category (ASCVD risk score ≥7.5%)* between the semaglutide 2.4 mg users and non-users at 12-month follow-up, and weighted linear regression models were used to compare 10-year ASCVD risk score at 12-month follow-up and change in the risk score from baseline. Odds ratios (ORs) and mean differences along with 95% confidence intervals (CIs) and p-values were reported.

Results

Study sample

- A total of 161 semaglutide 2.4 mg users and 43,578 non-users with overweight and ≥1 ORC or obesity who met all eligibility criteria were identified (**Figure 1**).

Figure 1: Study population flowchart for semaglutide 2.4 mg users and non-users



Patient characteristics

- Patient characteristics among the semaglutide 2.4 mg users and the non-users were well balanced for the characteristics included in the PS weighting model (**Table 1**).
- Semaglutide 2.4 mg users and non-users were comparable in age (mean: 48.0 vs. 48.7 years) and had similar proportions of Black or African American patients (11.2% vs. 10.8%). Mean BMI was slightly higher among semaglutide 2.4 mg users (38.3 vs. 37.5 kg/m²), with comparable rates of multimorbidity (65.8% vs. 64.7%) and polypharmacy (2.5% vs. 2.6%).

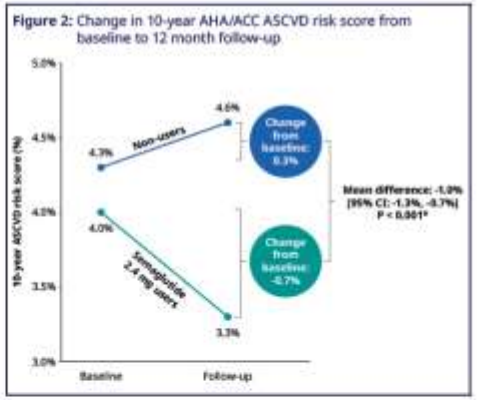
Table 1: Patient characteristics of balanced semaglutide 2.4 mg users and non-users

	Semaglutide 2.4 mg users N = 161	Non-users N = 43,578	Standardized difference
Duration of AOM eligibility date to index date, months, mean ± SD[a]	68.4 ± 19.3	67.4 ± 15.4	0.06
Demographics, as of the index date			
Age at index date (years), mean ± SD	48.0 ± 9.6	48.7 ± 11.4	0.06
Female, n (%)	121 (75.2%)	31,650 (72.6%)	0.06
Race/ethnicity, n (%)			
Black or African American[b]	18 (11.2%)	4,687 (10.8%)	0.01
White	113 (70.2%)	26,887 (61.7%)	0.18
Hispanic or Latino	9 (5.6%)	6,235 (14.3%)	0.29
Other/Unknown	21 (13.0%)	5,769 (13.2%)	0.01
Insurance coverage[c], n (%)			0.04
Commercial[d]	146 (90.7%)	38,973 (89.4%)	
Other[e]	17 (10.6%)	5,142 (11.8%)	
BMI closest to index date			
Available BMI[f], n (%)	122 (75.8%)	31,632 (72.6%)	0.07
BMI, kg/m², mean ± SD	38.3 ± 5.4	37.5 ± 5.8	0.13
Overweight[g], n (%)	6 (3.7%)	1,841 (4.2%)	0.03
Obesity[g], n (%)	116 (72.0%)	29,791 (68.4%)	0.08
Comorbidities			
CVD, n (%)	19 (11.8%)	5,253 (12.1%)	0.01
Dyslipidemia, n (%)	98 (60.9%)	26,929 (61.8%)	0.02
Hypertension, n (%)	75 (46.6%)	20,646 (47.4%)	0.02
Prediabetes, n (%)	75 (46.6%)	19,393 (44.5%)	0.04
Type II diabetes, n (%)	8 (5.0%)	2,434 (5.6%)	0.03
Multimorbidity (≥2 concurrent comorbidities), n (%)	106 (65.8%)	28,193 (64.7%)	0.02
Medication use			
AOMs other than semaglutide[h], n (%)	11 (6.8%)	3,190 (7.3%)	0.02
Diabetes medications, n (%)	18 (11.2%)	4,466 (10.2%)	0.03
Polypharmacy (≥5 concurrent medications), n (%)	4 (2.5%)	1,169 (2.6%)	0.01

10-year AHA/ACC ASCVD risk

- At 12 months, the average change in ASCVD risk score from baseline was -0.7% for those using semaglutide 2.4 mg, and 0.3% for non-users, with a difference of -1.0% (95% CI: -1.3% to -0.7%; p < 0.001) between the two groups (**Figure 2**).
- At 12 months, semaglutide 2.4 mg users had a significantly lower mean (median) ASCVD risk score compared to non-users (3.3 (2.0)% vs. 4.6 (2.8)%), with a mean difference of -1.3% (95% CI: -2.2% to -0.5%; p = 0.002).
- At 12 months, the proportion of patients in the *intermediate-high-risk* category (ASCVD risk score ≥7.5%) declined from 14.9% to 9.3% among semaglutide 2.4 mg users (absolute change: -5.6%, relative change: -37.5%), whereas it increased from 17.7% to 18.7% among non-users (absolute change: +1.0%, relative change: +5.6%) (**Figure 3**).
- Semaglutide 2.4 mg users had 70% lower odds of being in the *intermediate-high-risk* category at 12 months compared to non-users (OR: 0.3; 95% CI: 0.1–0.6; p < 0.001) (**Figure 3**).

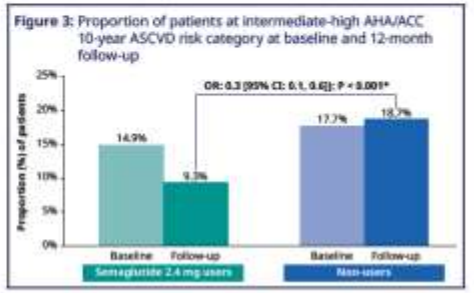
Figure 2: Change in 10-year AHA/ACC ASCVD risk score from baseline to 12 month follow-up



Limitations

- Laboratory and clinical measurements were obtained in real-world clinical practice, which may result in variability in timing and incomplete data availability. The study required all patients to have lab values and clinical observations to enable ASCVD risk score evaluation at both baseline and 12-month follow-up, which may have limited the generalizability of the findings.
- As in all observational studies, despite PS weighting, the results may in part reflect residual unmeasured confounding, and causal relationships cannot be definitively established.

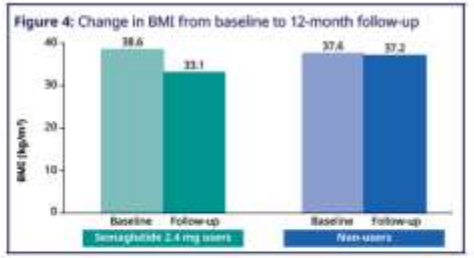
Figure 3: Proportion of patients at intermediate-high AHA/ACC 10-year ASCVD risk category at baseline and 12-month follow-up



Change in BMI

- Among patients with BMI measurements at both baseline and 12-month follow-up, semaglutide 2.4 mg users (N=86) showed a 14.2% reduction in BMI (from 38.6 to 33.1 kg/m²), while non-users (N=22,785) had a relatively stable BMI (from 37.6 to 37.2 kg/m²) from baseline to 12 months (**Figure 4**).

Figure 4: Change in BMI from baseline to 12-month follow-up



Conclusion

- In adults with overweight or obesity, semaglutide 2.4 mg was associated with a reduction in ASCVD risk at one year based on AHA/ACC criteria, while in non-users, the risk slightly increased in the same time frame. This highlights the potential role of semaglutide 2.4 mg on ASCVD prevention in addition to clinically meaningful weight reduction in the real-world.

[1]Novo Nordisk, Inc., Plainsboro Township, New Jersey, USA; [2]Analysis Group, Inc., Los Angeles, California, USA; [3]Groupe d'Analyse, Ltée, Montreal, QC, Canada; [4]Mayo Clinic, Rochester, Minnesota, USA

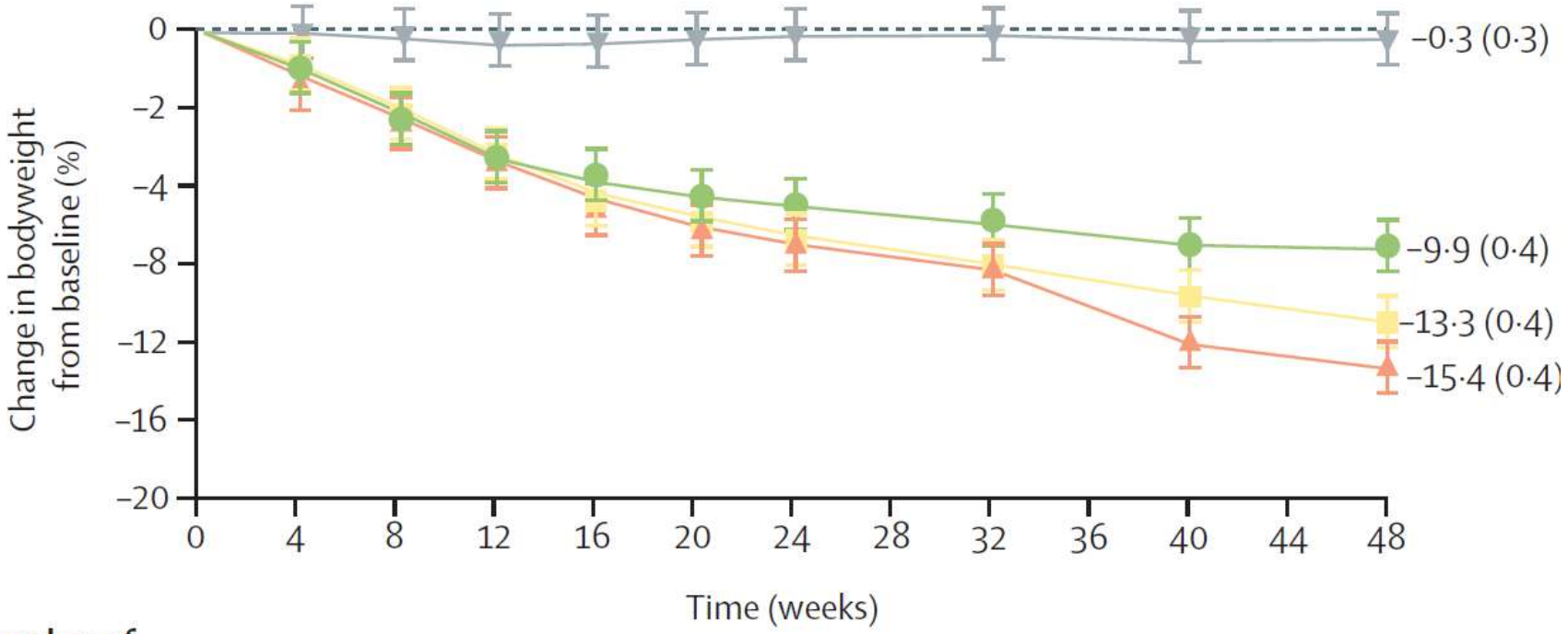
Abbreviations: AOM, anti-obesity medication; ASCVD, atherosclerotic cardiovascular disease; AHA/ACC, American Heart Association/American College of Cardiology; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; GLP-1, glucagon-like peptide-1; OR, odds ratio; ORC, obesity-related comorbidity; PS, propensity score; SD, standard deviation.

Funding for this research was provided by Novo Nordisk, Inc.; the study sponsor was involved in all stages of the study research and poster preparation.
Presented at the American Diabetes Association 85th Scientific Sessions, June 20 – 23, 2025, Chicago, IL.

References
(1) Henning RJ. Am J Cardiovasc Dis. 2021;11(4):344-525. (2) Powell-Wiley TM, et al. Circulation. 2021;143(21): e984-e1010. (3) Wilding JPH, et al. N Engl J Med. 2021;384: 989-1002. (4) Rubino, D. et al. JAMA. 2021;325, 1414-1425. (5) Lincoff, A. M. et al. N Engl J Med. 2023; 389: 2221-2232

Source: https://sciencehub.novonordisk.com/congresses/ada2025/Ruseva1.html

SciWind's Ecnoglutide Reports 15.1% Weight Loss at 48 Weeks in the *Lancet* in June



Number of participants										
Ecnoglutide 1·2 mg	166	166	166	163	162	161	161	159	160	158
Ecnoglutide 1·8 mg	166	164	164	162	159	156	158	157	154	148
Ecnoglutide 2·4 mg	167	167	164	161	160	160	160	159	153	150
Placebo	165	164	163	163	159	163	163	160	157	156

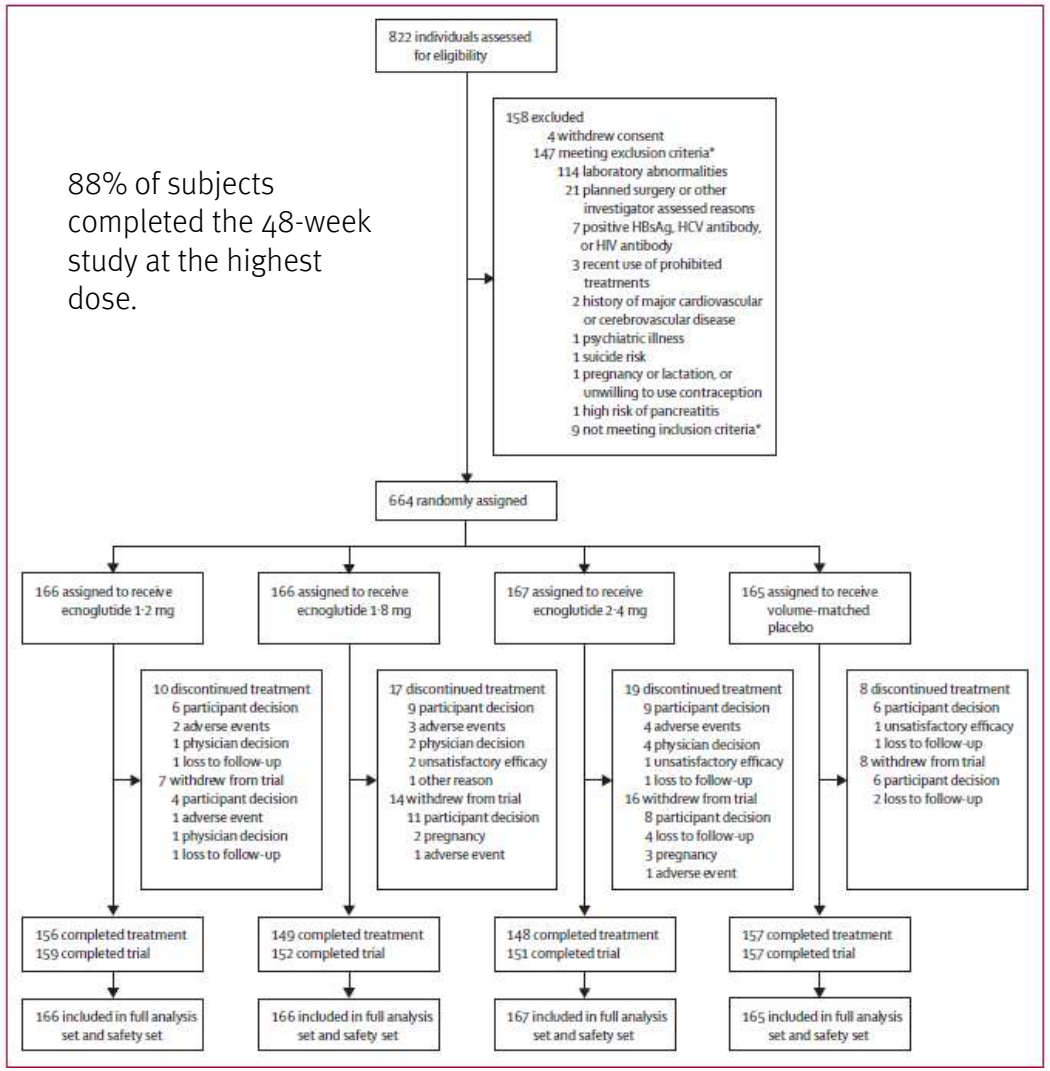
Source: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(25)00141-X/abstract

SciWind's SubQ VRB-101 (Ecnoglutide) Has Vomiting Rate in the Low 20's to High Teens at All Doses

	Ecnoglutide 1·2 mg (n=166)	Ecnoglutide 1·8 mg (n=166)	Ecnoglutide 2·4 mg (n=167)	Placebo (n=165)
Any treatment-emergent adverse events	155 (93%)	154 (93%)	156 (93%)	139 (84%)
Risk difference (95% CI)	9% (2 to 16)	9% (2 to 16)	9% (2 to 16)	..
Grade ≥3 treatment-emergent adverse events	10 (6%)	15 (9%)	12 (7%)	12 (7%)
Risk difference (95% CI)	−1% (−7 to 4)	2% (−4 to 8)	−0·1% (−6 to 6)	..
Serious adverse events	9 (5%)	15 (9%)	10 (6%)	8 (5%)
Risk difference (95% CI)	1% (−5 to 6)	4% (−1 to 10)	1% (−4 to 6)	..
Treatment-related serious adverse events	0	3 (2%)	2 (1%)	0
Risk difference (95% CI)	0% (−2 to 2)	2% (−1 to 5)	1% (−1 to 4)	..
Adverse events leading to treatment discontinuation	2 (1%)	3 (2%)	5 (3%)	0
Risk difference (95% CI)	1% (−1 to 4)	2% (−1 to 5)	3% (0 to 7)	..
Deaths	0	0	0	0
Risk difference (95% CI)	0% (−2 to 2)	0% (−2 to 2)	0% (−2 to 2)	..
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group				
Diarrhoea	53 (32%)	51 (31%)	55 (33%)	12 (7%)
Decreased appetite	47 (28%)	57 (34%)	52 (31%)	12 (7%)
Upper respiratory tract infection	41 (25%)	37 (22%)	32 (19%)	46 (28%)
Nausea	43 (26%)	41 (25%)	57 (34%)	6 (4%)
Vomiting	29 (18%)	28 (17%)	38 (23%)	4 (2%)

Discontinuation Rate Not Too Bad

88% of subjects completed the 48-week study at the highest dose.



Source: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(25)00141-X/abstract

Efficacy, Tolerability, and Safety of Efsubaglutide Alfa in Participants with Obesity or Overweight (LIGHT 1): A Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Phase 2a Trial.

Yuqian Bao[1*], Jian Zhou[1], Fei Gao[1#], Anna Shao[2], Yulong Xu[2], Qinghua Wang[2*], Weiping Jia[1*]

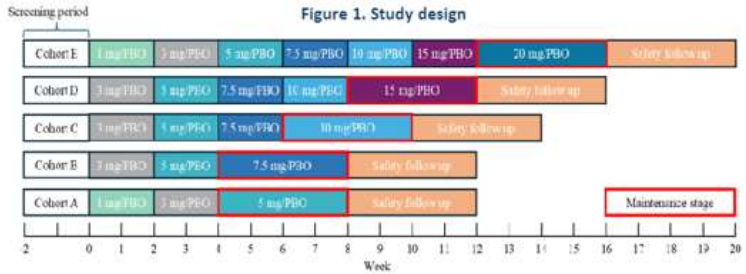
Background and objective

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are effective in promoting weight loss in individuals with overweight or obesity. Standard clinical practice typically involves gradual dose escalation every 4 to 8 weeks to improve gastrointestinal tolerability and ensure long-term adherence.[1-3] Efsubaglutide Alfa is a novel long-acting GLP-1RA with a favorable safety profile and lower gastrointestinal adverse events (GIAEs) observed in previous studies among patients with type 2 diabetes. Given the potential benefits of rapid therapeutic response in improving early adherence, this Phase 2a trial evaluated the efficacy, pharmacokinetics, and safety of Efsubaglutide Alfa using a bi-weekly, accelerated dose-escalation schedule.

Methods

Between April and November 2024, 68 individuals were screened and 50 were randomized to receive Efsubaglutide Alfa at target doses of 5, 7.5, 10, 15, or 20 mg (n=40) or placebo (n=10). Dosing was escalated bi-weekly to reach target doses more rapidly. The primary endpoints were percent change in body weight from baseline and the proportion of participants achieving ≥5% weight loss after four weeks at the target dose. Secondary endpoints included changes in BMI and metabolic markers. Body composition was assessed via height–weight analyzer, and fat and lean mass were expressed as proportions of total body weight.

Figure 1. Study design



A stepwise dose-escalation schedule was implemented in each cohort, with dose titration occurring every two weeks until the target maintenance dose was achieved.

Results

Participants had a mean age of 36.3 years, mean body weight of 92.9 kg, and mean BMI of 33.0 kg/m² at baseline. Efsubaglutide Alfa induced a mean weight reduction of 7.16% (95% CI: −8.08 to −6.24) versus 0.86% with placebo. A total of 84.6% of Efsubaglutide-treated participants achieved ≥5% weight loss, compared with 0% in the placebo group. Fat mass decreased by 4.47 kg and lean mass by 2.00 kg; the lean-to-fat mass ratio increased by 19.73 percentage points. Significant reductions were also observed in BMI, waist circumference, and systolic blood pressure.

Figure 2. Primary efficacy outcomes of Efsubaglutide Alfa vs. Placebo

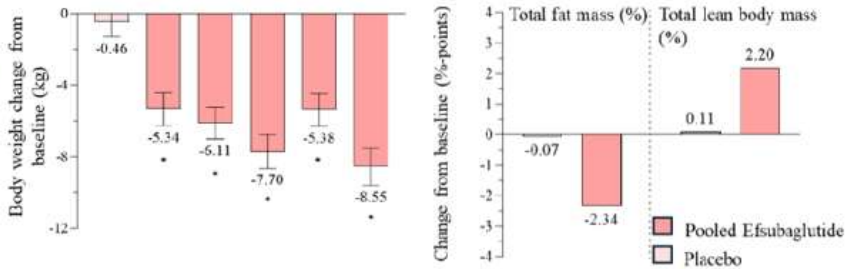
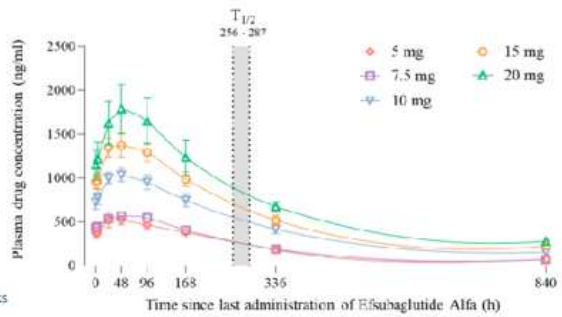


Figure 3. Drug concentration time course curve



Efsubaglutide Alfa exhibited dose-proportional pharmacokinetics across the 5–20 mg range, with linear increases in C_max and $AUC_{0-\infty}$. The median T_max ranged from 36 to 48 hours, and the mean terminal half-life (t_1/2) ranged from 256 to 287 hours. Geometric mean C_max and $AUC_{0-\infty}$ ranged from 524 to 1880 ng/mL and 74,600 to 275,000 ng·h/mL, respectively. Apparent clearance (CL/F) and volume of distribution (V_z/F) were 66.6–97.8 mL/h and 26.8–32.6 L, respectively.

Results

Figure 4. Prevalence of gastrointestinal adverse events over time

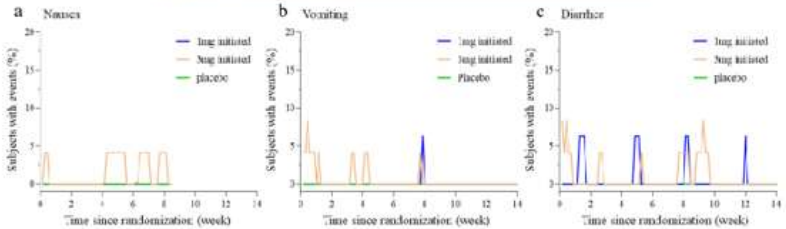


Figure presents the proportion of participants receiving semaglutide or placebo who reported: (a) nausea (b) vomiting (c) diarrhea over the treatment period. Cohorts A and E started at 1 mg (n = 16), while cohorts B, C, and D started at 3 mg (n = 24).

The majority of adverse events (AEs) were gastrointestinal in nature and occurred during the dose-escalation phase. Initiation at 3 mg was associated with a higher incidence of nausea and vomiting compared to initiation at 1 mg, while the incidence of diarrhea was similar between groups. During the maintenance phase, GIAE frequency was not correlated with the final target dose. Most treatment-related AEs were mild to moderate. No treatment-related serious adverse events, hypoglycemia, or treatment discontinuations were reported. PHQ-9 assessments indicated no mental health-related concerns

Conclusion

Efsubaglutide Alfa demonstrated substantial weight-loss efficacy, favorable metabolic effects, and a well-tolerated safety profile in participants with obesity or overweight. Its extended half-life supports the feasibility of less frequent dosing. These findings suggest that Efsubaglutide Alfa, when administered with a bi-weekly titration strategy, may offer a clinically effective and patient-friendly approach to obesity management.

[1]Shanghai Jiao Tong University School of Medicine Affiliated Sixth People's Hospital, Shanghai, China; [2]Innogen Pharmaceutical Co., Ltd., Shanghai China
This trial was sponsored by Innogen and is registered with ClinicalTrials.gov (NCT06732960). Presented at the American Diabetes Association in Chicago.

Abbreviation: AE: adverse event, GIAE: gastrointestinal adverse events, TRAE treatment related adverse event, PBO, placebo. All efficacy analyses were performed using ANCOVA unless otherwise specified, adjusting for baseline, treatment, and sex. Changes in lean and fat mass proportion are arithmetic means, and p-values are derived from group t-tests.

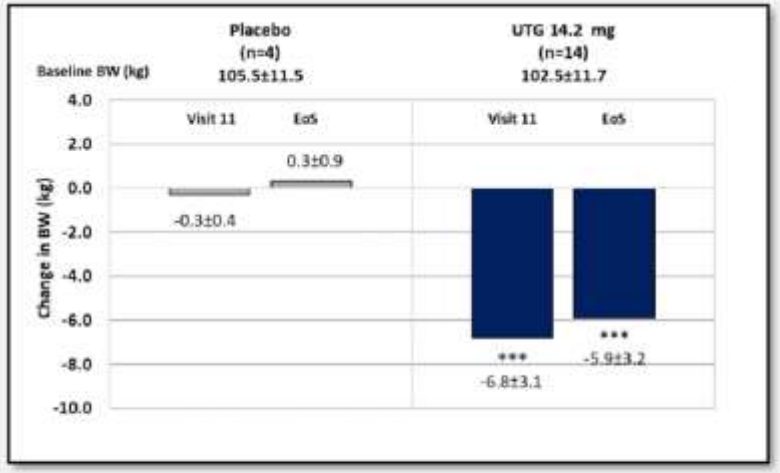
References: (1) Bonora E, et al. Effect of dulaglutide 3.0 and 4.5 mg on weight in patients with type 2 diabetes: Exploratory analyses of AWARD-11. Diabetes Obes Metab. 2021;23(10):2242-2250. (2) Kushner RF, et al. Semaglutide 2.4 mg for the Treatment of Obesity: Key Elements of the STEP Trials 1 to 5. Obesity (Silver Spring) 2020; 28(6): 1050-61. (3) Bi Y, et al. Efficacy and Safety of Tirzepatide in Patients with Type 2 Diabetes: Analysis of SURPASS-AP-Combo by Different Subgroups. Diabetes Ther. 2024;15(5):1125-1137.

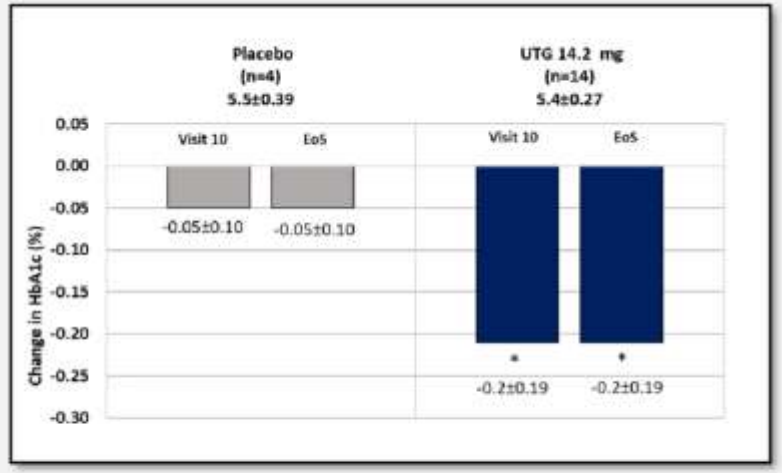
Source: https://www.innogenpharm.com/

Sun Pharma Reports 10-Week Data in Obese Pts with a GLP-1RA (Utreglutide)

RESULTS: BODY WEIGHT & GLYCATED HEMOGLOBIN

- At visit 11, 10-week treatment with utreglutide resulted in 6.8% body weight loss. Four weeks after the last dose (EoS) resulted in 5.9%.
- The mean HbA1c (%) reduced from 5.4 to 5.2 at Visit 11 and remained stable till the end of study.





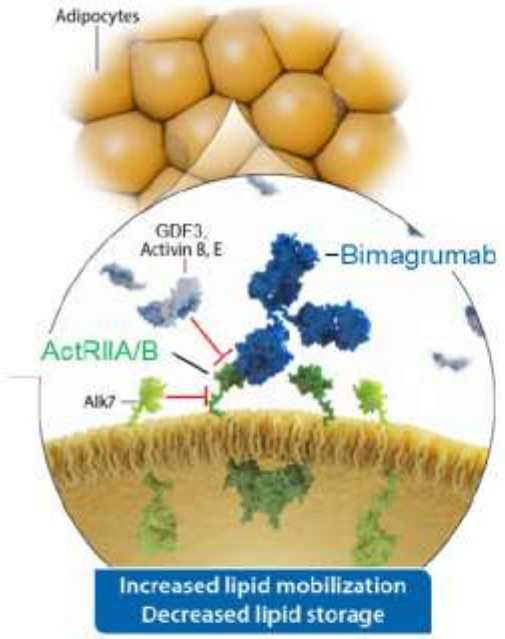
*P<0.05, **P<0.01 and ***P<0.001 vs respective D1 (BL); One-way ANOVA followed by Dunnett's test
(Left Panel): First bar represents Visit 11 and second bar represents EoS
(Right Panel): First bar represents Visit 10 and second bar represents EoS (Change in baseline for all)
BW, body weight; BL-Baseline; HbA1c, glycated hemoglobin; EoS, End of study; UTG, utreglutide

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/759-P/160520/759-P-Effects-of-Once-Weekly-Utreglutide-GL0034-in

Bimagrumab Data

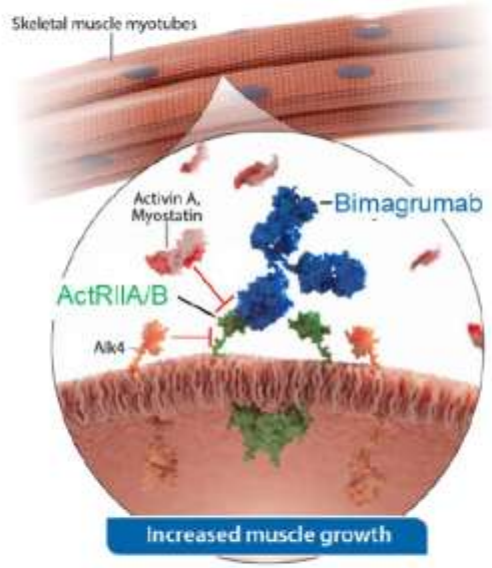
Lilly' Bimagrumab Preserves Muscle Via Activin Blockade

Adipose



Blocks activin E and GDF3 signaling with the goal of decreasing fat mass

Muscle



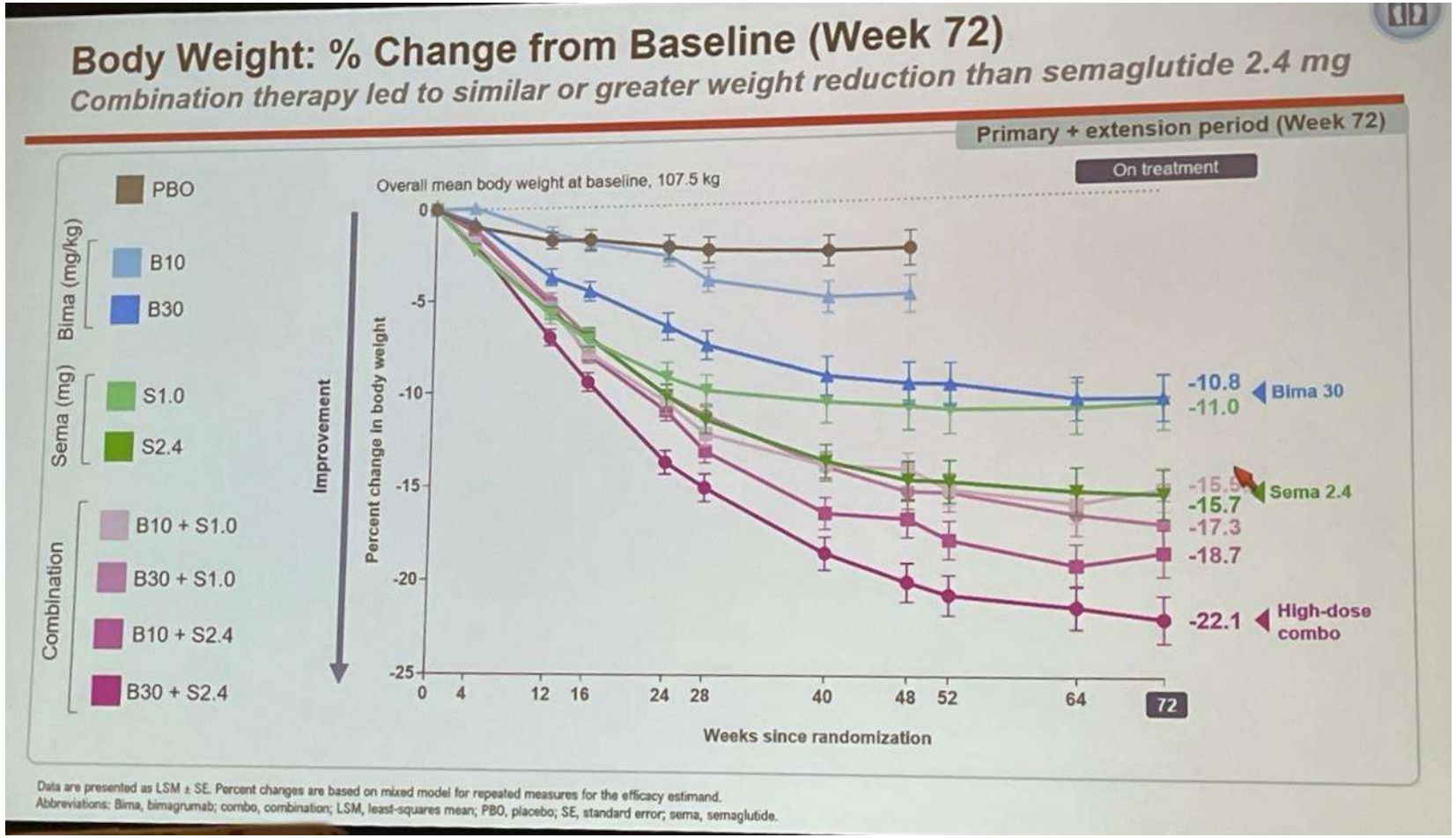
Blocks activin A and myostatin signaling with the goal of increasing muscle mass

Bimagrumab

- Monoclonal antibody that blocks activin type II receptors
- BELIEVE Phase 2B study evaluated IV bimagrumab dosed quarterly ± semaglutide
- Additional Phase 2 trials evaluating SC bimagrumab dosed weekly ± tirzepatide

Source: https://investor.lilly.com/static-files/36604492-7d65-4649-bc20-f7b4372c2b2b

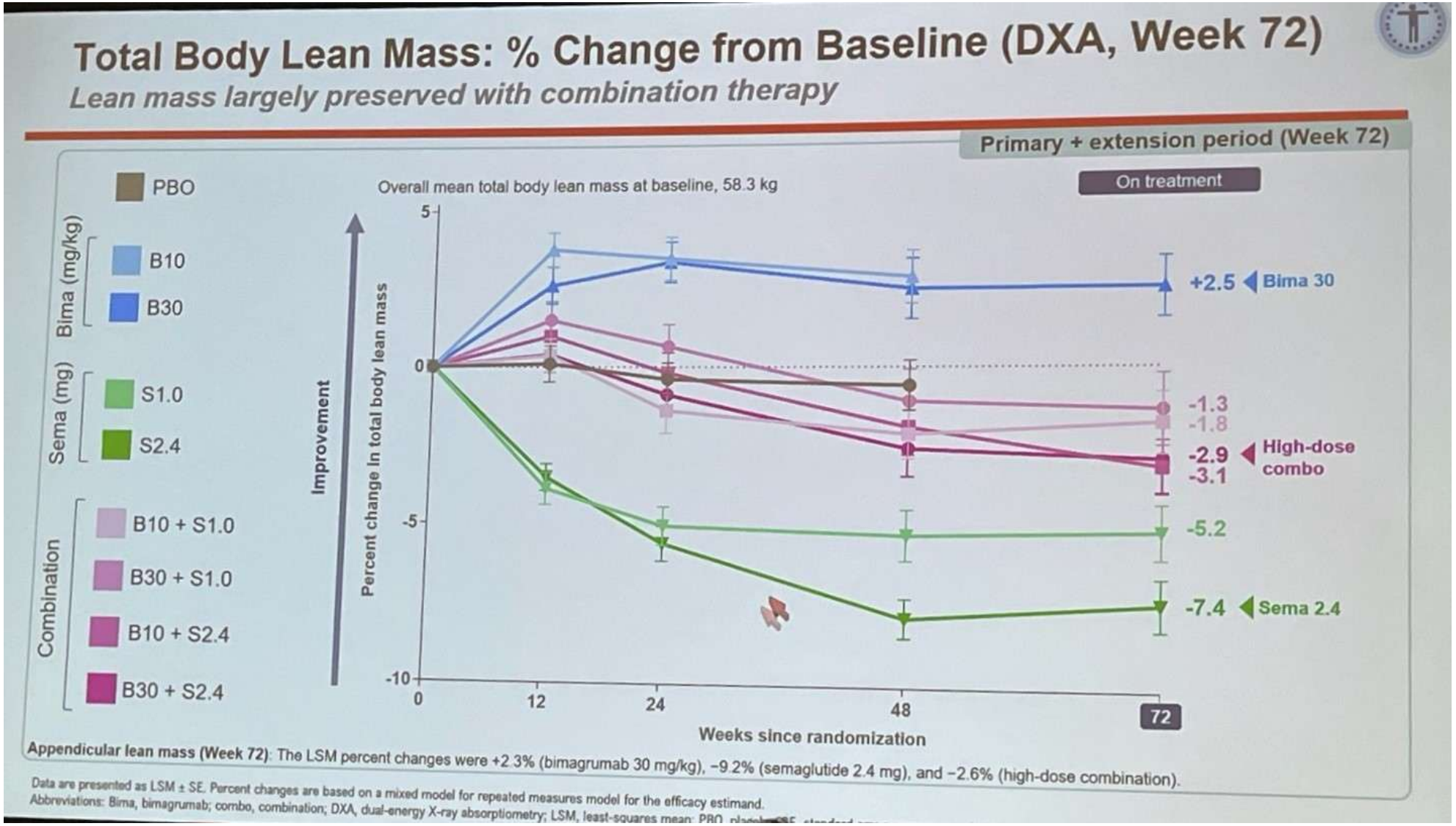
Bimagrumab Study at ADA Shows Impressive Weight Loss at 72 Weeks on Combo of Bima and Sema



In terms of safety, the results were consistent with the established profiles of both drugs, and no new safety signals emerged. The most common adverse events associated with bimagrumab included muscle spasms, diarrhea, and acne, while semaglutide was frequently linked to nausea, diarrhea, constipation, and fatigue. The incidence of adverse events was similar across all four combination groups, with 9% of participants receiving combination therapy discontinuing treatment due to adverse events over the 72-week period. No deaths were reported. Bimagrumab-containing groups experienced early, transient elevations in ALT and lipase, whereas semaglutide-containing groups showed a sustained increase in lipase levels.

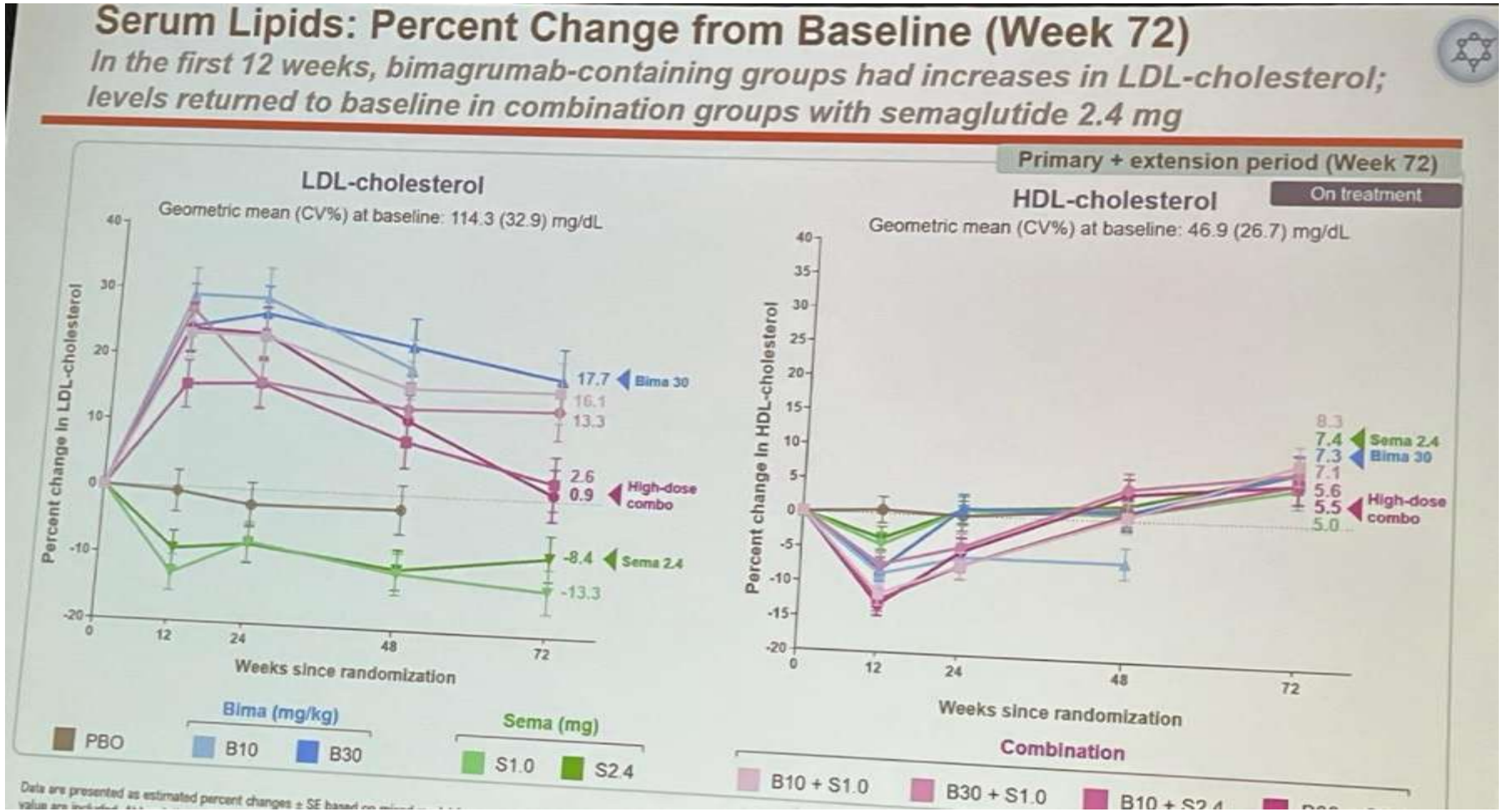
Source: Stifel photograph of presentation materials from Dr. Aronne at ADA, June 2025

Bimagrumab Associated with Preserved Lean Mass



Source: Stifel photograph of presentation materials from Dr. Aronne at ADA, June 2025

Some Effect of Bima on LDL Cholesterol



Over time LDL cholesterol increases improved with the bima/sema combo.

Importantly, in the ADA session it was noted that the transient increase in LDL should be manageable with statins.

The ultimate effect of bima and the combo on HDL cholesterol was notably positive.

Source: Stifel photograph of presentation materials from Dr. Aronne at ADA, June 2025

Investigator Comment

> “The combination of bimagrumab and semaglutide resulted in significant fat mass reduction … while lean mass was largely preserved.”

Louis J. Aronne, M.D., FACP, FTOS

Amylin Agonists

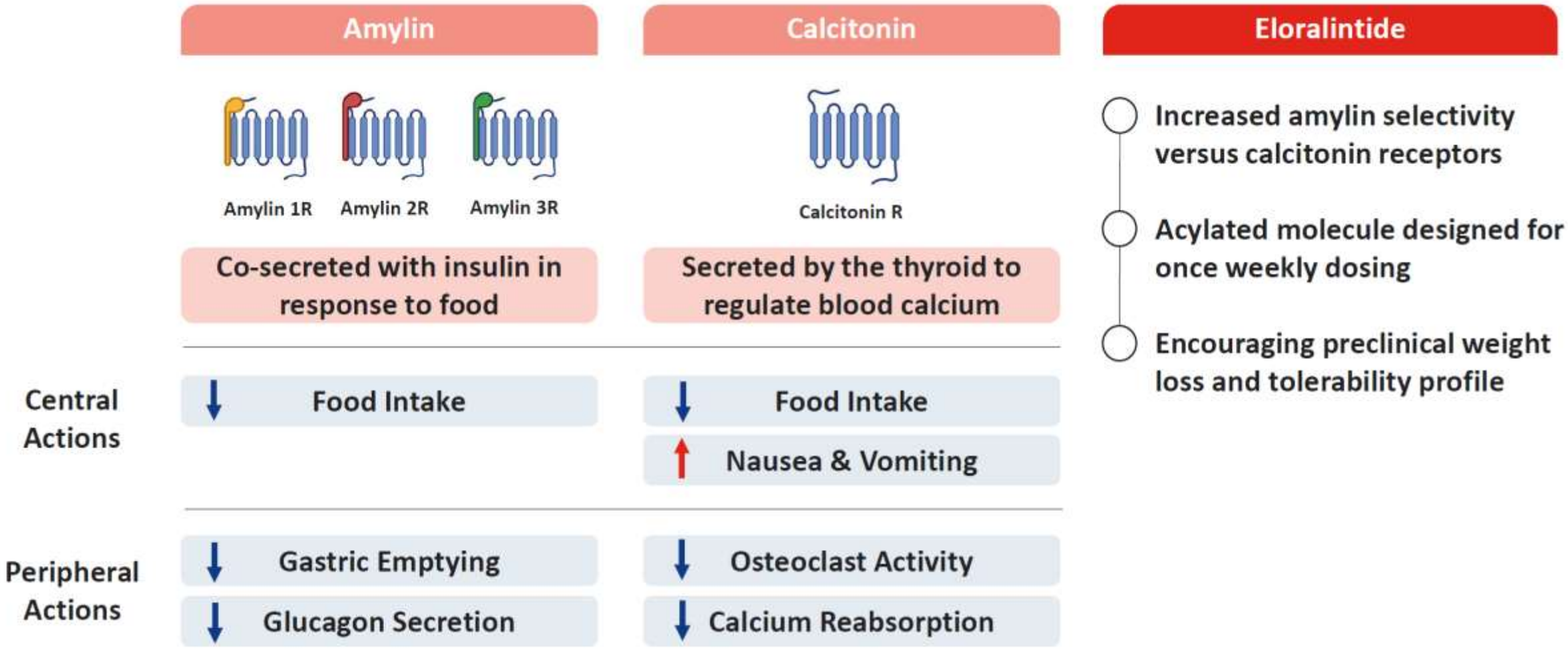
Weight Loss at 12 Weeks Among Various Amylin Agonists

Lilly's Eloralintide and Metsera's MET-233i both look quite impressive versus other molecules. AstraZeneca's AZD6234 and emerging programs from Structure, Verdiva and Viking have not reported sufficient data yet with which to draw a conclusion on weight loss efficacy but presumably some of these programs will also be highly competitive. A particularly important aspect of the amylin analogue drug class is that they can preserve muscle. Substantial research supports this perspective.

	Drug	Approx. % Weight Loss at ~12 Weeks (placebo-adjusted)	Patients in Efficacy Data Generative Monotherapy Trials	Notes
Today's Leader	Eloralintide (Lilly)	11.5%	100	New candidate; robust early effect seen in 2025 ADA data
	Cagrilintide (Novo)	5.5%	706	Novo amylin analogue / Lau et.al. (2021) Lancet
Major Contender	GUBamy (Gubra/AbbVie)	Est. 12%+ (6 wk WL of 9%)	36	Amylin analogue; higher in combo. Looks really good but has seen only 12 subjects at its high dose
Major Contender	Met-233i (Metsera)	Est. 12% + (4 week around -8%)	40	Disclosed 8% placebo-adjusted WL at ADA 2025. Looks really good but unlike eloralintide hasn't seen so many patients.
	Petrelintide (Zealand)	6.6%	54	Dual amylin/calcitonin receptor agonist / Data at ADA 2025
	Pramlintide (AZ)	~3–4%	› 1000	Approved amylin analogue (short-acting)

Source: Stifel Research

Lilly Developing Eloralintide as a Selective Amylin Agonist

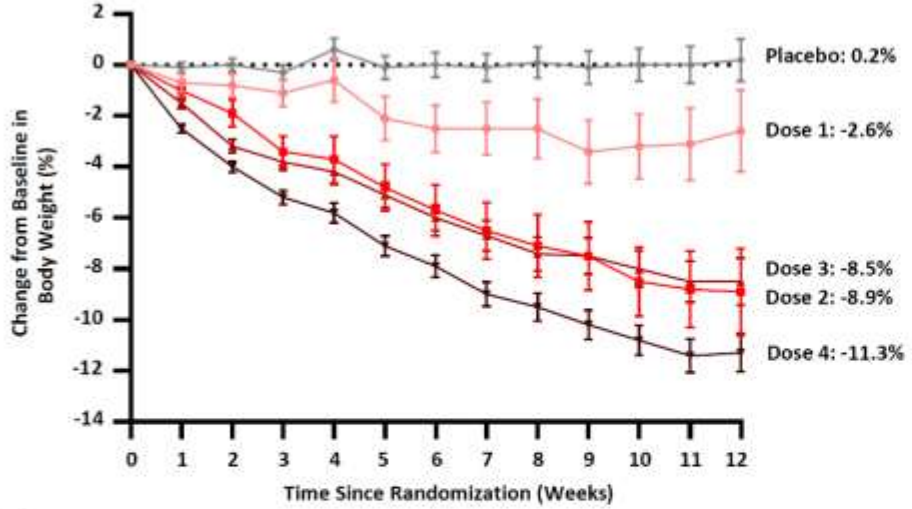


Source: https://investor.lilly.com/static-files/36604492-7d65-4649-bc20-f7b4372c2b2b

Eloralintide Phase 1 Data Shows Impressive 11.3% Weight Loss in Three Months with an 8% Vomiting Rate

Dose 3 delivered 9% weight loss in three months with a nil vomiting rate.

Eloralintide Phase 1 Efficacy



- Weight loss up to 11.3%
- Long half-life enables weekly dosing

Eloralintide Phase 1 Tolerability

% of participants with GI AEs	Placebo (N=27)	Eloralintide[1] Dose 2 (N=6)	Dose 3 (N=23)	Dose 4 (N=36)	Overall (N=73)
Decreased appetite	3.7%	16.7%	26.1%	19.4%	19.2%
Diarrhea	0%	16.7%	8.7%	11.1%	9.6%
Nausea	0%	0%	13.0%	8.3%	8.2%
Vomiting	0%	0%	0%	8.3%	4.1%

- Well-tolerated with <10% incidence of GI side effects
- No dose titration in Phase 1

Phase 2 monotherapy study completing 2H 2025; combination studies with tirzepatide in progress

[1]No GI AEs reported in Eloralintide Dose 1 (N=8)
GI=gastrointestinal; AE=adverse event

Source: https://investor.lilly.com/static-files/36604492-7d65-4649-bc20-f7b4372c2b2b

Metsera-233i Long-Acting Amylin Agonist Shows Data at ADA

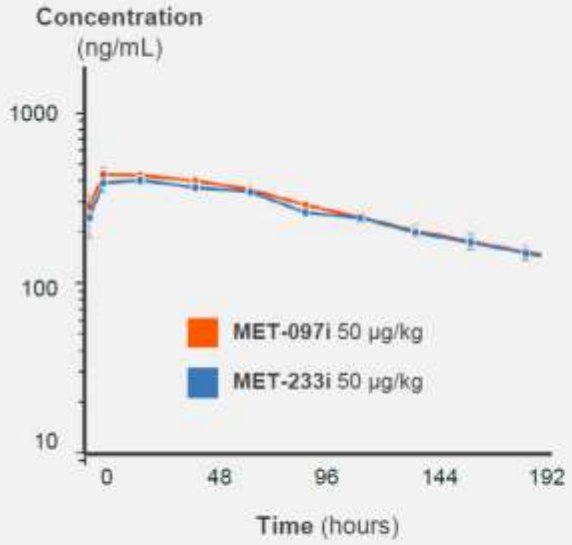
MET-233i WAS ENGINEERED TO BE AN IDEAL AMYLIN ANALOG

Pre-clinical profile demonstrated durability, potency, and combinability with MET-097i

DURABLE

Supports monthly dosing

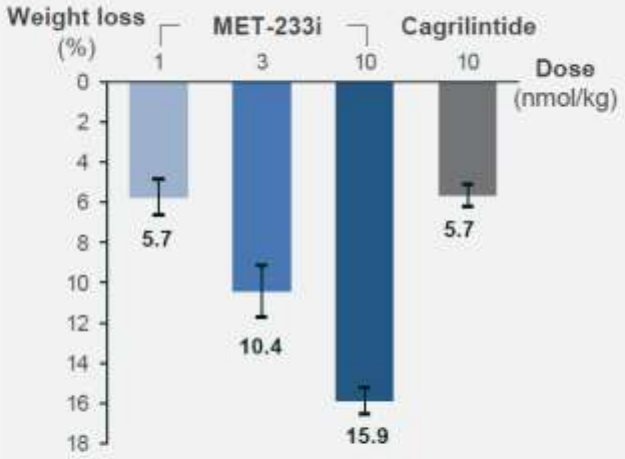
Exposure over time after a single dose of Metsera NuSH peptides in pigs



POTENT

~3x more potent than cagrilintide

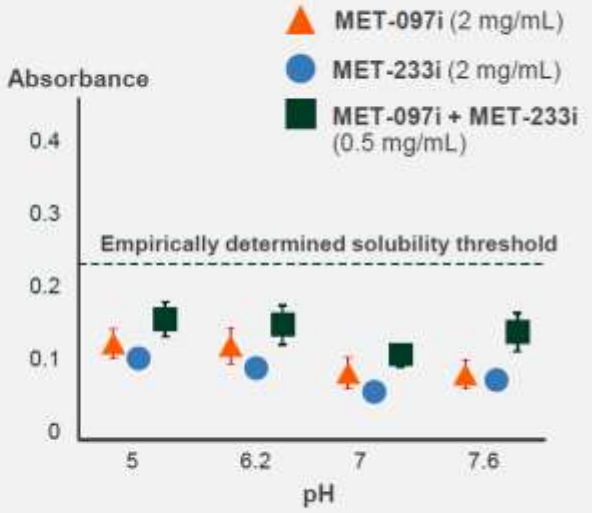
Body weight effects at Day 3 after a single dose in rats



COMBINABLE

Miscible with MET-097i (GLP-1RA)

Solubility of Metsera NuSH peptides and combination at different pH



7

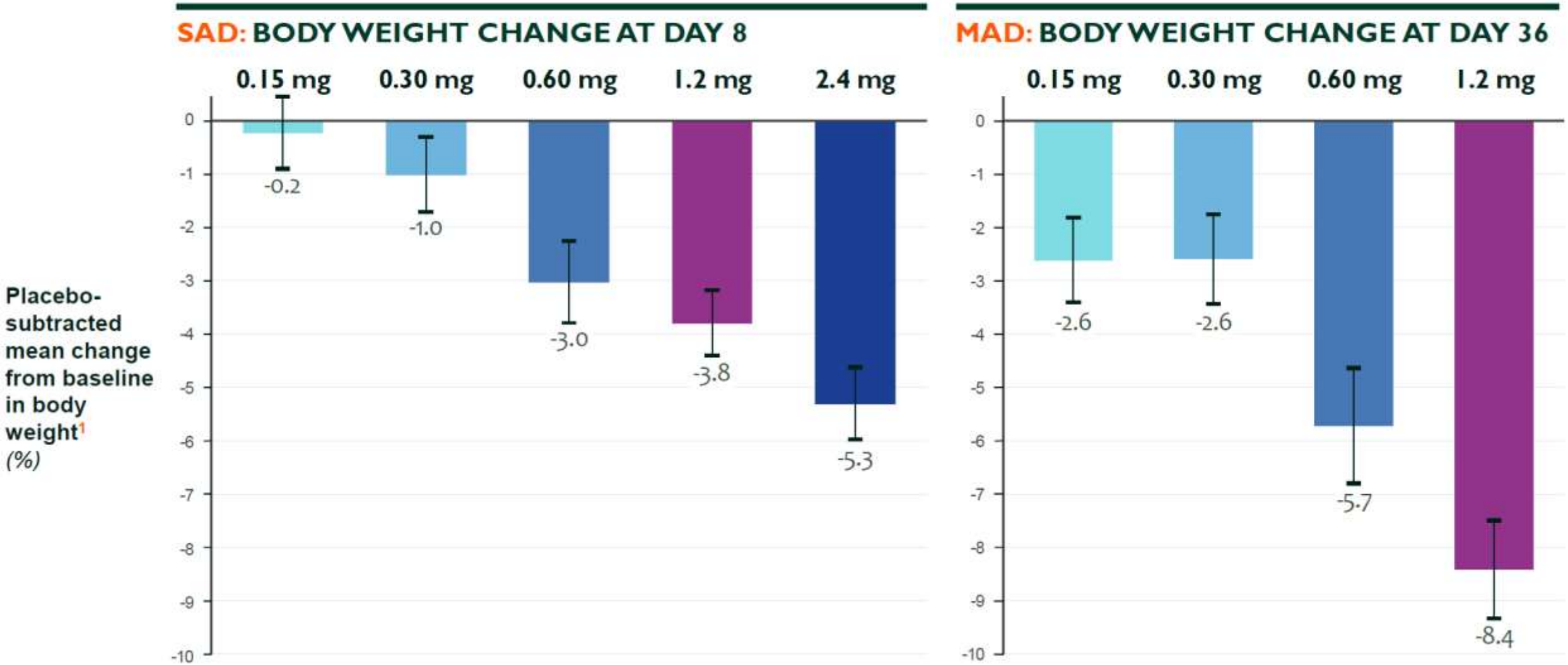
Data presented as means ± standard error of the mean. PK data reflect multiple doses in pigs. Body weight loss data reflect Day 3 body weight change after a single dose, adjusting for vehicle in rats.

Metsera

Source: https://investors.metsera.com/static-files/3e514c6b-fdba-49e5-84f8-aa3168936b8e

MET-233i SINGLE AND MULTIPLE-DOSE WEIGHT LOSS

Up to 8.4% placebo-subtracted mean weight loss after five doses



Source: https://investors.metsera.com/static-files/3e514c6b-fdba-49e5-84f8-aa3168936b8e

MET-233i WELL-TOLERATED

MAD: All gastrointestinal adverse events mild; starting doses with placebo-like tolerability

ONSET OF GASTROINTESTINAL ADVERSE EVENTS BY WEEK IN MAD

	NAUSEA					VOMITING					EXPOSURE
	Placebo	MET-233i				Placebo	MET-233i				MET-233i drug exposure level relative to Week 1
		0.15 mg	0.3 mg	0.6 mg	1.2 mg		0.15 mg	0.3 mg	0.6 mg	1.2 mg	
Week N size	8	8	8	8	8	8	8	8	8	8	
1	1 (12.5%)	1 (12.5%)	1 (12.5%)	6 (75.0%)	8 (100%)	0	1 (12.5%)	0	3 (37.5%)	3 (37.5%)	**1.0x**
2	0	0	0	0	0	0	0	0	0	0	**1.8x**
3	0	0	0	0	0	0	0	0	0	0	**2.3x**
4	0	0	0	0	1 (14.3%)	0	0	0	0	0	**2.4x**
5	1 (12.5%)	0	2 (25.0%)	0	1 (16.7%)	0	0	0	0	0	**2.8x**
Total	1 (12.5%)	1 (12.5%)	2 (25.0%)	6 (75.0%)	8 (100%)	0	1 (12.5%)	0	3 (37.5%)	3 (37.5%)	

Candidate starting doses

Candidate starting doses

All gastrointestinal adverse were mild. No safety signals.

Source: https://investors.metsera.com/static-files/3e514c6b-fdba-49e5-84f8-aa3168936b8e

Gubra/AbbVie GUBamy Shows Excellent Weight Loss

Apr 1, 2025

Gubra announces positive GUBamy Phase 1 interim MAD results

- GUBamy was well tolerated with adverse events being predominantly GI related, mild and consistent with data from the SAD study.
- Doses of 1 mg and 2 mg GUBamy administered once-weekly for six weeks led to a dose dependent mean weight loss. LS Mean weight loss in the 2 mg cohort was -7.77% on day 43. In the placebo group there was an LS Mean weight gain of +1.99% on day 43.
- The body weight loss was sustained in a manner consistent with the SAD study data.
- The study confirmed the favorable half-life of GUBamy of 11 days.
- This interim analysis of the first two cohorts was included in the original study protocol and is disclosed today to comply with Gubra's obligations under stock market rules.

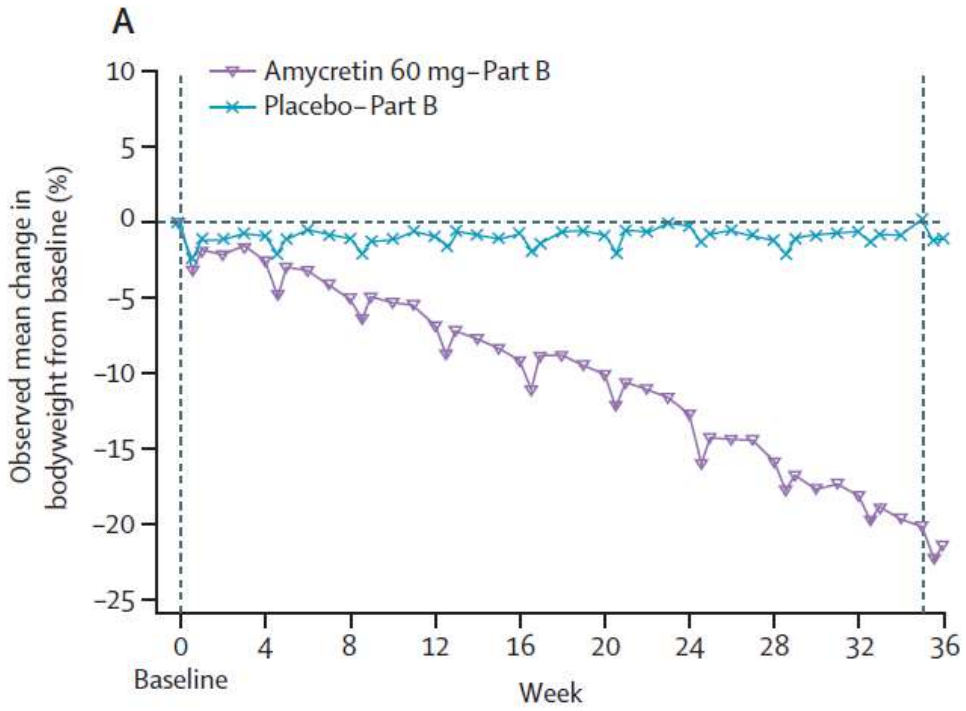
Henrik Blou, CEO of Gubra says:
"The interim topline results from the first part of the MAD study are very encouraging and builds upon and substantiates the results from the SAD study showing that GUBamy has potential to deliver significant body weight reduction with a favorable tolerability profile. We are very pleased with these results that have exceeded our expectations."

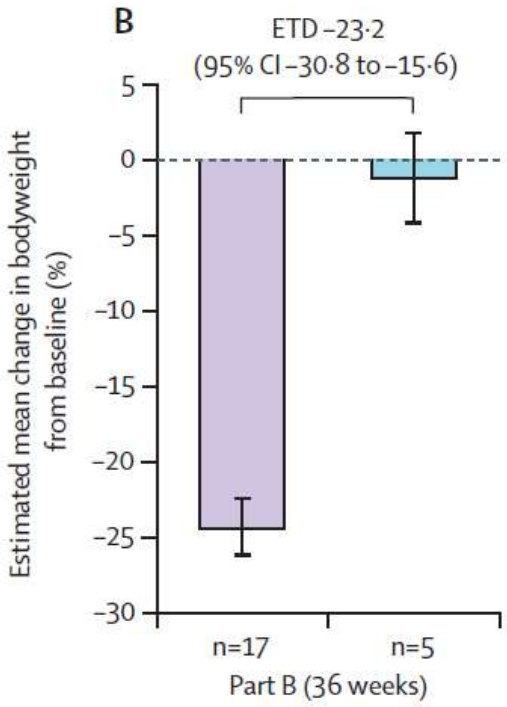
Source: https://www.gubra.dk/mfn_news/gubra-announces-positive-gubamy-phase-1-interim-mad-results/

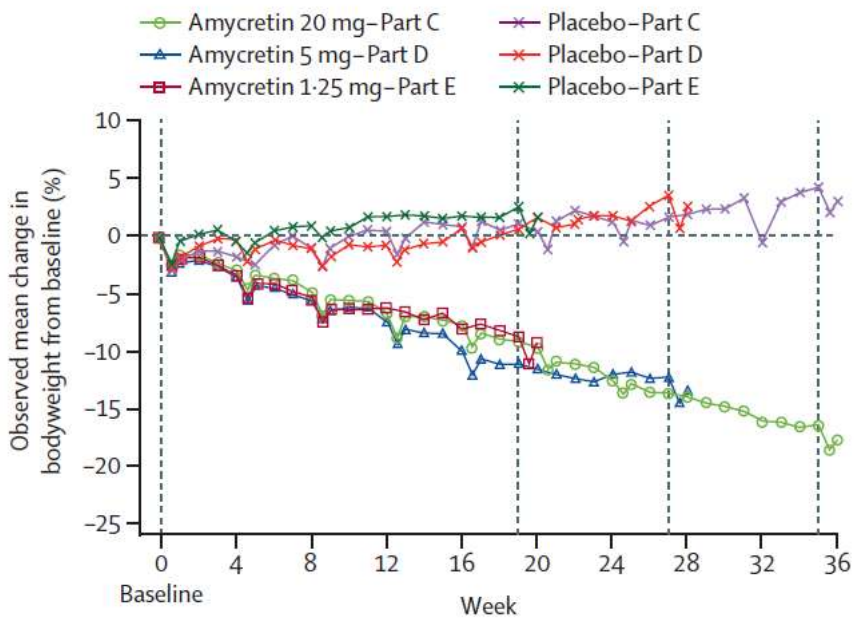
Doublet Incretin Drugs

Novo's Amycretin Delivers Excellent Weight Loss

The 60mg dose of amycretin was associated with a 23.2% placebo-adjusted weight loss at 36 weeks. This sets a new bar for weight loss in nine months. Importantly, this is an early study where patients are likely in a controlled environment. We have previously seen a major drop off in efficacy from Phase 1b studies to Phase 2 (e.g., MariTide). The key question is how well does this replicate in Phase 2 and Phase 3 studies. The better tolerated 20mg dose of SC amycretin was associated with an 20% placebo-adjusted weight loss at 36 weeks.







Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)01185-7

Amycretin 60Mg Dose Likely Too High

	Part B		Part C		Part D		Part E	
	Amycretin 60 mg (n=17)	Placebo (n=5)	Amycretin 20 mg (n=34)	Placebo (n=5)	Amycretin 5 mg (n=16)	Placebo (n=4)	Amycretin 1·25 mg (n=16)	Placebo (n=4)
Treatment-emergent adverse events	17 (100%), 136	5 (100%), 29	33 (97%), 234	5 (100%), 19	16 (100%), 63	4 (100%), 13	14 (88%), 63	4 (100%), 11
Serious adverse events								
Yes	0	0	1 (3%), 1	0	0	0	0	0
No	17 (100%), 136	5 (100%), 29	33 (97%), 233	5 (100%), 19	16 (100%), 63	4 (100%), 13	14 (88%), 63	4 (100%), 11
Events leading to withdrawal	6 (35%), 8	0	7 (21%), 15	1 (20%), 1	1 (6%), 1	1 (25%), 2	0	0
Severity								
Severe	0	0	1 (3%), 1	0	0	0	0	0
Moderate	10 (59%), 16	1 (20%), 2	11 (32%), 18	0	1 (6%), 2	1 (25%), 1	1 (6%), 1	0
Mild	17 (100%), 120	5 (100%), 27	33 (97%), 215	5 (100%), 19	16 (100%), 61	4 (100%), 12	14 (88%), 62	4 (100%), 11
Gastrointestinal adverse events*	16 (94%), 56	4 (80%), 14	32 (94%), 113	3 (60%), 8	15 (94%), 34	1 (25%), 1	10 (63%), 25	2 (50%), 4
Nausea	14 (82%), 17	3 (60%), 3	27 (79%), 36	2 (40%), 2	12 (75%), 12	1 (25%), 1	8 (50%), 8	2 (50%), 2
Vomiting	8 (47%), 15	3 (60%), 3	18 (53%), 20	1 (20%), 1	4 (25%), 5	0	5 (31%), 5	1 (25%), 1
Diarrhoea	7 (41%), 10	1 (20%), 4	11 (32%), 13	1 (20%), 1	4 (25%), 4	0	4 (25%), 4	1 (25%), 1
Constipation	2 (12%), 2	1 (20%), 1	15 (44%), 16	1 (20%), 1	2 (13%), 2	0	2 (13%), 2	0
Dyspepsia	3 (18%), 3	0	12 (35%), 12	0	5 (31%), 6	0	2 (13%), 2	0
Abdominal pain	3 (18%), 3	1 (20%), 1	2 (6%), 3	0	1 (6%), 1	0	1 (6%), 1	0
Gastroesophageal reflux disease	1 (6%), 1	1 (20%), 1	6 (18%), 7	2 (40%), 2	2 (13%), 2	0	1 (6%), 2	0
Eructation	0	1 (20%), 1	1 (3%), 1	1 (20%), 1	1 (6%), 1	0	1 (6%), 1	0

With 35% of subjects dropping out on 60mg amycretin by week 36, versus 0% with placebo, it looks to us like the 20mg dose is more likely to be the commercially viable option for patients. Vomiting rates look high on this dose but this trial did not necessarily feature the type of run in that Novo would use in a Phase 2 study to manage tolerability.

Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)01185-7

Some Increase in Heart Rate Seen with Amycretin

While patients saw an increase in heart rate on amycretin it does not appear concerning. Novo indicates that it will monitor this parameter. We hypothesize that patients may be using beta blockers less as their blood pressure comes under better control on the drug.

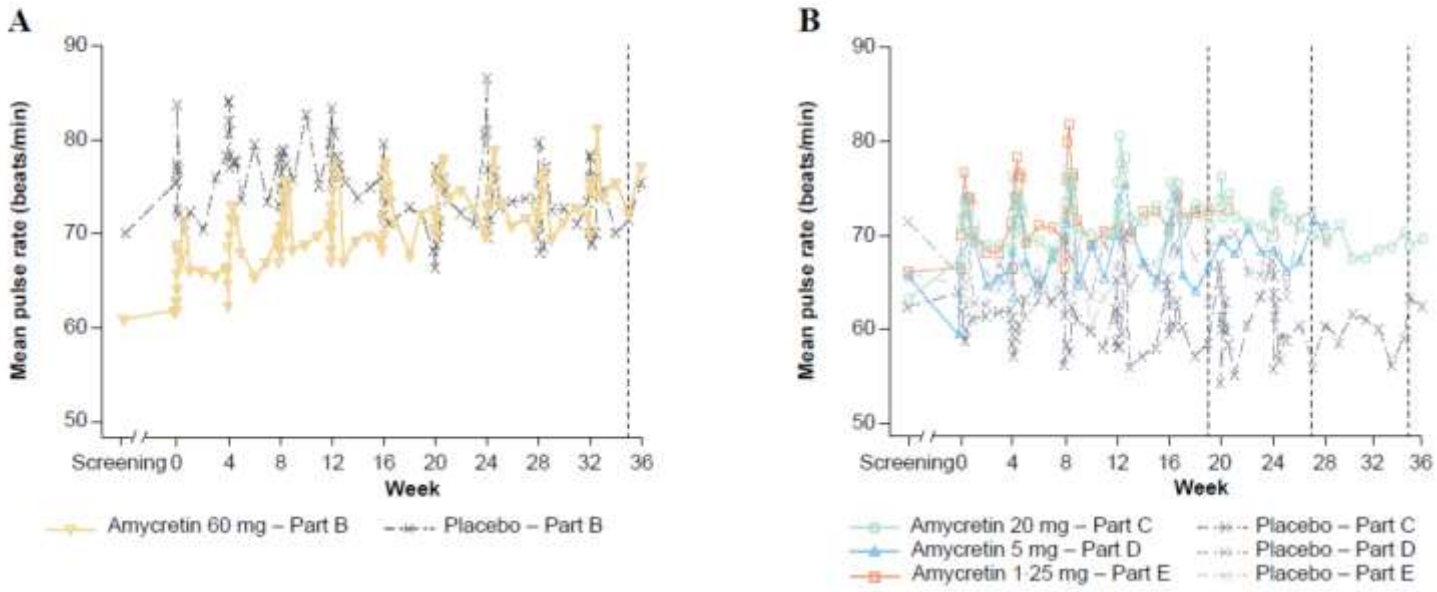
Increases in heart rate observed in Parts B–E were consistent with the previously reported effects of amycretin[23] and an early-phase study of CagriSema,[19] and higher than the increases observed with semaglutide and tirzepatide.[30] This safety parameter will be closely followed during future clinical development. Reductions in blood pressure have previously been reported following weight reduction,[31] treatment with a GLP-1 receptor agonist,[1] and early-phase assessment of fixed-dose combinations of GLP-1 and amylin receptor agonists (CagriSema).[19] Furthermore, a 3–9 mm Hg reduction in systolic blood pressure was observed after 12 weeks of oral amycretin treatment in people with overweight or obesity.[23] In contrast, no effects of subcutaneous amycretin on blood pressure were reported here. This could in part be attributable to the relatively low baseline blood pressure (<120 mm Hg systolic blood pressure) of this small study population, but will need to be explored in larger, future studies. Similar to oral amycretin

Figure S2: **Vital signs – Pulse rate – Parts B–E**

Mean pulse rate from baseline to EOT, in (A) Part B, and (B) Parts C–E.

Vertical reference lines at 19, 27, and 35 weeks represent the last dosing of amycretin for Part E, Part D, and Parts B and C, respectively.

EOT=end of treatment.



Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)01185-7

Amycretin Poster at ADA

2002-LB

Amycretin, a Novel, Unimolecular GLP-1 and Amylin Receptor Agonist: Results of a Phase 1b/2a Clinical Trial

Kirsten Dahl[1], Kasper Adelborg[2], Sohan Dey[3], Ruben Duque do Vale[2], Cassandra Key[4], Søren Toubro[2], **Ania M. Jastreboff[5]**

Aim

- To investigate the safety, tolerability, pharmacokinetics, and effects on body weight of subcutaneous (s.c.) amycretin in people with overweight or obesity.

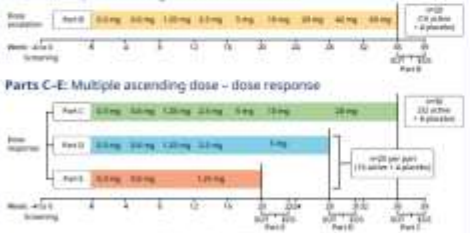
Introduction

- Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, have provided clinically significant reductions in body weight[1] and improvements in additional outcomes.[2]
- Amylin, a peptide hormone co-secreted with insulin, helps regulate body weight by reducing appetite and energy intake, and increasing satiety.[3]
- Amycretin (NNC0487-0111) is a novel, unimolecular GLP-1 and amylin receptor agonist targeting both complementary biological pathways.
- In a first-in-human study, once-daily oral amycretin led to reductions in body weight in individuals with overweight or obesity after 12 weeks.[4]

Methods

- In this phase 1b/2a randomized, placebo-controlled, single-center, double-blind study (NCT06064006), adults with a body mass index 27.0–39.9 kg/m² and glycated hemoglobin (HbA_{1c}) <6.5% were eligible.
- The study had five parts. Part A investigated three single ascending doses of amycretin to identify a tolerable starting dose for Parts B–E. This poster focuses on Parts B–E.
- The study design for Part B (multiple ascending dose [MAD] – dose escalation) and Parts C-E (MAD – dose response) are shown in **Figure 1**.

Figure 1. Study design for Parts B–E



- The primary endpoint was the number of treatment-emergent adverse events (TEAEs). Secondary endpoints were the area under the amycretin plasma concentration-time curve (AUC) from pre-dose of final dose to end of treatment (EOT), maximum plasma concentration from pre-dose of final dose to end of study (EOS), and relative change in body weight from baseline (pre-dose on day 1) to EOT for Parts B–E.
- Prespecified exploratory endpoints for Parts B–E included changes in fasting plasma glucose and HbA_{1c} from baseline to EOT.

Results

- A total of 125 participants were randomized to s.c. amycretin (n=101) or placebo (n=24).
- Across Parts A–E, 41 participants withdrew, 24 due to non-TEAE reasons (mainly withdrawal of consent or recreational drug use) and 17 due to TEAEs, most frequently gastrointestinal in nature.
- For Parts B–E, 22, 39, 20, and 20 participants, respectively, were included in the full analysis set and safety analysis set.
- Demographics and baseline characteristics for participants in Parts B–E are shown in **Table 1**.

Table 1. Demographics and baseline characteristics for Parts B–E

	Part B	Part C	Part D	Part E
	Amycretin 60 mg	Placebo	Amycretin 20 mg	Placebo	Amycretin 5 mg	Placebo	Amycretin 1.25 mg	Placebo
Number of participants	17	5	34	6	16	4	16	4
Age, mean (SD), years	42 (10)	34 (12)	49 (9)	28 (5)	36 (9)	33 (5)	39 (7)	28 (6)
Sex, n (%)[a]								
Male	7 (41)	2 (40)	14 (41)	3 (50)	6 (38)	–	12 (75)	3 (75)
Female	10 (59)	3 (60)	20 (59)	3 (50)	10 (63)	4 (100)	4 (25)	1 (25)
Body weight, mean (SD), kg	89.4 (13.8)	83.8 (18.5)	90.4 (15.9)	99.4 (8.7)	92.3 (15.3)	88.3 (15.3)	99.1 (20.4)	96.1 (1.7)
BMI, mean (SD), kg/m²	31.5 (3.4)	30.0 (2.5)	32.0 (3.7)	30.8 (1.7)	32.8 (3.2)	32.5 (2.9)	32.2 (3.6)	33.1 (3.0)
HbA_{1c}, mean (SD), %-point	5.5 (0.3)	5.3 (0.1)	5.4 (0.3)	5.7 (0.2)	5.2 (0.3)	4.9 (0.5)	5.4 (0.2)	5.2 (0.3)
Fasting plasma glucose, mean (SD), mmol/L	5.3 (0.4)	5.6 (0.4)	5.6 (0.4)	5.9 (0.3)	5.2 (0.3)	4.9 (0.3)	5.2 (0.4)	5.0 (0.1)

Data are for the safety analysis set. [a]Sex was self-reported by participants. BMI, body mass index; HbA_{1c}, glycated hemoglobin; SD, standard deviation.

- Following 36 weeks of dose escalation (Part B), dose levels up to 60 mg appeared safe and tolerable, with no new safety signals observed.
- Most TEAEs were mild to moderate in severity and resolved by EOS.
- The most common TEAEs were gastrointestinal and were observed at a higher frequency at higher amycretin doses (**Table 2**).
- Plasma concentration-time profiles of s.c. amycretin for Parts B–E were consistent with dose-proportionality.
- Across all active treatment arms in Parts B–E, geometric mean t_{max} (min; max) was approximately 23–30 hours (8; 96) post-dose. The geometric mean $t_{1/2}$ at steady state in Parts B–E ranged from approximately 88–99 hours.
- Observed percentage body weight changes are presented in **Figure 2A** for Part B and **Figure 2B** for Parts C–E.
- In Part B, estimated changes in body weight were significantly ($p<0.0001$) greater with amycretin versus placebo (**–24.3% vs –1.1%**, respectively; week 36) (**Figure 2C**).
- Estimated changes in body weight were significantly ($p<0.0001$) greater with amycretin versus placebo in Part C (**–22.0% vs 1.9%**, respectively; week 36), Part D (**–16.2% vs 2.3%**, respectively; week 28), and Part E (**–9.7% vs 2.0%**, respectively; week 20) (**Figure 2D**).

Table 2. Summary of TEAEs in Parts B–E

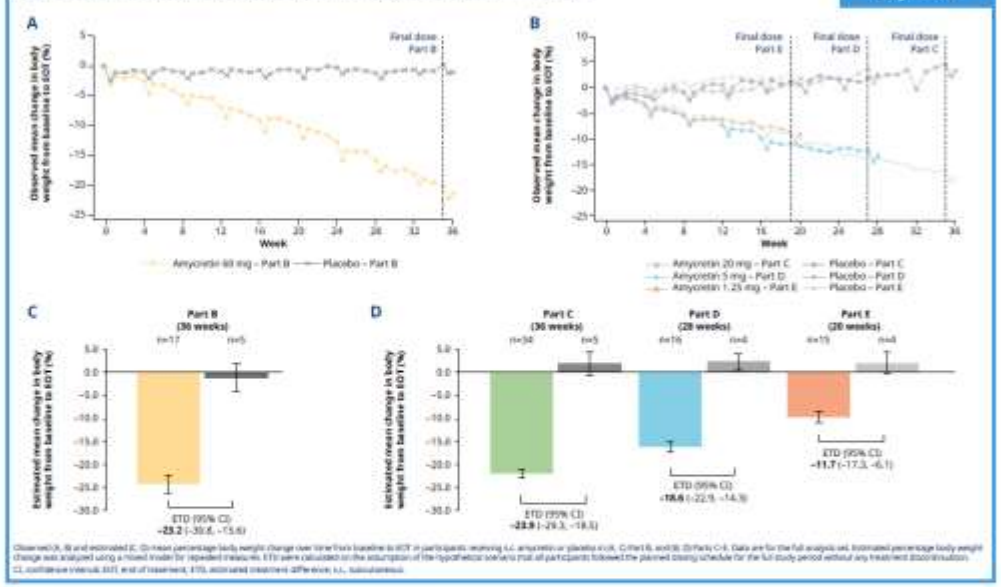
	Part B	Part C	Part D	Part E
	Amycretin 60 mg	Placebo	Amycretin 20 mg	Placebo	Amycretin 5 mg	Placebo	Amycretin 1.25 mg	Placebo
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Number of participants	17		5		34		6		16		4		16		4	
TEAEs	17 (100)	136	5 (100)	29	33 (97)	234	5 (100)	19	15 (100)	63	4 (100)	13	14 (88)	63	4 (100)	11
SAEs	–		–		1 (3)	1	–		–		–		–		–	
Events leading to withdrawal	4 (25)	4	–		7 (21)	15	1 (20)	1	1 (6)	1	1 (25)	2	–		–	
Severity																
Severe	–		–		1 (3)	1	–		–		–		–		–	
Moderate	10 (59)	16	1 (20)	2	11 (32)	90	–		1 (6)	2	1 (25)	1	1 (6)	1	–	
Mild	17 (100)	120	5 (100)	27	33 (97)	210	5 (100)	19	15 (100)	61	4 (100)	12	14 (88)	62	4 (100)	11
Related to trial product																
Probably	17 (100)	85	4 (80)	20	32 (94)	155	5 (83)	12	15 (100)	47	3 (75)	7	13 (81)	44	3 (75)	8
Possibly	12 (71)	28	3 (60)	2	26 (77)	54	3 (60)	2	6 (50)	13	1 (25)	2	6 (38)	10	1 (25)	1
Unlikely	12 (71)	19	3 (60)	7	15 (44)	25	4 (80)	5	3 (19)	3	4 (100)	4	6 (38)	5	2 (50)	2
Most common TEAEs by SOC and PT in ≥20% of participants in any treatment arm																
Gastrointestinal AEs	16 (94)	56	4 (80)	14	32 (94)	110	3 (60)	8	15 (94)	44	1 (25)	1	13 (81)	29	2 (50)	4
Nausea	14 (82)	17	3 (60)	6	27 (79)	36	2 (40)	2	12 (75)	12	1 (25)	1	8 (50)	8	2 (50)	2
Vomiting	8 (47)	15	3 (60)	9	18 (53)	20	1 (20)	1	4 (25)	5	–		5 (31)	5	1 (25)	1
Diarrhea	7 (41)	10	1 (20)	4	11 (32)	14	1 (20)	1	6 (25)	6	–		6 (25)	6	1 (25)	1
Constipation	2 (12)	2	1 (20)	1	15 (44)	16	1 (20)	1	2 (13)	2	–		3 (19)	2	–	
Dyspepsia	3 (18)	4	–		12 (35)	12	–		3 (21)	6	–		3 (19)	2	–	
Metabolism and nutrition AEs	10 (59)	11	3 (60)	3	21 (62)	22	2 (40)	2	12 (75)	12	3 (75)	4	11 (69)	11	3 (75)	3
Decreased appetite	10 (59)	11	3 (60)	3	21 (62)	22	2 (40)	2	12 (75)	12	3 (75)	4	11 (69)	11	3 (75)	3
General AEs and administration-site conditions	11 (65)	18	2 (40)	3	15 (56)	22	3 (60)	3	5 (31)	6	1 (25)	1	8 (50)	11	2 (50)	2
Early satiety	4 (24)	5	1 (20)	1	9 (27)	10	1 (20)	1	1 (6)	1	1 (25)	1	5 (31)	5	2 (50)	2
Fatigue	7 (41)	7	2 (40)	2	10 (29)	10	2 (40)	2	2 (13)	2	–		4 (25)	3	–	
Nervous system AEs	13 (77)	25	3 (60)	5	23 (68)	39	1 (20)	1	6 (38)	7	2 (50)	2	7 (44)	8	2 (50)	2
Headache	10 (59)	16	2 (40)	5	14 (41)	20	1 (20)	1	5 (31)	6	1 (25)	1	7 (44)	8	2 (50)	2
Infections and infestations	4 (24)	6	2 (40)	2	5 (15)	6	2 (40)	2	1 (6)	1	1 (25)	1	2 (13)	3	–	
COVID-19	2 (12)	2	2 (40)	2	5 (15)	5	2 (40)	2	–		–		2 (13)	2	–	

Data are for the safety analysis set. AE, adverse event; E, number of events; PT, preferred term; SAE, serious adverse event; SOC, system organ class. TEAE, treatment-emergent adverse event.

- In participants receiving amycretin, there was no indication of a plateauing of body weight reduction.
- Estimated mean changes from baseline to EOT in fasting plasma glucose ranged from **0 to –0.8 mmol/L** across the amycretin treatment arms compared with **0 to –0.2 mmol/L** for placebo.
- An estimated mean change in HbA_{1c} of between **–0.2% and –0.6%** was observed in amycretin groups (changes with placebo were ≥0.1%).

Figure 2. Supportive secondary endpoint – percentage body weight change in Parts B–E

Key result



Discussion

- Amycretin, a unimolecular GLP-1 and amylin receptor agonist, is the first treatment to harness the two distinct biological pathways stimulated by GLP-1 and amylin in a single molecule.
- Significantly greater body weight reduction was observed with s.c. amycretin versus placebo in Parts B–E.
- Significant dose-dependent body weight reduction, sustained during 12-week maintenance dose periods, was consistent with the phase 1 study of oral amycretin at week 12.[4]
- Gastrointestinal TEAEs were the most frequently reported and the overall profile of TEAEs was similar to those reported in early-phase studies of GLP-1 receptor, GLP-1/gastric inhibitory polypeptide receptor, and amylin receptor agonists.[5,6]
- The high participation burden, including weekly visits and regular in-house stays, was likely to have contributed to participant fatigue and the high proportion of participants who withdrew due to non-TEAE reasons (59% across Parts A–E).

Conclusion

- In this phase 1b/2a study, once-weekly s.c. amycretin treatment up to 60 mg in individuals with overweight or obesity appeared safe and tolerable, with a safety profile consistent with those of GLP-1 and amylin receptor agonists.
  - No new safety signals were observed. While the frequency of gastrointestinal TEAEs was high, this was in line with early phase studies for these drug classes.[4,6]
- The estimated dose-dependent body weight reduction, ranging from 9.7% to 22.0% in Parts C–E, occurred with no observed plateauing at the end of the 12-week maintenance dose periods, suggesting a longer treatment duration may provide additional body weight reductions.
- The amycretin clinical development program will further assess the benefits of amycretin as a potential new therapeutic option for weight management and type 2 diabetes.

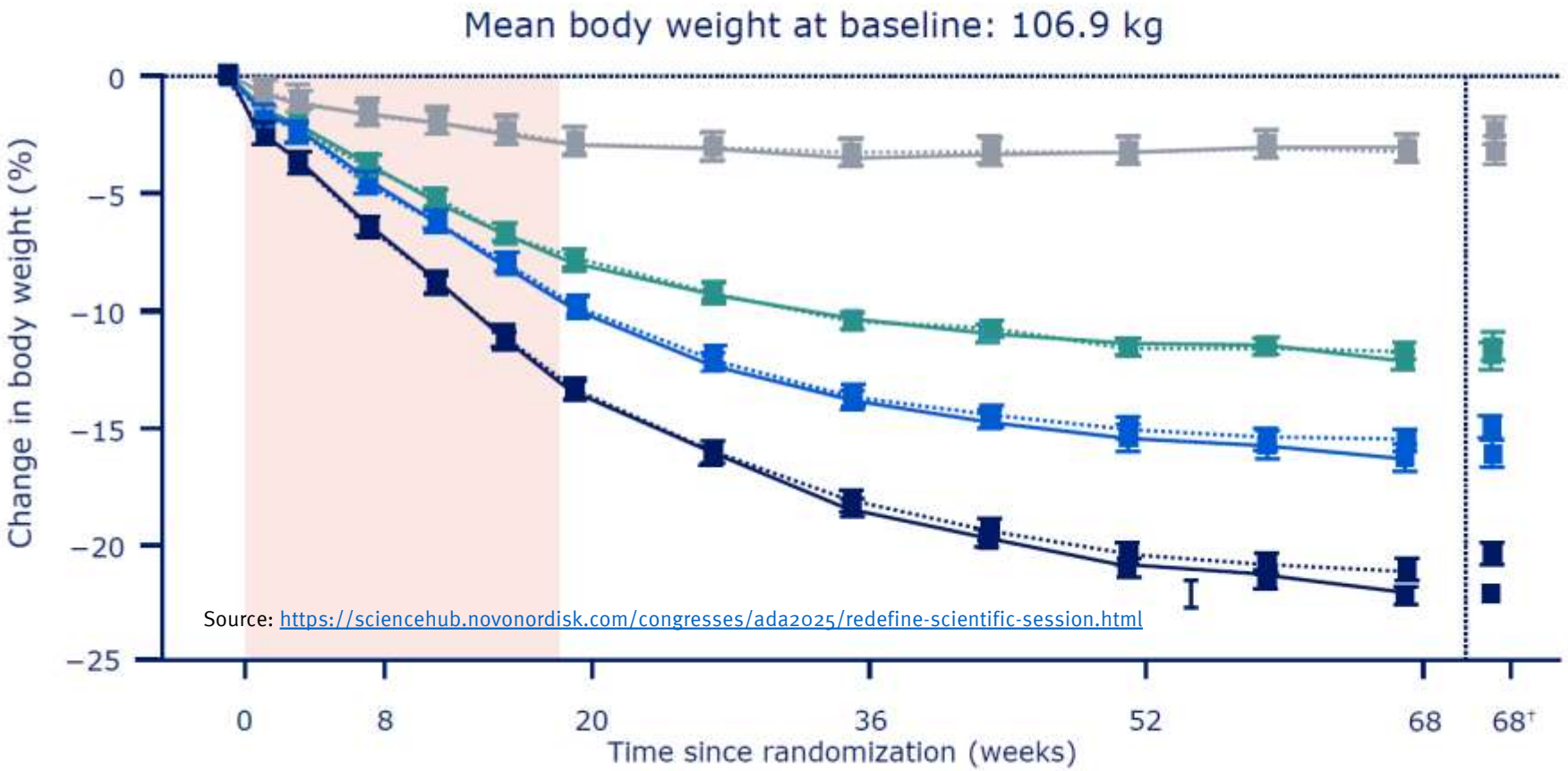
Source: https://sciencehub.novonordisk.com/congresses/ada2025/Jastreboff.html

CagriSema Data at ADA

REDEFINE 1

Participants treated with CagriSema 2.4 mg/2.4 mg achieved weight reduction of up to 22.7%

Change from baseline to week 68 in body weight (%)



Source: https://sciencehub.novonordisk.com/congresses/ada2025/redefine-scientific-session.html

	Trial product estimand (on-treatment)	Treatment policy estimand (in-trial)
Placebo	−2.3%	−3.0%
Cagrilintide 2.4 mg	−11.8%	−11.5%
Semaglutide 2.4 mg	−16.1%	−14.9%
CagriSema 2.4 mg/2.4 mg	−22.7%	−20.4%

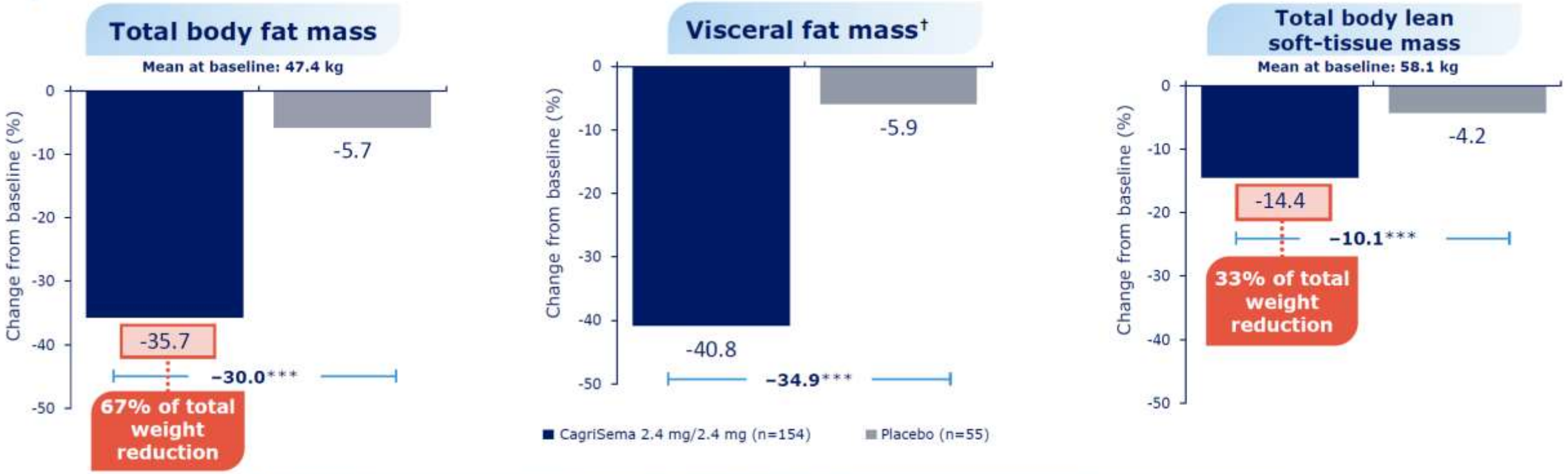
†Estimated means from the statistical analysis. Trial product estimand: The difference in mean change in body weight from baseline to week 68 for all randomized participants, had all participants remained on randomized treatment (regardless of dose level) without initiation of rescue intervention, where trial product is used as adjunct to a reduced-calorie diet and increased physical activity. Treatment policy estimand: The difference in mean change in body weight from baseline to week 68 for all randomized participants, irrespective of adherence to treatment or initiation of anti-obesity rescue intervention, where trial product is used as adjunct to a reduced-calorie diet and increased physical activity. Error bars are ± standard error of the mean.

CagriSema Data at ADA

REDEFINE 1

CagriSema 2.4 mg/2.4 mg improved body composition with majority of improvement driven by reduction in total body fat mass

Change at week 68 in body composition parameters, relative to baseline, as assessed by DXA: trial product estimand



Lean soft-tissue mass and fat-free/lean body mass are not synonymous; the latter includes tissue such as bone, while lean soft-tissue mass does not

****Estimated treatment difference CagriSema vs placebo, p<0.0001; †No baseline value presented due to differences between equipment in the size of the area scanned for visceral fat assessment. Percentages are based on randomized participants for the DXA subgroup of in the full analysis set. Trial product estimand: The difference in mean change in body weight from baseline to week 68 for all randomized participants, had all participants remained on randomized treatment (regardless of dose level) without initiation of rescue intervention, where trial product is used as adjunct to a reduced-calorie diet and increased physical activity. DXA, dual-energy X-ray absorptiometry.*

Source: https://sciencehub.novonordisk.com/congresses/ada2025/redefine-scientific-session.html

Hengrui (Kailera) Update GLP-1/GIP Agonist Data at ADA

Efficacy and Safety of HRS9531, a Novel Dual GLP-1/GIP Receptor Agonist, in Chinese Adults with Obesity without Diabetes—Up to 52-Week Treatment

Lin Zhao[1], Dan Zhu[2], Tianrong Pan[3], Dongji Wang[4], Hongwei Ling[5], Ya Li[6], Hanqing Cai[7], Zhifeng Cheng[8], Dexue Liu[9], Yuan Hu[10], Xianfeng Zhang[11], Hong Chen[12], Yue Zuo[12], Yuqi Sun[12], Xiaoying Li[1]

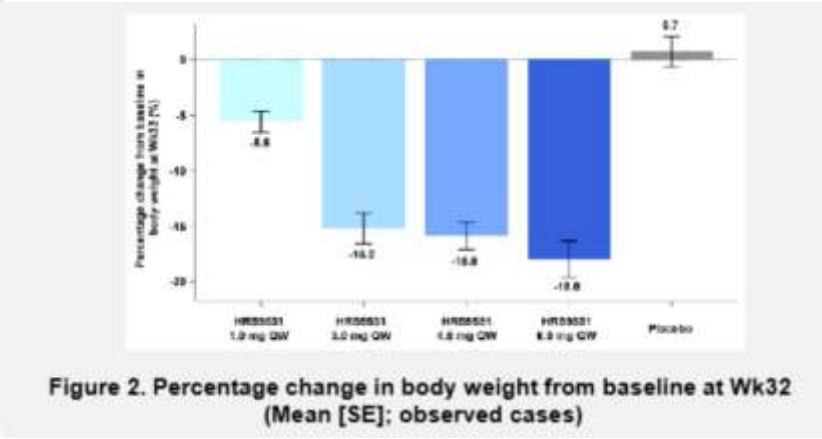


Figure 2. Percentage change in body weight from baseline at Wk32 (Mean [SE]; observed cases)

Table 2. Treatment-emergent adverse events during the 32-week placebo-controlled treatment period

	HRS9531 1.0 mg QW (n=49)	HRS9531 3.0 mg QW (n=51)	HRS9531 4.5 mg QW (n=50)	HRS9531 6.0 mg QW (n=49)	Placebo (n=49)
Any TEAEs	37 (75.5)	45 (88.2)	40 (80.0)	45 (91.8)	42 (85.7)
TESAEs	1 (2.0)	2 (3.9)	3 (6.0)	0	3 (6.1)
TEAEs leading to treatment discontinuation	1 (2.0)	1 (2.0)	0	0	1 (2.0)
Gastrointestinal disorders with ≥5% frequency in any arm					
Nausea	8 (16.3)	14 (27.5)	16 (32.0)	16 (32.7)	4 (8.2)
Diarrhea	5 (10.2)	18 (35.3)	15 (30.0)	16 (32.7)	4 (8.2)
Vomiting	3 (6.1)	10 (19.6)	12 (24.0)	14 (28.6)	1 (2.0)
Abdominal distension	1 (2.0)	9 (17.6)	3 (6.0)	4 (8.2)	0
Dyspepsia	0	4 (7.8)	1 (2.0)	1 (2.0)	0
Constipation	1 (2.0)	3 (5.9)	1 (2.0)	3 (6.1)	0

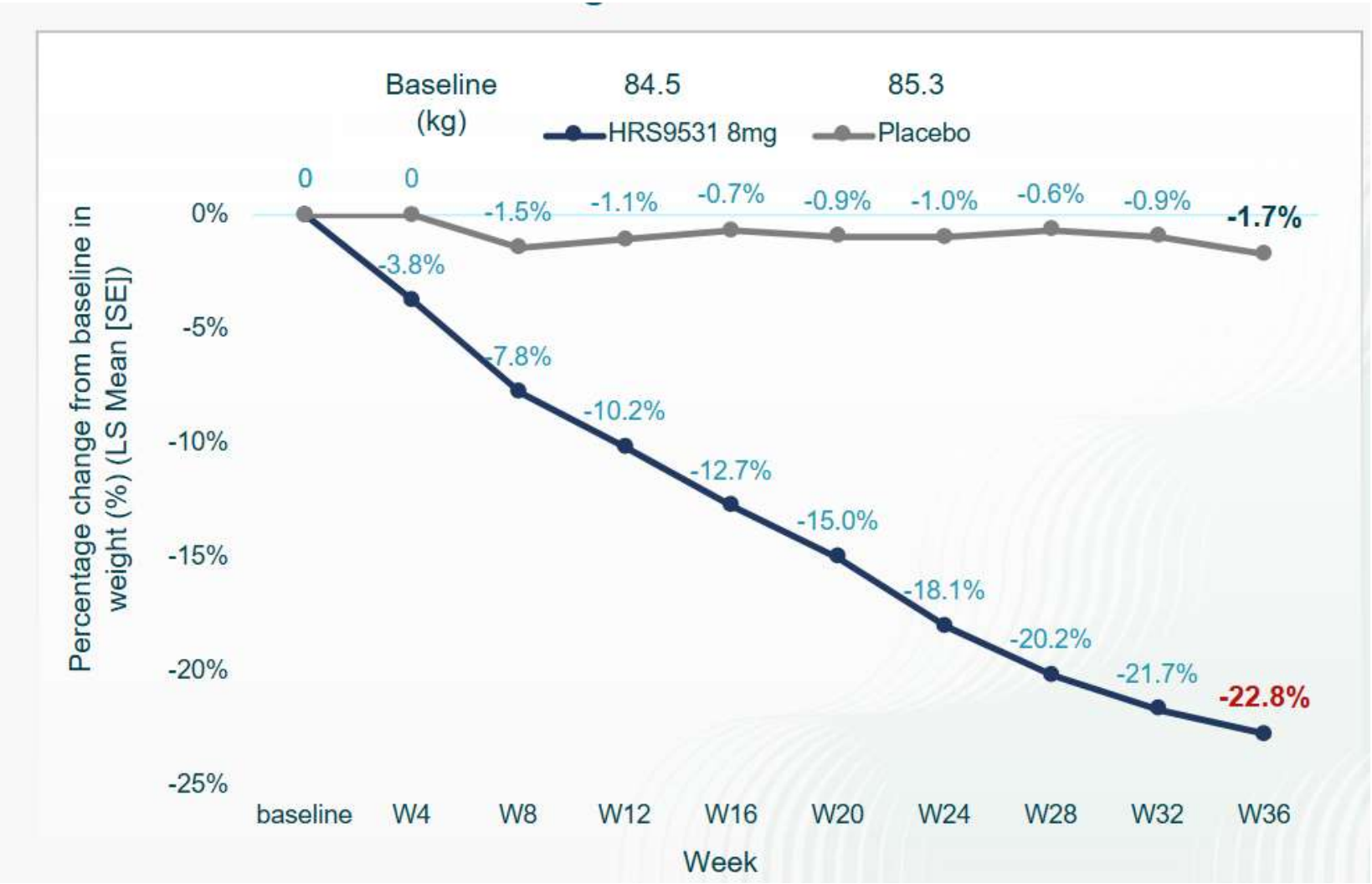
Discontinuation rates were low in this study and the efficacy effect was quite strong at 32 weeks. While vomiting rates at the higher doses were in the mid-20s (similar to other competitive drugs.

Hengrui was able to get the nausea and vomiting rate down when using a lower starting dose.

We presume that Kailera will be able to manage down the tolerability issues seen in this study in its U.S. Phase 3 work.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/853-P/159922/853-P-Efficacy-and-Safety-of-a-Novel-Dual-GLP-1

Weight Loss on Hengrui's (Kailera) HRS-9531 is the Only Real Match for Retatrutide So Far That We Have Seen at 36 Weeks



Patients on the 8mg dose of HRS-9531 lost a stunning 21.1% of weight at 9 months on a placebo-adjusted basis.

This is quite a strong result. We look forward to seeing the first round of Phase 3 data from Hengrui / Kailera later this year.

Source: Kailera Poster at ADA.

Verdiva/Sciwind Developing an Alternative to Amycretin

EFFICACY OF A NOVEL ORAL AMYLIN ANALOG AND THE DEVELOPMENT OF AN ORAL AMYLIN/GLP-1 COFORMULATED TABLET TO PRODUCE HIGH IN VIVO PLASMA EXPOSURES

Verdiva Bio

Haixia Zou[2], Yinle Wu[2], Wanjun Guo[2], Jianhui Deng[2], Catherine Jones[1], Susan Trieu[1], Richard Ho[1], Mohamed Eid[1], Jane Hughes[1], Weidong Zhong[1], Martijn Fenaux[1], Yan Li[2] | 1. Verdiva Bio, London, UK. 2. Sciwind Biosciences, Hangzhou, China.

Background

- Amylin and GLP-1 peptide hormones independently reduce food intake, delay gastric emptying, and decrease glucagon release[1,2]
- Amylin agonists have the potential to be effective monotherapies or supplement GLP-1 receptor agonists (RA) in combination therapy for improved efficacy[3]
- VRB-103, a novel oral amylin analog, is being developed for the treatment of obesity and was designed as a dual amylin and calcitonin receptor agonist (DACRA)
- VRB-103 was designed leveraging rational peptide engineering to improve potency and half-life. In addition to proprietary oral delivery technology (T2026) to provide a once-weekly oral VRB-103 formulation
- VRB-103 in development with VRB-101, a GLP-1 analog, is explored in this poster as a once-weekly oral combination therapy (fixed dose oral combination)

Methods

PK study

- An oral coformulated tablet of VRB-103, VRB-101, and T2026 was dosed daily in cynomolgus monkeys for 7 days and PK samples were collected and analyzed

***In vitro* potency study**

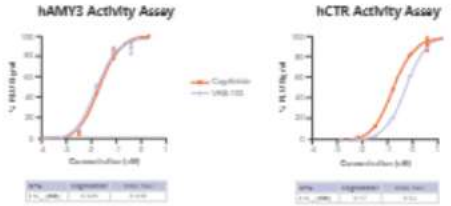
- CHO-K1 CRE reporter cells overexpressing either the rat, cynomolgus monkey, or human amylin receptor complex (calcitonin receptor and RAMP3) (hAMY3), or calcitonin receptor alone (hCTR) were treated with VRB-103 or a comparator (cagrilintide, an amylin analog); receptor activation was measured by luciferase expression

Efficacy in a DIO rat model

- DIO rats (n=8 animals per group; 17 weeks on a high-fat diet [research diets, D12492]) received QD subcutaneous injections for 3 weeks of either vehicle, VRB-103, VRB-101, or VRB-103 in combination with VRB-101

Results #1

FIGURE 1. VRB-103 WAS DESIGNED FOR POTENT hAMY3 AND hCTR ACTIVITY[4]



- VRB-103 activated hAMY3 and hCTR with similar potency to cagrilintide

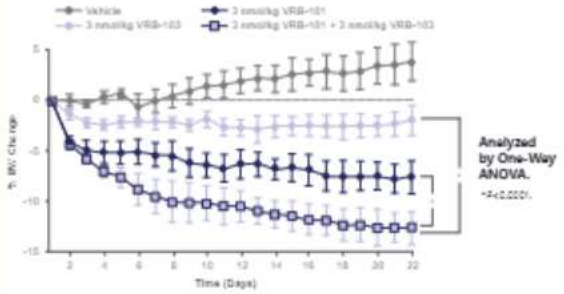
Results #2

TABLE 1. CROSS SPECIES *IN VITRO* POTENCY OF VRB-103 AND CAGRILINTIDE IN CHO-K1 CRE REPORTER CELLS EXPRESSING HUMAN, MONKEY, OR RAT AMY3[4]

Sample ID	Average EC_{50} (nM) ± SD		
	Human	Monkey	Rat
Cagrilintide	0.701 ± 0.130	0.731 ± 0.075	23.095 ± 3.195
VRB-103	1.122 ± 0.553	2.012 ± 0.156	292.2 ± 50.3

- Oral amylin peptide VRB-103 has high potency against the human AMY3 receptor
- VRB-103 has reduced potency on rodent AMY3 receptors, making rodent obesity models less predictive for clinical performance

FIGURE 2. DESPITE LOWER POTENCY IN STIMULATING RODENT AMY3, VRB-103 INDUCES SIGNIFICANT WEIGHT REDUCTION IN MONOTHERAPY AND IN COMBINATION WITH VRB-101[4]

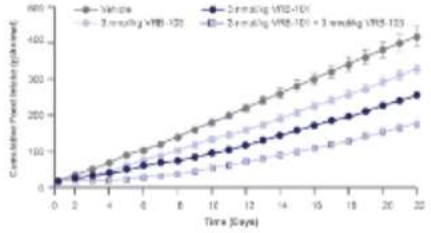


Analyzed by One-Way ANOVA.

- Despite the reduced potency on rodent amylin receptors, VRB-103 induces significant weight reduction and reduced food intake in rodents
- Combination dosing with GLP-1 (VRB-101) significantly increased BW reduction relative to VRB-101 or VRB-103 alone

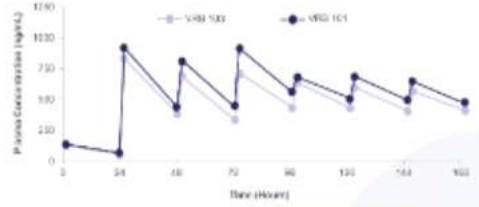
Results #3

FIGURE 3. VRB-103 ALONE OR IN COMBINATION WITH VRB-101 RESULTS IN SUSTAINED REDUCED FOOD INTAKE



- In DIO rats, the combination of VRB-103 and VRB-101 resulted in significantly greater weight reduction and less food intake than either alone

FIGURE 4. VRB-103 AND VRB-101 DELIVER THERAPEUTIC PLASMA EXPOSURES WHEN DOSED ORALLY IN A COFORMULATED TABLET IN CYNOMOLGUS MONKEYS[5]



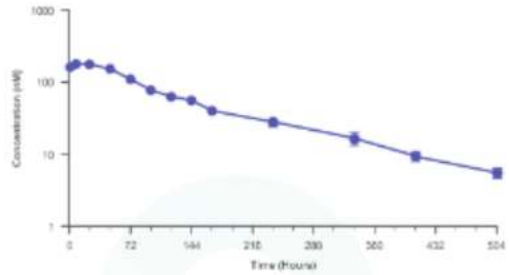
Cyno PK confirms high exposure with a single fixed-dose coformulated tablet (7 mg/7 mg per animal, QD)

Candidate	MoA	PD AUC$_{0-6h}$ (h*ng/mL)
VRB-101	GLP-1RA	93,249
VRB-103	Amylin-RA	70,252

ANOVA=analysis of variance. AUC$_{0-t}$=area under the plasma concentration-time curve from time zero to time t. AUC$_{0-\infty obs}$=observed area under the plasma concentration-time curve from time zero to infinity. BW=body weight. cAMP=cyclic adenosine monophosphate. C_{max}=maximum concentration. CHO-K1=chinese hamster ovary cell line K1. CRE=cAMP response element. h=hour. DIO=diet-induced obesity. EC_{50}=half maximal effective concentration. F=food intake. GLP-1=glucagon-like peptide-1. MOA=mechanism of action. MRT$_{0-\infty obs}$=observed mean residence time from time zero to infinity. PO=per os (by mouth). PK=pharmacokinetic. QD=once-daily. RLU=relative light unit. SD=standard deviation. SC=subcutaneous. $t_{1/2}$=half-life. T_{max}=time to maximum concentration.

Results #4

FIGURE 5. PK OF SINGLE-DOSE VRB-103 (0.1 mg/kg SC) IN CYNOMOLGUS MONKEYS[5]



Parameter	Unit	21021015	21022403	22030109	Average
$t_{1/2}$	h	12.1.2	10.4.6	11.7.2	11.4.4
T_{max}	h	24.0	8.0	24.0	18.7
C_{max}	ng/mL	188.1	183.4	182.9	191.4
AUC$_{0-t}$	ng/mL*h	25546.7	25457.6	27442.5	24482.3
AUC$_{0-\infty obs}$	ng/mL*h	26718.1	21054.7	26534.9	25435.9
MRT$_{0-\infty obs}$	h	148.6	127.0	148.7	138.1

Conclusions

- In a preclinical model, the combination of the amylin analog VRB-103 and GLP-1 analog VRB-101 demonstrated an additive effect on body weight reduction
- Both VRB-103 and VRB-101 achieved high plasma exposures in cynomolgus monkeys when dosed daily from a single coformulated oral tablet containing VRB-103, VRB-101, and the oral absorption enhancer T2026
- This work supports continued development of the once-weekly oral VRB-103 as a potential monotherapy and combination therapy with VRB-101 (GLP-1 analog), as well as the optionality for a fixed dose combination of VRB-101 and VRB-103 for the treatment of obesity and cardiometabolic diseases

Contact

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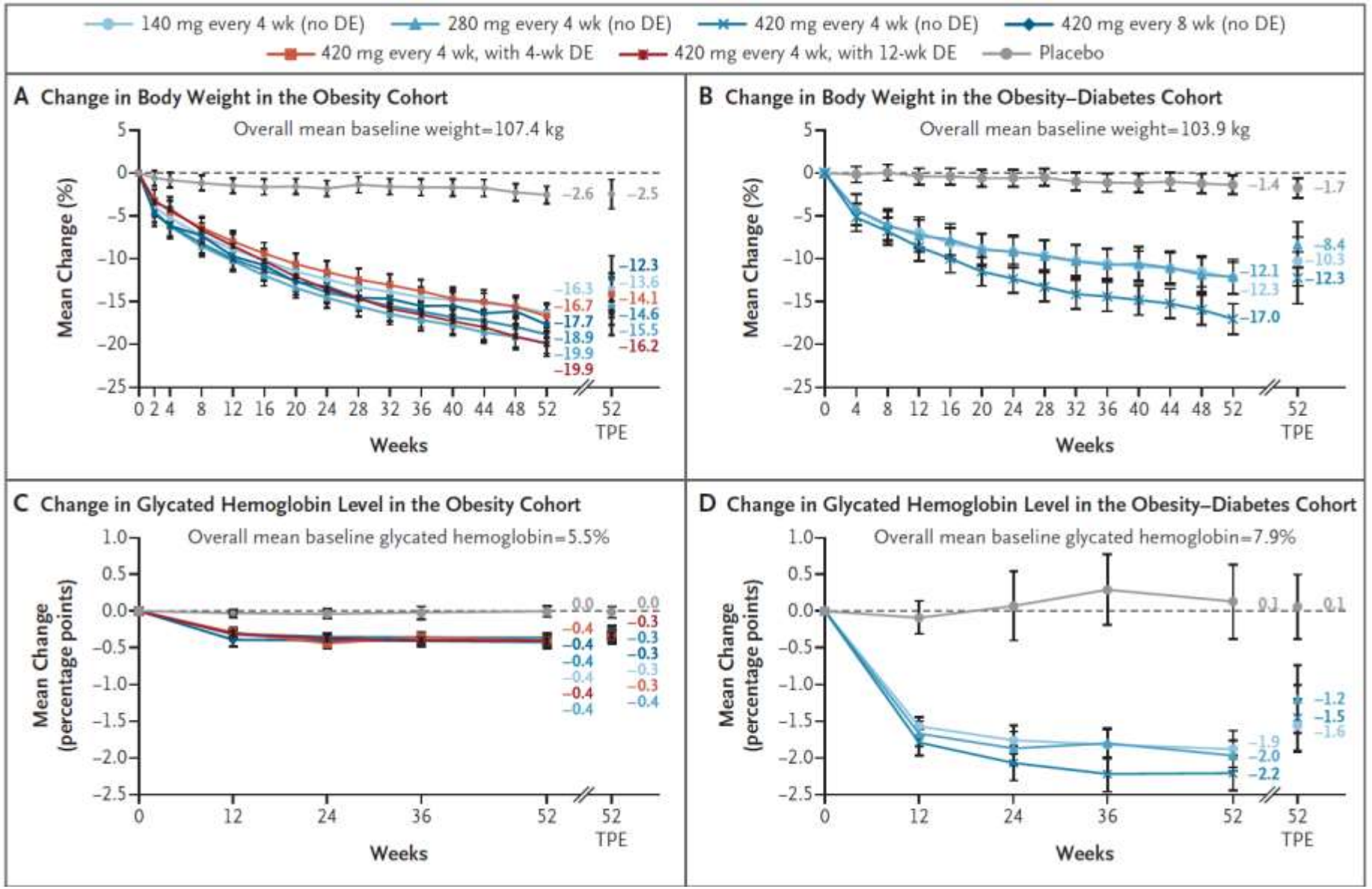
info@verdivabio.com

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/733-P/159426/733-P-Efficacy-of-a-Novel-Oral-Amylin-Analog-and

Amgen MariTide Data at ADA and NEJM



52-week placebo-adjusted weight loss with 12-week dose escalation of 17.3% could be commercially viable even if retatrutide is approved. The reason is that patients only need to dose this drug once monthly.

The 2.2 point drop in HbA1c for diabetes is particularly notable.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2504214

MariTide Phase 2 Discontinuation and AE Data

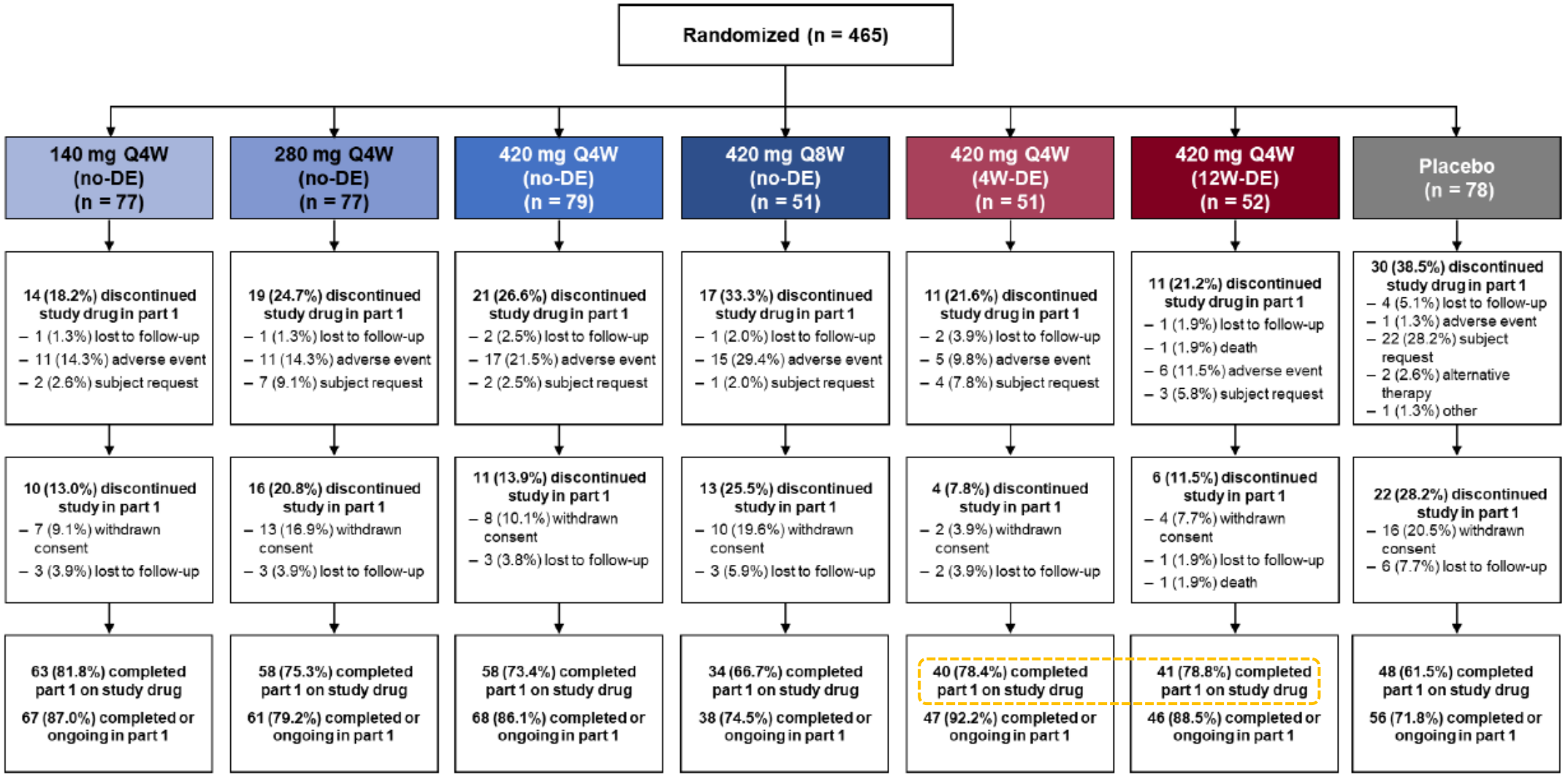
Table 3. Safety and Adverse Events.*

Event	Obesity Cohort							Obesity–Diabetes Cohort			
	Maridebart Cafraglutide, No Dose Escalation			Maridebart Cafraglutide, Dose Escalation (DE)			Placebo (N=76)	Maridebart Cafraglutide, No Dose Escalation			Placebo (N=32)
	140 mg Every 4 Wk (N=77)	280 mg Every 4 Wk (N=77)	420 mg Every 4 Wk (N=79)	420 mg Every 8 Wk (N=51)	420 mg Every 4 Wk, with 4-Wk DE (N=51)	420 mg Every 4 Wk, with 12-Wk DE (N=52)		140 mg Every 4 Wk (n=31)	280 mg Every 4 Wk (N=32)	420 mg Every 4 Wk (N=32)	
	number of participants (percent)										
Overall											
Any adverse event	73 (95)	75 (97)	78 (99)	49 (96)	46 (90)	49 (94)	52 (68)	29 (94)	29 (91)	31 (97)	26 (81)
Serious adverse event	4 (5)	4 (5)	5 (6)	7 (14)	0	3 (6)	5 (7)	1 (3)	2 (6)	4 (12)	0
Death†	0	0	0	0	0	1 (2)	0	0	1 (3)	0	0
Adverse events leading to discontinuation of trial regimen	11 (14)	11 (14)	17 (22)	15 (29)	5 (10)	6 (12)	1 (1)	4 (13)	6 (19)	5 (16)	1 (3)
GI adverse event leading to discontinuation	10 (13)	9 (12)	13 (16)	14 (27)	4 (8)	4 (8)	0	2 (6)	5 (16)	4 (12)	0
Most frequent adverse events leading to discontinuation‡											
Vomiting	9 (12)	8 (10)	12 (15)	12 (24)	3 (6)	1 (2)	0	1 (3)	3 (9)	4 (12)	0
Nausea	6 (8)	7 (9)	11 (14)	8 (16)	3 (6)	1 (2)	0	1 (3)	2 (6)	1 (3)	0
Retching	2 (3)	1 (1)	1 (1)	3 (6)	0	0	0	0	0	0	0
Headache	1 (1)	1 (1)	2 (3)	2 (4)	0	0	0	0	0	0	0
Diarrhea	0	1 (1)	3 (4)	0	1 (2)	0	0	1 (3)	1 (3)	0	0

Discontinuation rates in the teens with dose escalation have concerned some MariTide observers who note that this drug is given for a month so a patient cannot easily deescalate if they are having tolerability issues.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2504214

MariTide Discontinuation Rates with Dose Escalation Not Great



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2504214

Amgen's Obesity Drug Led to High Discontinuation Rates in Mid-Stage Trial, as Company Plans to Adjust Dosing

Elaine Chen, *Stat+*, June 23, 2025 (excerpt)

CHICAGO — Amgen's monthly obesity candidate led to substantial weight loss but a high rate of side effects and discontinuations in a mid-stage trial, results that support the company's decision to use a slower dosing schedule to make the drug more tolerable in further testing.

In the Phase 2 study, patients with obesity taking the injectable drug, called MariTide, lost up to 16.2% of their weight in one year when taking into account all participants regardless of discontinuations. Patients lost up to 19.9% when analyzing only those who stayed on treatment.

Rates of discontinuation due to side effects were high, ranging from 10% to 29% within different cohorts that received MariTide, and rates of vomiting ranged from 43% to 92%. The groups that underwent dose escalation had lower rates of discontinuations and vomiting than those that didn't.

In a smaller pharmacokinetics study that used even slower escalation schedules, the two cohorts with the lowest starting initial doses experienced rates of vomiting of 23% and 24%, and there were no discontinuations due to side effects, according to results also included in the NEJM paper. Amgen said Monday that this data informed its decision to use a slow titration schedule over an eight-week period going forward in its Phase 3 program.

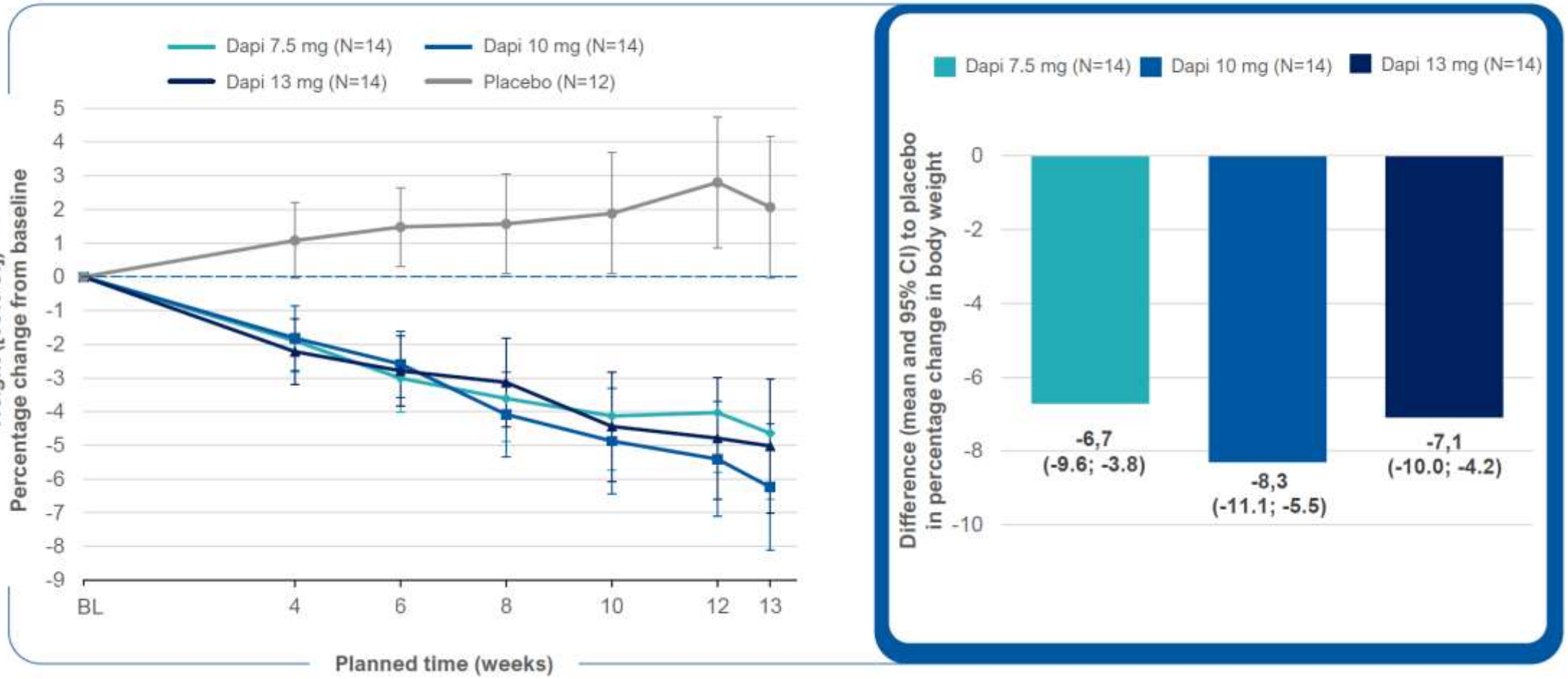
Even if MariTide shows greater weight loss in Phase 3 testing, though, it's not clear how competitive it would be against next-generation candidates from major players Novo Nordisk and Eli Lilly.

Source: https://www.statnews.com/2025/06/23/amgen-maritide-obesity-drug-trial-discontinuations-side-effects-dosing-changes/

Zealand's Dapiglutide Weight Loss at 13 Weeks Solid

Relative body weight change from baseline to week 13

Estimated mean percent change in body weight



Estimated based on the hypothetical estimand = treatment effect if all participants adhered to treatment (also known as the efficacy estimand).
Source: Data on file. Full analysis set: all randomised participants with a post-baseline measurement (N=14, N=14, N=13, N=10). BL=Baseline; CI=Confidence interval; ETD=Estimated treatment difference.

Source: https://www.zealandpharma.com/media/cldopofo/zealand-pharma-at-ada-2025-presentation.pdf

Dapi Vomiting Rates Appear Far Too High at 10mg+ Doses

Most common TEAEs

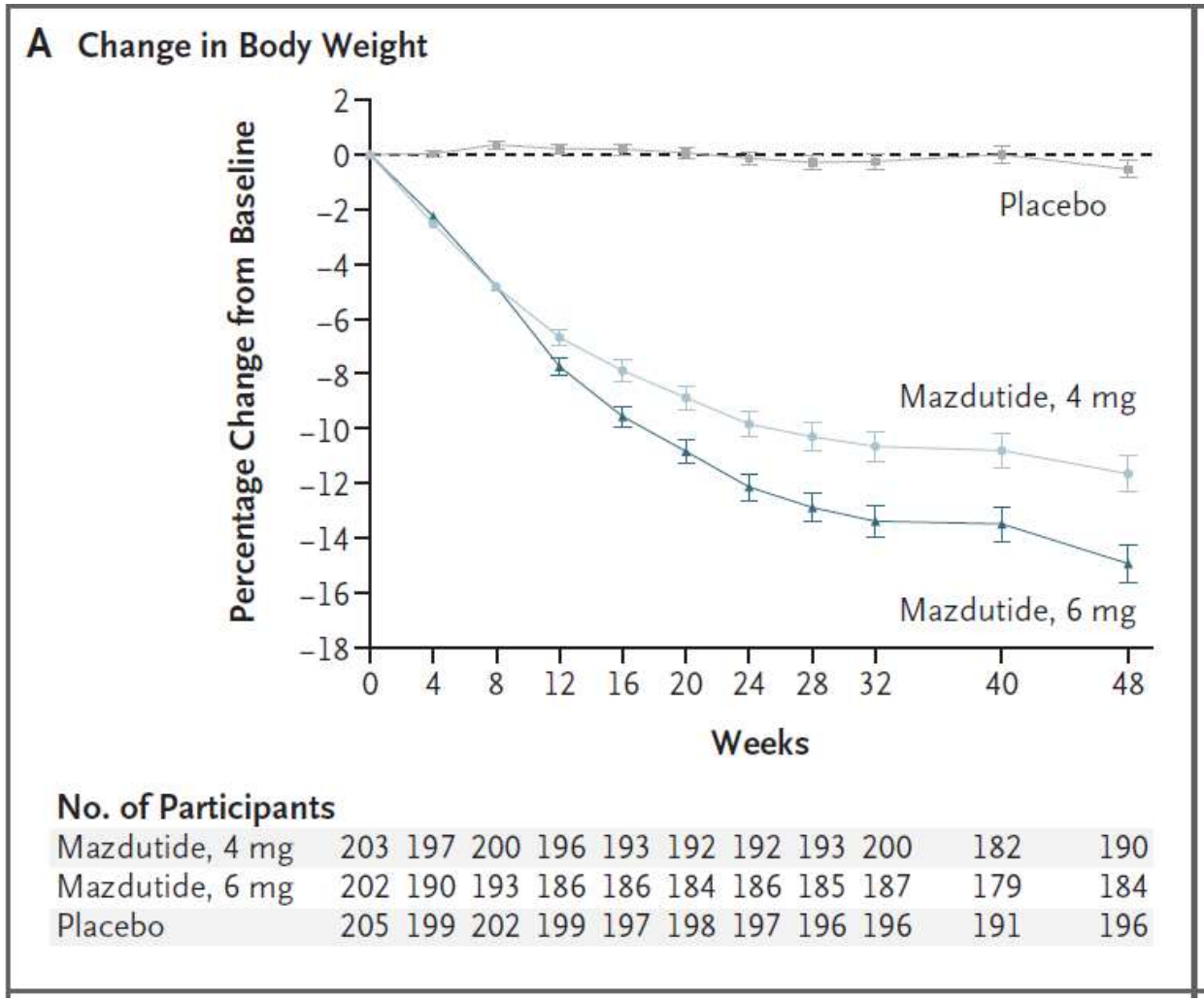
13-weeks dose escalation cohorts – dose escalation every 2nd week

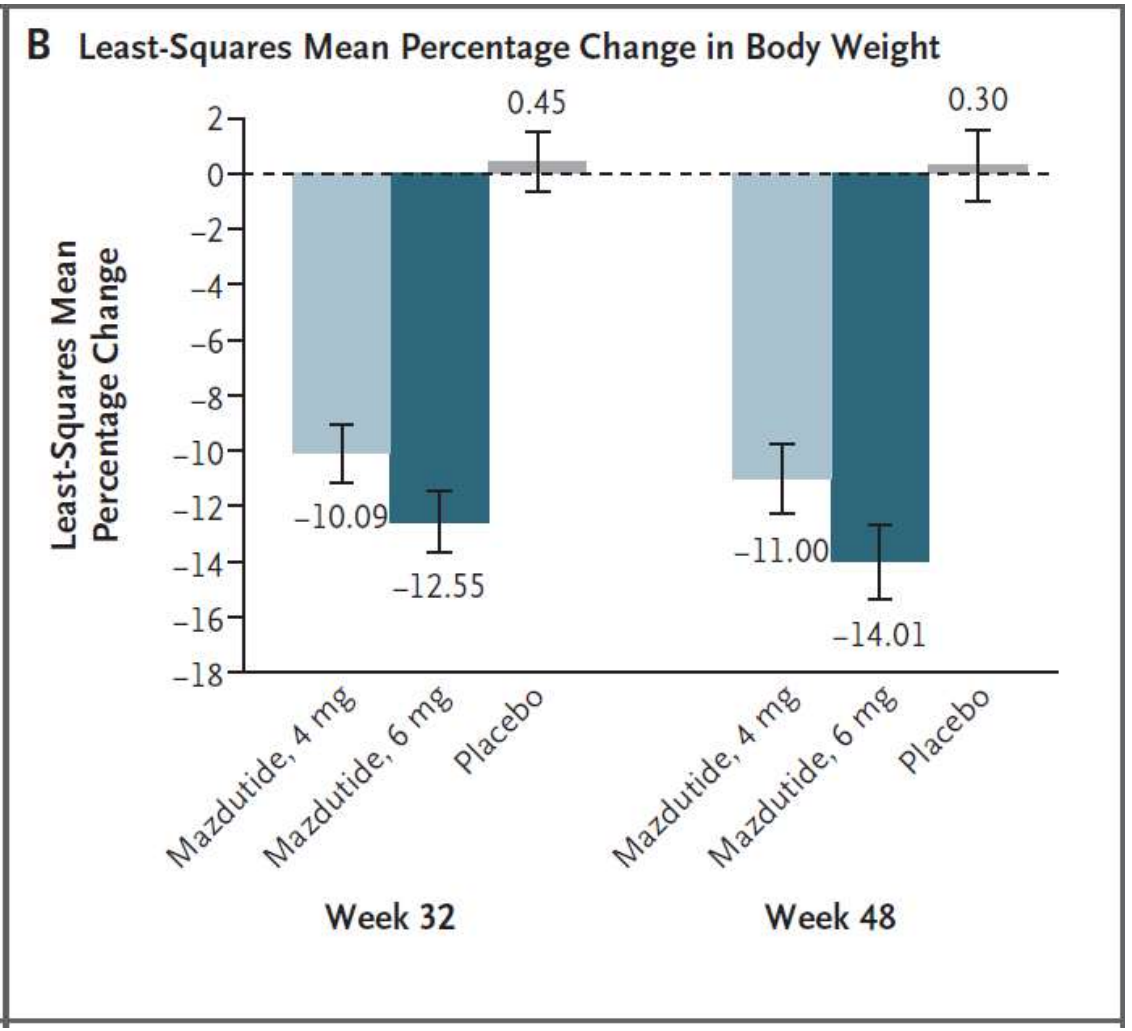
System Organ Class Preferred Term	Placebo (N=12)		Dapiglutide 7.5 mg (N=14)		Dapiglutide 10 mg (N=14)		Dapiglutide 13 mg (N=14)	
	N (%)	E	N (%)	E	N (%)	E	N (%)	E
Gastrointestinal disorders	**5 (41.7%)**	**8**	**10 (71.4%)**	**23**	**12 (85.7%)**	**80**	**12 (85.7%)**	**69**
Nausea	1 (8.3%)	1	3 (21.4%)	**5**	10 (71.4%)	**17**	10 (71.4%)	24
Vomiting	0		2 (14.3%)	2	7 (50.0%)	30	6 (42.9%)	16
Dyspepsia	1 (8.3%)	1	5 (35.7%)	5	4 (28.6%)	5	4 (28.6%)	7
Diarrhoea	0		1(7.1%)	2	4 (28.6%)	6	6 (42.9%)	11
Eructation	1 (8.3%)	1	2 (14.3%)	3	6 (42.9%)	8	3 (21.4%)	3
Metabolism and nutrition disorders	**0**		**3 (21.4%)**	**4**	**7 (50.0%)**	**8**	**10 (71.4%)**	**12**
▶ Decreased appetite	0		3 (21.4%)	3	7 (50.0%)	7	10 (71.4%)	11
Nervous system disorders	0		**6 (42.9%)**	**7**	**10 (71.4%)**	**12**	**1 (7.1%)**	**7**
Headache	0		6 (42.9%)	7	8 (57.1%)	9	1 (7.1%)	7
Respiratory, thoracic and mediastinal disorders	**4 (33.3%)**	**4**	**8 (57.1%)**	**9**	**4 (28.6%)**	**7**	**5 (35.7%)**	**5**
Nasopharyngitis	2 (16.7%)	2	7 (50.0%)	8	4 (28.6%)	5	2 (14.3%)	2

Most frequently reported TEAEs by dapiglutide treated participants (≥10 subjects overall).
E=number of events; N=number of participants; TEAE=treatment-emergent adverse event.

Source: https://www.zealandpharma.com/media/cldopofo/zealand-pharma-at-ada-2025-presentation.pdf

Innovent's Mazdutide (GLP-1/Glucagon Agonist) Shows 48-Week Data in NEJM Paper in June





Source: https://www.nejm.org/do/10.1056/NEJMdoo08023/full/

Mazdutide Vomiting Rates Quite High

Table 4. Adverse Events (Safety Population).*

Event	Mazdutide, 4 mg (N = 203)	Mazdutide, 6 mg (N = 202)	Placebo (N = 205)
		number (percent)	
Any adverse event	195 (96.1)	196 (97.0)	183 (89.3)
Serious adverse event	12 (5.9)	8 (4.0)	13 (6.3)
Death	0	0	0
Adverse event leading to discontinuation of mazdutide or placebo	3 (1.5)	1 (0.5)	2 (1.0)
Adverse events occurring in ≥10% of participants in any group†			
Nausea	66 (32.5)	102 (50.5)	12 (5.9)
Diarrhea	71 (35.0)	78 (38.6)	13 (6.3)
Vomiting	53 (26.1)	87 (43.1)	6 (2.9)
Decreased appetite	70 (34.5)	58 (28.7)	10 (4.9)
Covid-19	39 (19.2)	50 (24.8)	40 (19.5)
Upper respiratory tract infection	42 (20.7)	45 (22.3)	41 (20.0)
Urinary tract infection	24 (11.8)	25 (12.4)	22 (10.7)

Source: https://www.nejm.org/do/10.1056/NEJMd0008023/full/

BrightGene GLP-1/GIPR Agonist Data at ADA

Efficacy and Safety of BGM0504 in Chinese Patients With Obesity: A Multicenter, Randomized, Double-blind, Placebo-controlled phase 2 Trial

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8 These authors jointly supervised this work (Correspondence): Jiandong Yuan, Guoping Yang and Linong Ji , *email: jiandong_yuan@bright-gene.com; ygp9880@126.com; jiln@bjmu.edu.cn.

Introduction & Objective

BGM0504 is a dual agonist targeting glucagon-like peptide-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR). This study evaluated the safety and efficacy of BGM0504 in Chinese patients with obesity during multiple-dose administration.

Methods

A randomized, double-blind, placebo-controlled, parallel-group design was employed. A total of 120 overweight Chinese adults (BMI ≥ 24kg/m^2, mean BMI at enrollment ≥ 27kg/m^2) with prediabetes and/or at least one obesity-related comorbidity, or adults with obesity (BMI≥ 28kg/m^2, mean BMI at enrollment ≥ 30kg/m^2) were randomized in a 3:1 ratio into three dosage groups of BGM 0504 (5 mg, 10 mg, 15 mg) or placebo: 5mg (n = 30), 10mg (n = 30) 15mg (n = 30) and placebo (n = 30). The study consisted of a titration phase (2–6 weeks), 24-week treatment with once-weekly dosing, and a 2-week follow-up. It was registered with the Chinese NMPA (CTR20233198).The primary endpoint was the percentage change in body weight from baseline to week 24. Key secondary endpoints included body weight, the change in waist circumference, and the proportion of participants achieving weight loss targets. Additional secondary outcomes were also evaluated from baseline to week 24. Safety was assessed through adverse event (AE) monitoring, laboratory tests, and vital signs.

Results

Preliminary data indicate that BGM0504 injection demonstrated a favorable safety and tolerability profile. The mean percentage changes from baseline to week 24 in body weight were −10.68% (SD 4.68%) with BGM0504 5 mg, −16.07% (7.39%) with 10mg, −18.33% (7.49%) with 15mg and 0.13%
(3.48%) with placebo(see **Figure 1**). The mean changes in waist circumference from baseline to week 24 were -8.88cm (SD:5.85cm) with BGM0504 5mg,
-12.71cm(7.01cm) with 10mg, -14.38cm (8.03cm) with 15mg and-1.03(2.91com) with placebo(see **Figure 2**). From baseline to week 24, least-squares mean (LSM) percentage changes in body weight relative to placebo were:

- **5 mg group**: −10.77% (95% CI: −12.93 to −8.61), −10.2 kg (−12.3 to −8.2)
- **10 mg group**: −16.21% (95% CI: −19.20 to −13.23), −15.5 kg (−18.3 to −12.6)
- **15 mg group**: −19.78% (95% CI: −23.02 to −16.54), −20.1 kg (−23.4 to −16.8)

The body weight reduction of all BGM0504 groups with ≥ 5%, ≥ 10% and ≥ 15% reductions were significantly superior to the placebo group ($p<0.001$) and the ≥ 20% body weight reduction of BGM0504 10mg and 15mg groups was significantly superior to the placebo group ($p<0.05$), see **Figure 3.**

In addition, all doses of BGM0504 significantly improved both systolic blood pressure (LSM from -11.60mmHg to -13.03mmHg) and diastolic blood pressure (LSM from -5.98mmHg to -7.50mmHg) from baseline to week 24 compared to the placebo group ($p<0.05$) and other secondary outcomes further supported the efficacy of BGM0504. All BGM0504 doses were well tolerated, including the most common AE.

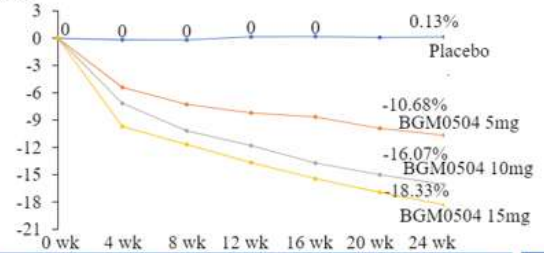


Figure 1 Percentage changes from baseline to week 24 in body weight

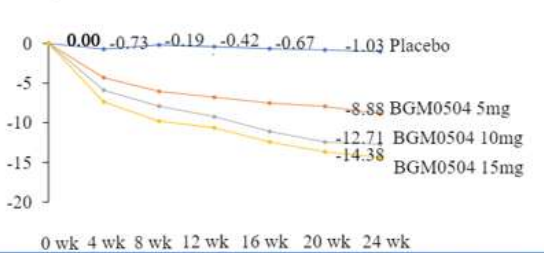


Figure 2 Changes in waist circumference from baseline(cm) to week

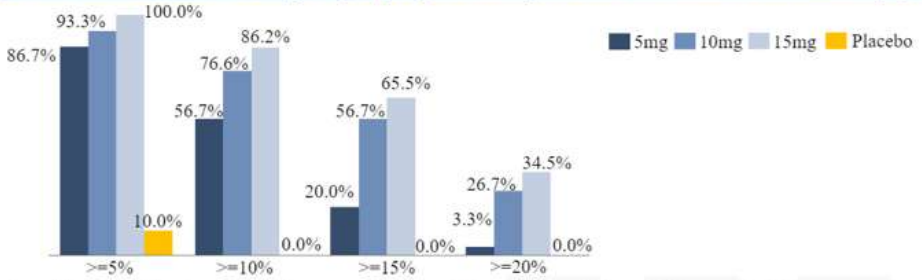


Figure 3 The proportion of participants achieving weight loss targets (with ≥ 5%, ≥ 10%, ≥ 15%, ≥ 20%)at week 24

Conclusions

In adults with obesity, BGM0504 treatment for 24 weeks resulted in substantial reductions in body weight and waist circumference. BGM0504 demonstrates significant potential for weight management and metabolic risk reduction in overweight and obese non-diabetic individuals.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/744-P/158588/744-P-Efficacy-and-Safety-of-BGM0504-in-Chinese

Triple/Quad Incretin Drugs

Emerging Triple / Quad Incretin Drug Combo's

	Lilly	Biomed	Hanmi	上海民为生物 SHANGHAI MINWEI BIOTECH	novo nordisk	Pep2Tango Therapeutics	Protagonist Therapeutics
Headquarters	Indianapolis, IN	Bay Area	South Korea	China	Denmark	Potomac, MD	Bay Area
Program	Retatrutide	NA-931 (Bioglutide)	HM-15275	MWN109	UBT251	ND	PN-477
Target	GLP-1 / GIPr / Glucagon Agonist	IGF-1 / GLP-1 / GIP / Glucagon Agonist	GLP1+GIP+GCG	GLP/GIP/GCG (oral) / GLP1 weighted	GLP/GIPr / Glucagon Agonist	GLP-1+ GIP+Amlyin+ Calcitonin	GLP-1 / GIP / Amylin / Calcitonin Agonist (oral)
Phase	Phase 3	Phase 2	Phase 1	Phase 1	Phase 1	Preclinical	Preclinical
Efficacy Data	In a Phase 2 trial, weekly retatrutide achieved up to 24.2% mean weight loss at 48 weeks, the most ever reported for an obesity medication. It also significantly improved glycemic control, lowering HbA1c by more than 1.5%, with primarily GI side effects.	In a 28-day Phase 1 trial, NA-931 achieved mean body weight reductions of approximately 6.4–6.8%, translating to about 5.1% superiority over placebo, with minimal gastrointestinal side effects and no muscle loss. A subsequent 12-week study saw weight loss double to ~12.7% while maintaining its favorable tolerability profile	(39.9%) change in BW in obese mice vs. (15.0%) and (25.3%) for semaglutide and tirzepatide, respectively	Starting Phase 1 in Q3 2025	Average weight loss of 15.1% after 12 weeks in Phase 1b trial	NA	NA
Upcoming Milestones	**2025** – Phase 3 trials underway	**H2 2025** – Start of Phase 3	**1H25** – Ph1 results **2H25** – Ph2 start	**1H 2026** – Phase 2 start	**2026** – IND submisstion	**2026** – IND submission	2026 – IND submission

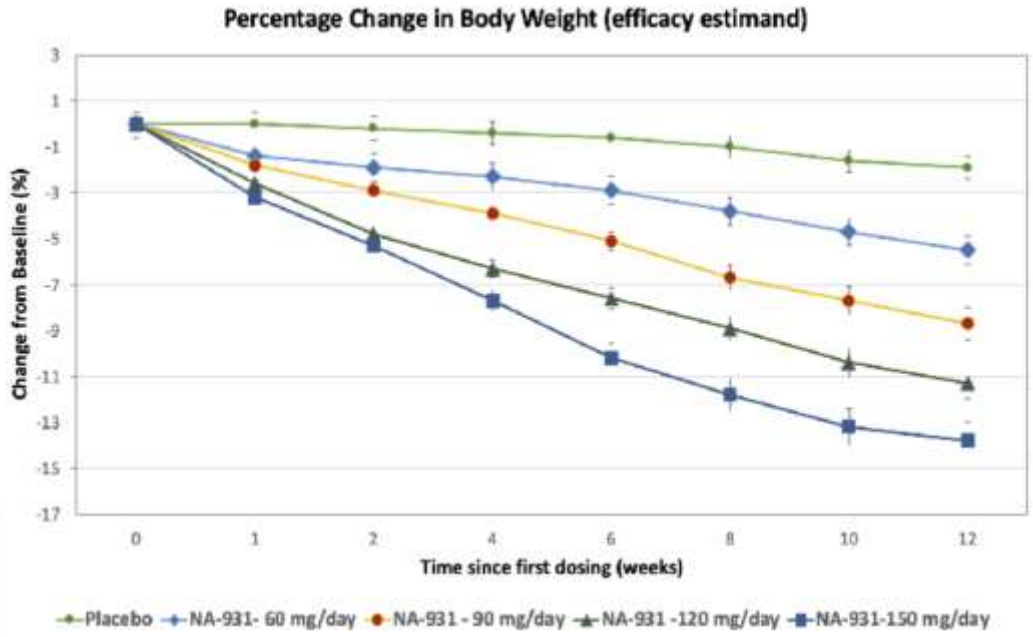
Source: Stifel analysis of press releases and company data.

ADA: Biomed NA-931 Quad Shows Impressive Weight Loss and Tolerability

This drug was tested with tirzepatide but some slides during their ADA presentation seem to show their weight loss is a bit less than tirzepatide but the data below show striking weight loss in an Australia trial. A bit hard to interpret.

Multiple Ascending Dose Level	Placebo (n=29)	NA-931 60 mg (n=24)	NA-931 90mg (n=24)	NA-931 120 mg (n=24)	NA-931 150 mg (n=24)
Mean baseline body weight	96.2 kg	96.8 kg	97.9 kg	100.3 kg	99.8 kg
Mean change from baseline body weight	-1.8 kg	-5.3kg	-9.2 kg	-11.3 kg	-13.8 kg
Mean percent change from baseline	-1.9%	-5.5%	-8.7%	-11.3%	-13.8%
Placebo-adjusted mean percent change from baseline	-	-3.6%	-6.8%	-9.4%	-11.9%
p-value vs. placebo	-	-	-	0.002	0.001

Common AEs, No. of Subjects reporting, (%)	Placebo (n=29)	NA-931 60 mg (n=24)	NA-931 90 mg (n=24)	NA-931 120 mg (n=24)	NA-931 150mg (n=24)	NA-931 Combined (n=96)
Nausea						
Mild	3 (10.3 %)	1 (4.2 %)	1 (4.2 %)	2 (8.3 %)	3 (12.5 %)	7 (7.3 %)
Moderate	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	2 (6.9 %)	1 (4.2 %)	1 (4.2 %)	1 (4.2 %)	2 (8.3 %)	5 (5.2 %)
Diarrhea	2 (6.9 %)	1 (4.2 %)	1 (4.2 %)	2 (8.3 %)	2 (8.3%)	6 (6.3%)
Constipation	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)



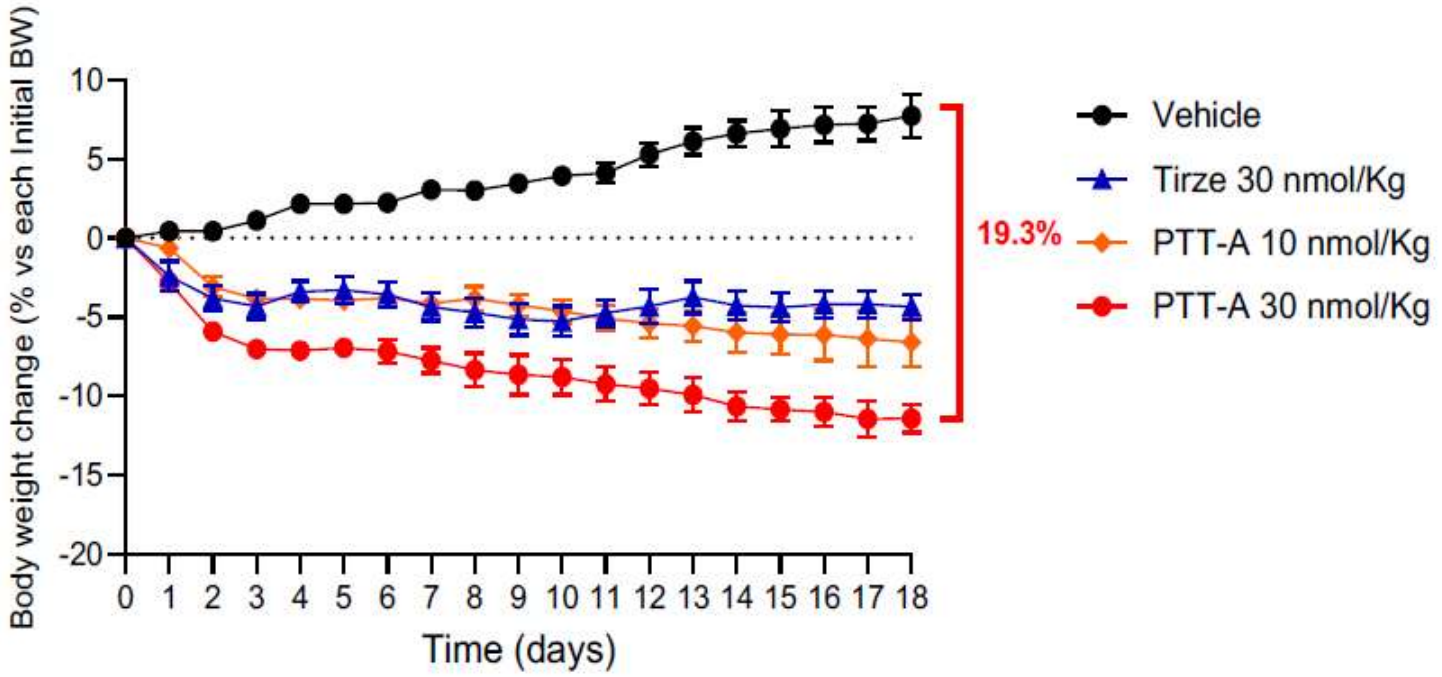
Conclusion

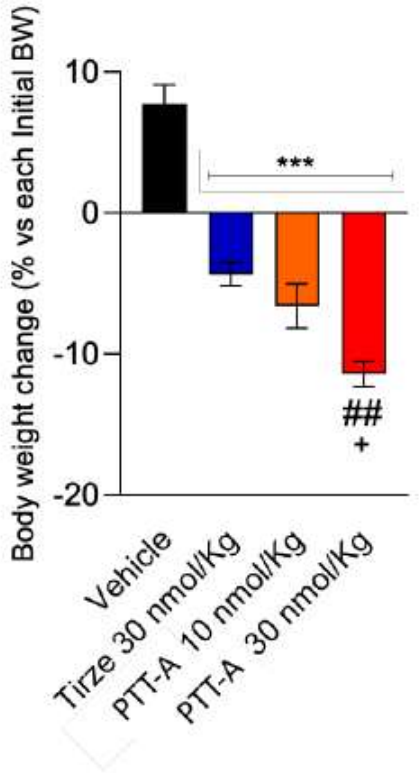
The topline results of the Phase 2 of NA-931 showed its potential as a first-in-class oral quadruple receptor agonist for weight loss, with excellent safety and efficacy. The Company is advancing NA-931 to Phase 3 trials

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/2189-LB/160162/2189-LB-Phase-2-Clinical-Trials-of-NA-931-to-Study

Pep2Tango Quad Incretin Delivers Strong Weight Change in DIO Rat Model

85-OR: A Novel Unimolecular Peptide Tetra-agonist (PTT-A) Targeting GLP-1, GIP, Amylin, and Calcitonin Receptors with Superior Weight Loss Effects vs. Tirzepatide While Preserving Muscle in DIO Rats

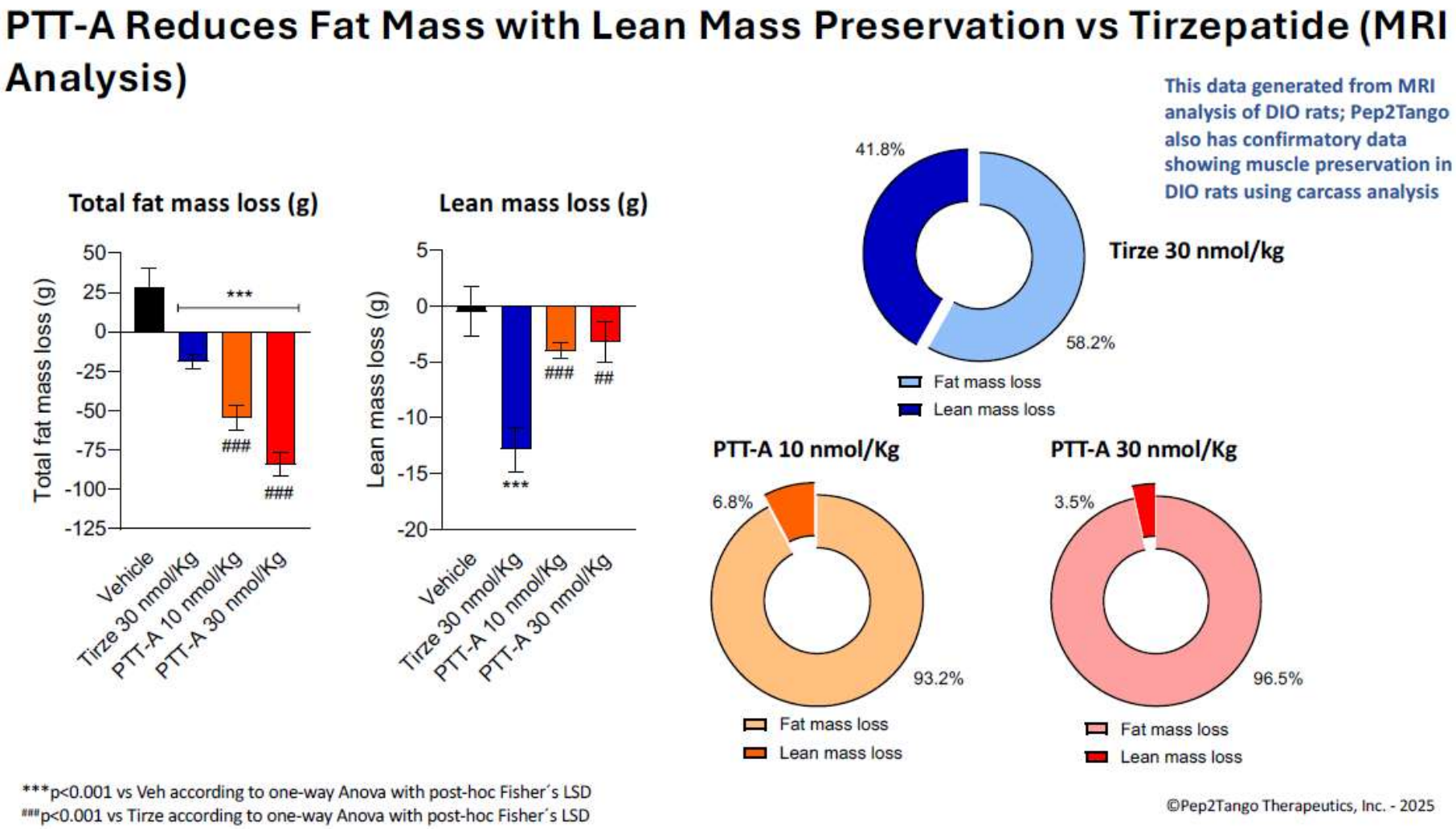




***p<0.001 vs Vehicle according to one-way Anova with post-hoc Fisher´s LSD
##p<0.01 vs Tirze at the same dose according to one-way Anova with post-hoc Fisher´s LSD
+p<0.05 vs PTT-A 10 nmol/Kg at the same dose according to one-way Anova with post-hoc Fisher´s LSD

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/85-OR/158315/85-OR-A-Novel-Unimolecular-Peptide-Tetra-agonist

Pep2Tango Molecule Associated with Lean Mass Preservation



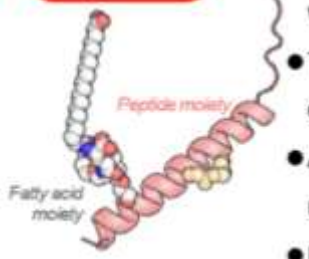
Source: Pep2Tango Corporate Presentation

ADA: Hanmi Triple › High WL Plus Muscle Preservation

Background

HM15275 is a novel long-acting GLP-1/GIP/Glucagon triple agonist conjugated with fatty acid moiety, optimally designed for treatment of obesity and relative complications.

HM15275



- Designed and optimized to maximize body weight reduction (activity balance)
- The extended half-life is sufficient for weekly dosing
- Additional CVRM benefits expected by proper utilization of glucagon
- P1 study in United States completed

GLP-1	GIP	Glucagon
Weight loss by appetite regulation		Weight loss by energy expenditure
Indirect effects from BW loss and BG control and CVRM benefits		Direct tissue effect for CVRM benefits

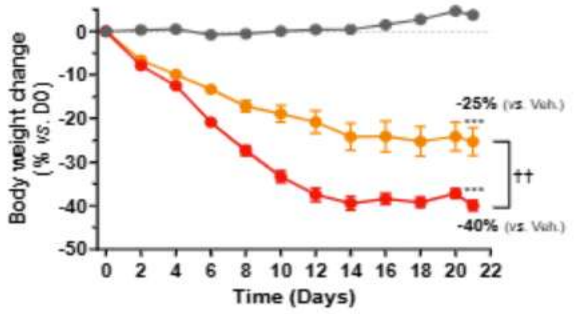
Results:

Transcriptomic analysis revealed that HM15275 sustained fat metabolic pathways, while down-regulated in TZP, contributing to greater fat mass loss under fasting-related metabolic challenges. HM15275 suppressed amino acid catabolic pathways relative to TZP, supporting lean mass preservation. HM15275 activated pathways related with glucose generation greater than TZP revealed by enrichment of gluconeogenesis and lactate recycling pathway, however, fasting blood glucose remained lower than vehicle treated implying limited effect on glucose intolerance. Furthermore, HM15275 downregulated ketone body synthesis compared to TZP, priming production of glucose rather than ketone body.

Weight Loss Effect & Glycemic Control

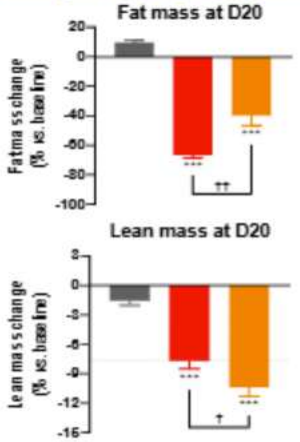
Figure 1. Comparison of weight loss effect & glycemic control

A. BW change over time



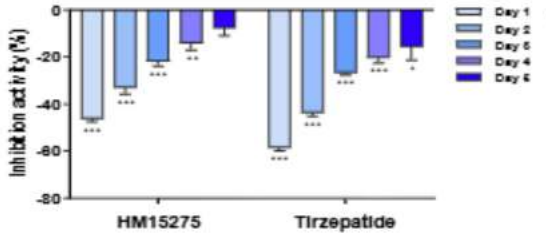
*** p<0.001, vs. Vehicle, by One-way ANOVA test.
†~†† p<0.05~0.01, vs. HM15275 20 nmol/kg by an unpaired t-test.

B. Changes in body composition



- In DIO mice, HM15275 significantly reduced body weight and favorably regulated fat-to-lean composition , yielding enhanced therapeutic benefits than TZP

C. Changes in AUC_{BG} during ipGTT



- In normal mice, HM15275 demonstrated improved glucose tolerance comparable to TZP (ipGTT).

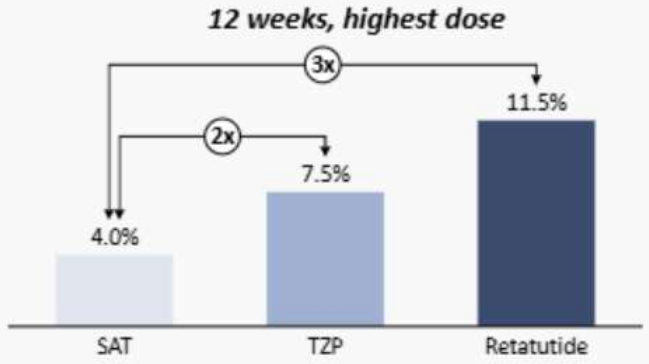
*~*** p<0.05~0.001, vs. Normal, vehicle by One-way ANOVA test

Source: https://www.hanmi.co.kr/science-pdf/HM15275/2025_ADA_Poster_HM15275_755-P.pdf

ADA: Minwei Oral Triple G in the Clinic – Competitive vs. Retatrutide

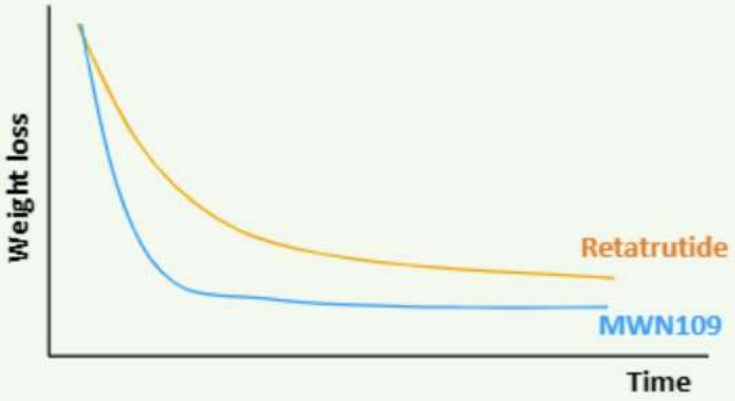
Injectables Are Potent BUT Not Oral

- Potency gets increasingly better for injectable incretin drugs with 4-12% weight loss in 12 weeks, threatening to achieve surgical level weight reduction
- Poly GLP appear to be more efficacious (~1-2×) than GLP alone with weight reduction
- But oral is still preferred for convenience, comfort and cost



MWN109
A Clinical Stage Potent Oral Triple G

- More potent than Retatrutide
- With a widened therapeutic window
- Oral: high potency enables low dose (scalable) and efficacious oral formulation, PK and GLP tox supportive for FIH



Oral SM are Preferred BUT Not Potent

- Small molecules, while scalable, has demonstrated limited potency required for >10% weight loss in 12 weeks
- Small molecules also raise toxicity concerns, especially with long-term use, due to high rates of treatment-emergent severe adverse events (TESAE), e.g. liver or renal toxicity

Oral Peptide are Not Easily Scaled

- GLP based incretin oral reformulations face challenges related to either low dose (low potency) or high dose (scalability issues).
- Enhancing potency is crucial to unlocking the full potential of GLP-1 incretin oral formulations

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/1967-LB/158767/1967-LB-MWN109-A-Novel-Fatty-Acid-Modified-GLP-1

ADA: Minwei Oral Triple G Positioning

(a)

~ 3X GLP-1 receptor agonist action vs. Retatrutide

↑ **Efficacy in**
- Weight loss
- Glycemic control
- Lower dose and oral dosage available

~ 1X GCG receptor agonist action vs. Retatrutide

↓ **Cardiovascular risk***

↓ **LDL-c and uric acid**

~ 1X GIP receptor agonist action vs. Retatrutide

↔ **GI AE profile**

(b)

EC50 (ng/ml)	2% human serum albumin (human or NHP activities)			Non serum albumin (free peptide activities)		
	GLP-1	GCG	GIP	GLP-1	GCG	GIP
MWN109	118.9	17.36	2.892	0.790	0.047	0.021
Retatrutide	540.0	25.98	3.291	0.932	0.072	0.014
Tirzepatide	395.3	-	0.788	1.478	-	0.013

**when using at lower dose than Retatrutide but achieving comparable efficacy in weight loss*

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/1967-LB/158767/1967-LB-MWN109-A-Novel-Fatty-Acid-Modified-GLP-1

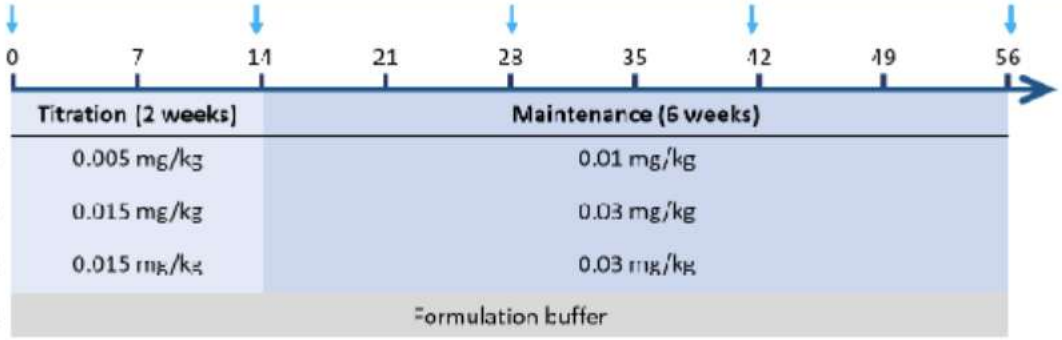
MWN109 Primate Data Look Interesting

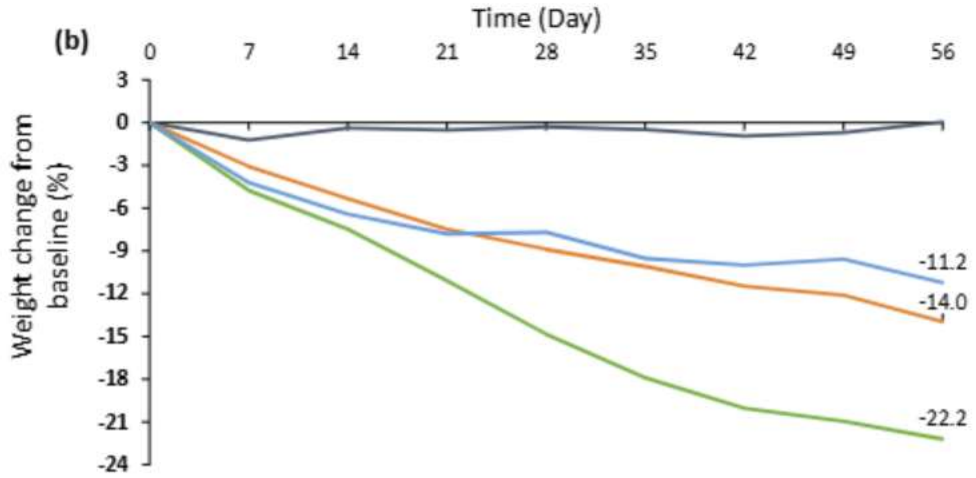
Obese NHP: MWN109 Demonstrated 2-3× Activity of Retatrutide

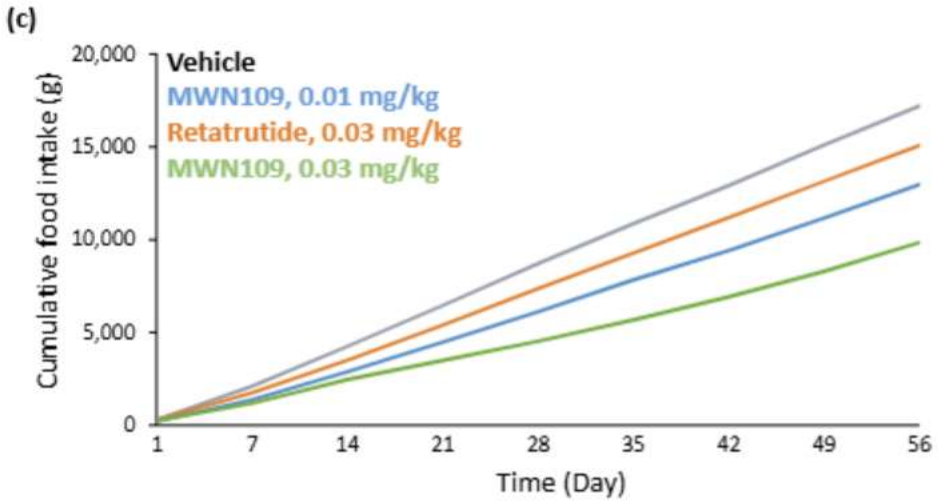
- Dose-dependent, comparable weight reduction was observed with MWN109 at 1/3 dose of Retatrutide
- Both retatrutide and MWN109 reduced food intake

(a)

Spontaneously obese rhesus macaque







Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/1967-LB/158767/1967-LB-MWN109-A-Novel-Fatty-Acid-Modified-GLP-1

Novel Drugs for T2DM

Semaglutide Associated with -1.7 Change in HbA1c at 72 Weeks

1978-LB

Efficacy and Safety of Semaglutide 7.2 mg in Obesity and Type 2 Diabetes: The STEP UP T2D Trial

Ildiko Lingvay[1], Sara J. Bergenheim[2], John Buse[3], Paula Freitas[4,5], W. Timothy Garvey[6], Nina M. Harder-Lauridsen[2], Julio Rosenstock[7], Kushal Sahu[2], Sean Wharton[8,9]

Aim

- To assess the efficacy and safety of semaglutide 7.2 mg versus placebo in adults with obesity and T2D.
- To assess the efficacy of semaglutide 7.2 mg versus 2.4 mg in exploratory analyses.
- To assess the safety of semaglutide 7.2 mg versus semaglutide 2.4 mg and versus placebo.

Introduction

- Once-weekly s.c. semaglutide 2.4 mg is FDA-approved for weight management in people with overweight/obesity and for risk reduction of major adverse cardiovascular events in people with overweight/obesity and established CV disease.[1]
- Once-weekly s.c. semaglutide 0.5 mg, 1 mg, and 2 mg is approved for glycemic control in people with T2D.[2]
- In the STEP 2 trial of people with overweight/obesity and T2D, semaglutide 2.4 mg reduced body weight by 9.6% and HbA_{1c} by 1.6% (mean HbA_{1c} after 68 weeks: 6.4%).[3]
- Despite the efficacy of semaglutide 2.4 mg, some individuals do not reach their weight management goals with this dose and can potentially benefit from intensification of treatment.

Methods

- In the multicenter, double-blind STEP UP T2D trial (NCT05649137),* people with BMI ≥30 kg/m² and T2D were randomized 3:1:1 to once-weekly s.c. **semaglutide 7.2 mg**, **2.4 mg**, or placebo, plus lifestyle intervention, for 72 weeks (**Figure 1**).
- Co-primary endpoints were change in body weight (%) and proportion of participants reaching ≥5% weight loss, for semaglutide 7.2 mg versus placebo.
- Confirmatory secondary endpoints were the proportions of participants reaching ≥10%, ≥15%, and ≥20% weight loss, change in waist circumference (cm), and change in HbA_{1c} (%), for semaglutide 7.2 mg versus placebo.
- Semaglutide 7.2 mg versus 2.4 mg comparisons were evaluated in exploratory analyses due to their clinical relevance, although the trial was not powered for these analyses.
- Safety was also assessed.

Results

Baseline characteristics

- Baseline characteristics were generally well-balanced across treatment groups (**Table 1**).

Table 1. Baseline characteristics

Baseline characteristic	Semaglutide 7.2 mg (n=307)	Semaglutide 2.4 mg (n=153)	Placebo (n=154)	Total (N=612)
Female, n (%)	166 (54.1)	87 (56.9)	82 (53.2)	335 (54.7)
Race or ethnicity, n (%)				
Asian	19 (6.2)	7 (4.6)	6 (3.9)	32 (5.2)
Black or African American	22 (7.2)	13 (8.5)	9 (5.8)	44 (7.2)
White	258 (84.0)	133 (86.9)	137 (88.9)	528 (86.3)
Other*	8 (2.6)	0	2 (1.3)	10 (1.6)
Age, years	57 (10)	58 (10)	55 (10)	56 (10)
Body weight, kg	110.5 (22.3)	107.0 (23.0)	112.1 (22.9)	110.1 (22.7)
BMI, kg/m²	38.7 (7.1)	37.7 (8.4)	39.0 (7.6)	38.6 (7.7)
Waist circumference, cm	121.8 (15.2)	119.1 (15.2)	123.9 (15.5)	121.7 (15.4)
HbA_{1c}, %	8.0 (0.8)	8.1 (0.9)	8.2 (0.9)	8.1 (0.9)
Duration of diabetes, years	8.4 (6.5)	8.4 (6.5)	8.2 (5.9)	8.4 (6.4)

Data are mean (SD) unless otherwise noted.
*Includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multiple.

Body weight loss

- For the treatment policy estimand, semaglutide 7.2 mg reduced mean body weight versus placebo (–13.2% vs –3.9%; ETD [95% CI]: –9.3% [–11.0, –7.7]; p<0.001), and versus semaglutide 2.4 mg (–13.2% vs –10.4%; ETD [95% CI]: –2.8% [–4.7, –0.9]; p=0.003; **Figure 2A**).
- Semaglutide 7.2 mg also led to more participants reaching ≥5% to ≥20% WL versus placebo (p<0.001 for all; **Figure 2C**).
- Results for the trial product estimand were similar (**Figure 2B** and **2D**).

Waist circumference

- Semaglutide 7.2 mg led to a reduction in waist circumference versus placebo (–12.3 cm vs –5.8 cm; ETD [95% CI]: –6.5 cm [–9.0, –4.1]; p<0.001).

Glycemic control

- For the treatment policy estimand, semaglutide 7.2 mg led to a greater reduction in HbA_{1c} versus placebo (–1.7% vs –0.2%; ETD [95% CI]: –1.5% [–1.8, –1.2]; p<0.001). Reductions were similar for semaglutide 7.2 mg versus 2.4 mg (–1.7% vs –1.6%; ETD [95% CI]: –0.1% [–0.4, –0.1]; p=0.234; scan the QR code for additional data).

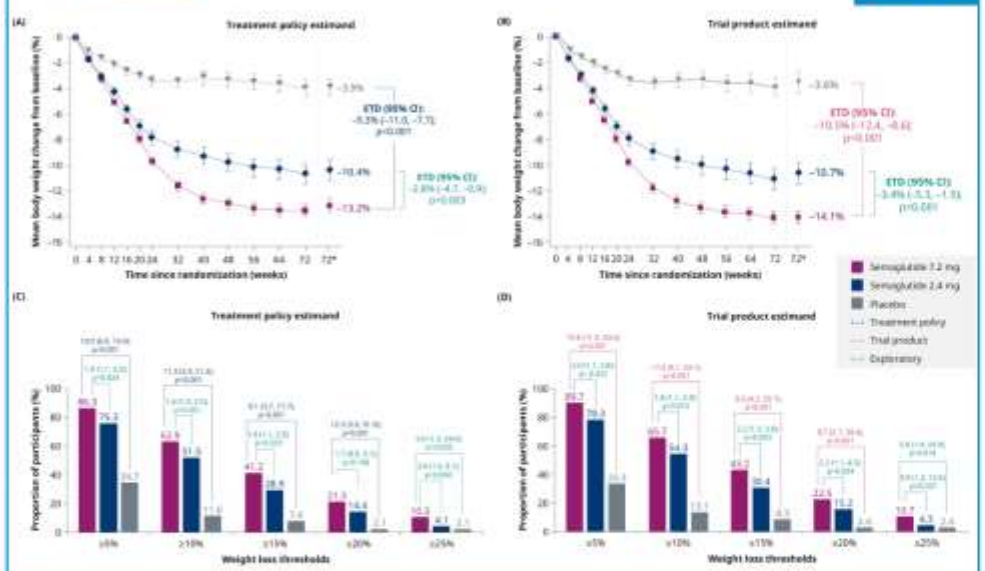
Safety

- **Table 2** summarizes AEs; **Figure 3** shows the time to onset of first gastrointestinal AE and any gastrointestinal AEs over time.
- Dysesthesia events in the semaglutide groups were all non-serious, mostly mild to moderate and generally resolved without dose reduction. One participant in the semaglutide 7.2 mg group permanently discontinued treatment due to dysesthesia (scan the QR code for additional data).
- No severe hypoglycemic episodes were reported for semaglutide 7.2 mg or 2.4 mg.

Figure 1. Trial design

Figure 2. Change in body weight (%) (A and B) and proportion of participants reaching different weight loss thresholds (C and D) from baseline to week 72

Key results



Conclusion

- In people with obesity and T2D, semaglutide 7.2 mg was superior to placebo for reductions in body weight, waist circumference, and HbA_{1c}.
- Exploratory analyses suggested that semaglutide 7.2 mg was superior to semaglutide 2.4 mg for weight reduction, with a small additional glycemic improvement noted in the trial product estimand exploratory analysis only (scan the QR code for additional data).
- The proportions of gastrointestinal AEs with the increased 7.2 mg dose were similar to those observed with the approved 2.4 mg dose.
- Overall, the safety and tolerability profiles of the semaglutide doses were similar, except for an increased proportion of dysesthesia events with the 7.2 mg dose versus the 2.4 mg dose.
- No severe hypoglycemic episodes were reported for semaglutide 7.2 mg or 2.4 mg, and the proportions of clinically significant hypoglycemia were similar between semaglutide doses and lower than for placebo.
- The results from the STEP UP T2D trial support a favorable benefit–risk profile of semaglutide 7.2 mg for weight management in people with obesity and T2D.

Figure 3. Time to onset of first gastrointestinal AE (A) and any gastrointestinal AEs (B) over time.

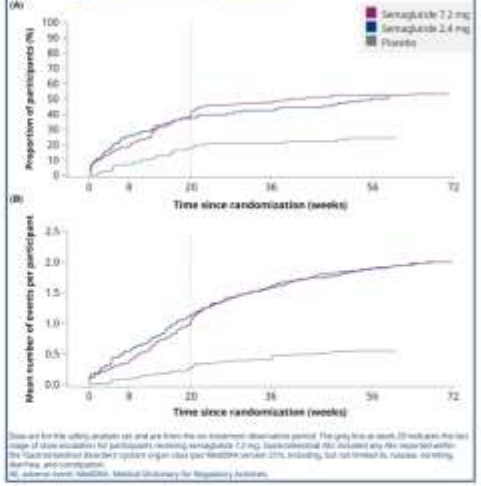


Table 2. Summary of adverse events

AE, n (%)	Semaglutide 7.2 mg (n=307)	Semaglutide 2.4 mg (n=153)	Placebo (n=152)
All AEs	246 (80.1)	117 (76.5)	114 (75.0)
Mild	222 (72.3)	110 (71.9)	103 (67.8)
Moderate	126 (41.0)	65 (42.5)	51 (33.6)
Severe	25 (8.1)	8 (5.2)	7 (4.6)
Serious AEs	28 (9.1)	9 (5.9)	9 (5.9)
AEs leading to dose reduction	62 (20.2)	19 (12.4)	2 (1.3)
AEs leading to permanent treatment discontinuation	17 (5.5)	6 (3.9)	3 (2.0)
Fatal AEs (†)	1 (0.3)	1 (0.7)	1 (0.7)
Level 2 hypoglycemia‡	6 (2.0)	2 (1.3)	3 (2.0)
Level 3 hypoglycemia§	0	0	1 (0.7)
Gastrointestinal AEs	163 (53.1)	83 (54.2)	39 (25.7)
Dysesthesia AEs¶	58 (18.9)	14 (9.2)	0

Observed proportions are for the on-treatment period, unless otherwise noted. Hypoglycemic episodes rated using ADA criteria.[4]
*Dysesthesia AEs were identified by a pre-defined MedDRA search narrow (73) and included AEs with preferred terms of allodynia, burning sensation, dysesthesia, hyperesthesia, paresthesia, tactile allodynia, skin burning sensation, skin discomfort, and skin tightness.
ADA, American Diabetes Association; AE, adverse event; ET, to treat; MedDRA, Medical Dictionary for Regulatory Activities.

Source: https://sciencehub.novonordisk.com/congresses/ada2025/Lingvay.html

CagriSema Effect on HbA1c at ADA

REDEFINE 2

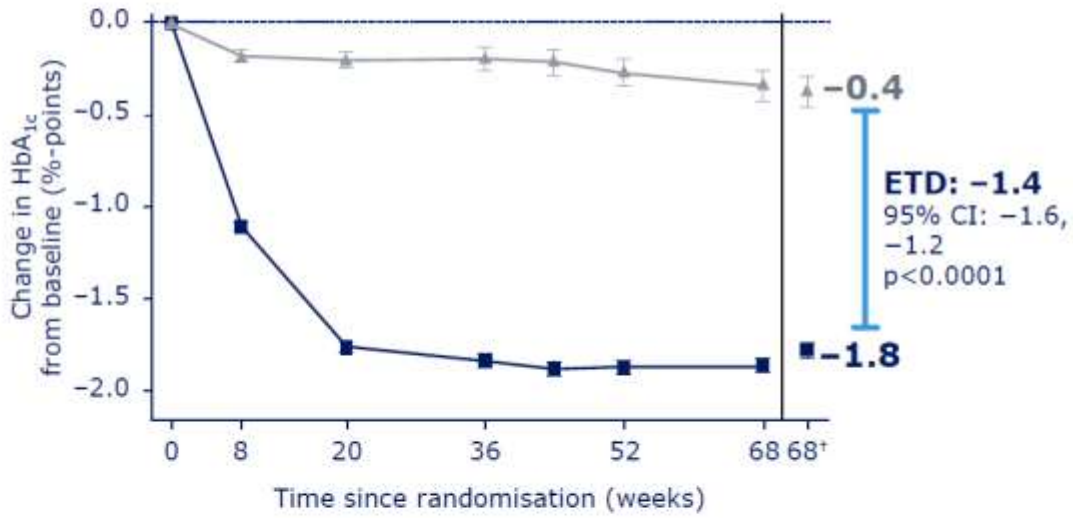
CagriSema 2.4 mg/2.4 mg treatment provided significant reductions in HbA_{1c}

Change from baseline to week 68 in HbA_{1c} (%)

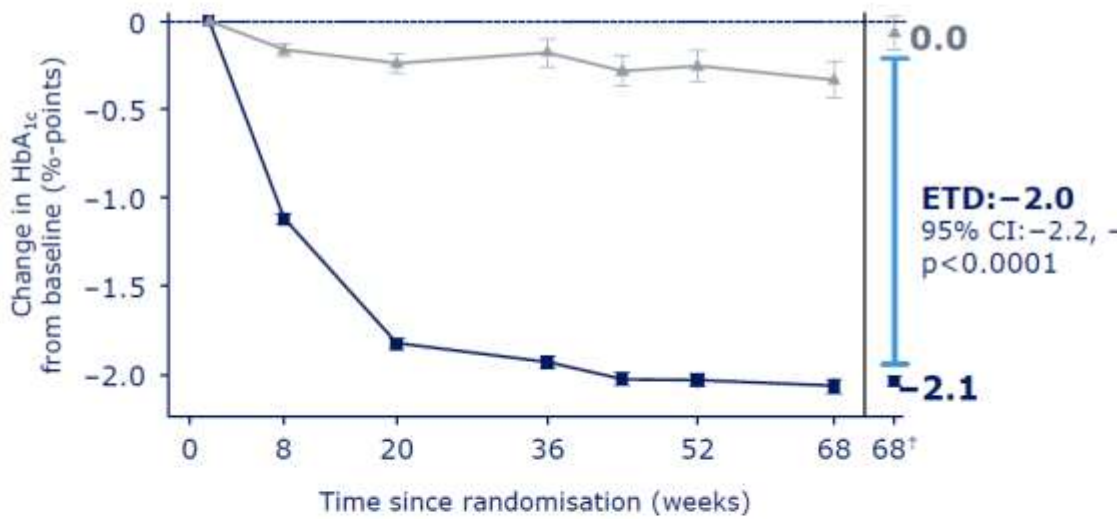
Treatment policy estimand

Trial product estimand

Mean HbA_{1c} in blood at baseline 8.0%/64.2 mmol/mol



CagriSema 2.4 mg/2.4 mg	904	880	860	843	842	822	904
Placebo	302	293	287	280	270	271	302



CagriSema 2.4 mg/2.4 mg	904	826	727	665	635	581	904
Placebo	302	272	222	186	147	127	302

CagriSema 2.4 mg/2.4 mg Placebo

CI, confidence interval; HbA_{1c}, glycated haemoglobin.
Observed data from on-treatment without rescue period. A time-point is considered as on-treatment without rescue from first administration of trial product up to the first treatment discontinuation (date where no trial product has been administered for 14 days) or the date of rescue intervention, whichever comes first. Error bars are +/- standard error of the mean.
†Estimated means from the statistical analysis. Lower panel: Numbers of participants contributing to the mean.

Source: https://sciencehub.novonordisk.com/congresses/ada2025/redefine-scientific-session.html

Biomea Data in T2DM at ADA

272-OR - COVALENT-111: 26-Week Efficacy and Safety after 8 and 12 Weeks of Daily Oral Icovamenib in Patients with Poorly Controlled Type 2 Diabetes

Introduction and Objective: Icovamenib, an oral covalent menin inhibitor, is in development for the treatment of diabetes. In the MAD phase of the COVALENT-111 trial, 4 wks of daily icovamenib in patients with T2D significantly improved A1C at 26 wks. This was most pronounced in insulin deficient T2D subtypes (mild age-related diabetes [MARD] and severe insulin-deficient diabetes [SIDD]). Here we report 26-wk results of the expansion phase of COVALENT-111.

Methods: This 52-wk, double-blind, randomized, PBO-controlled trial enrolled adults with T2D (A1C 7.0-10.5%, BMI 25-40 kg/m², up to 3 antidiabetics). Icovamenib or PBO (3:1) was administered in 3 arms: Arm A (100 mg QD for 8 wks), Arm B (100 mg QD for 12 wks), and Arm C (100 mg QD for 8 wks then 100 mg BID for 4 wks). Primary endpoint was change in A1C at 26 wks.

Results: The per protocol population consisted of 115 icovamenib- (age 54±8 yr, T2D duration 4.4±1.9 yr, A1C 8.2±0.96%, BMI 31.9±4.7 kg/m2, mean±SD) and 50 PBO-treated (age 55±7 yr, T2D duration 4.3±2.0 yr, A1C 8.3±0.93%, BMI 32.6±4.1 kg/m2) patients. Across the 3 arms, icovamenib demonstrated a PBO-corrected A1C change of -0.36% (p=0.022) at Wk 26. Patients receiving 12 wks of icovamenib (Arms B and C) had a greater change in A1C (-0.42%, p=0.015) than 8 wks of treatment (Arm A, -0.27%, p=NS). In a prespecified analysis of MARD and SIDD subtype patients, PBO-corrected change in A1C was -0.73% (p=0.009). SIDD patients treated for 12 wks (Arms B and C) had a -1.17% change in A1C (p=0.038), with those in Arm B having the greatest PBO-corrected A1C change (-1.47%, p=0.022). Icovamenib was well-tolerated, with no serious AEs or discontinuations due to AEs.

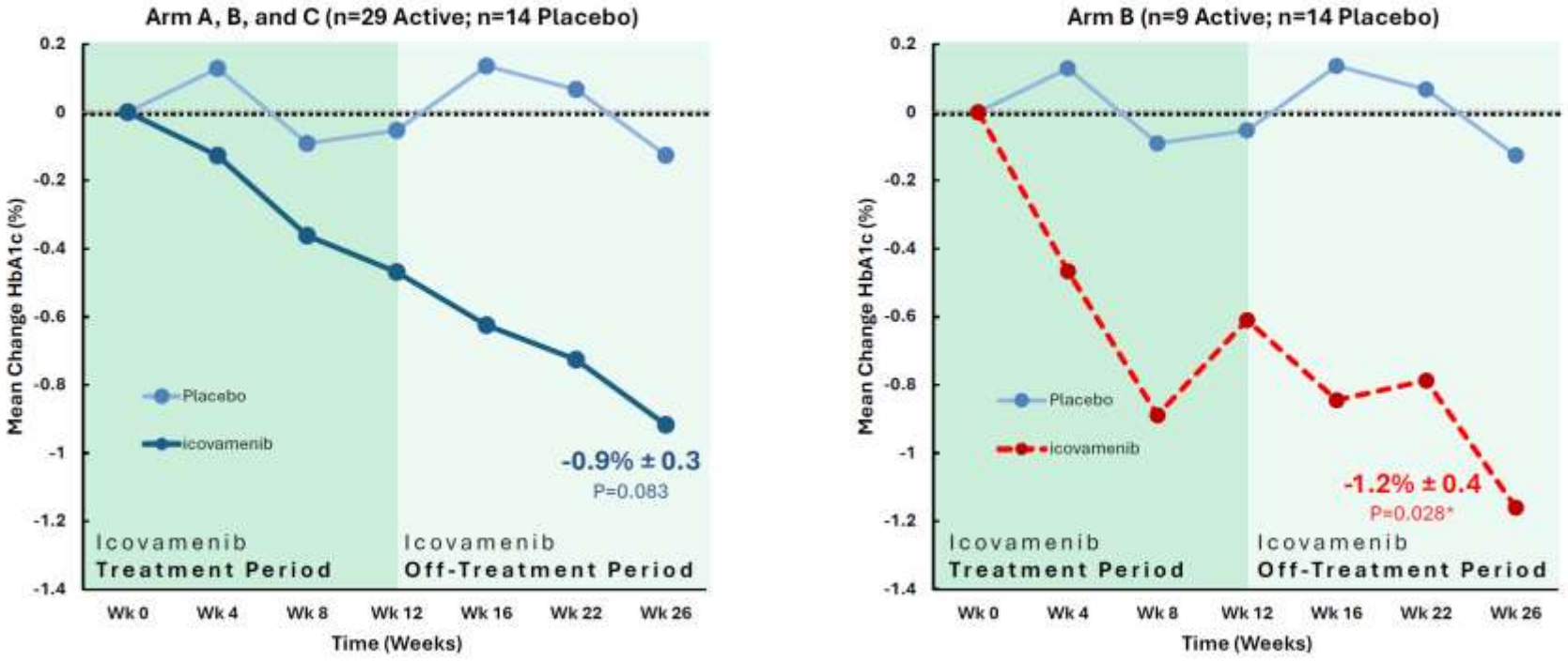
Conclusion: Icovamenib for 8 or 12 wks resulted in significant improvements in A1C at 26 wks in poorly controlled T2D. As expected, based on icovamenib's mechanism of action, this effect was most pronounced in insulin-deficient T2D. These results support icovamenib as a potential first-in-class menin inhibitor for the management of T2D.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/272-OR/159649/272-OR-COVALENT-111-26-Week-Efficacy-and-Safety

Biomea Fusion Sees Nice Improvement in HbA1c in Severe Insulin Deficient T2DM

Mean Change in HbA1c from Baseline to Week 26 in Participants with SIDD

Per Protocol Population – SIDD by study arm



SIDD, severe insulin-deficient diabetes

We like what Biomea Fusion is doing here. They are subsetting Type 2 diabetes to find those that would best respond to Icovamenib (a drug that improves beta cell function). Interestingly, Hua Medicine's dorzagliatin also works on beta cell dysfunction (as does VTV) but these companies have not taken the type of precision approach used here by Biomea.

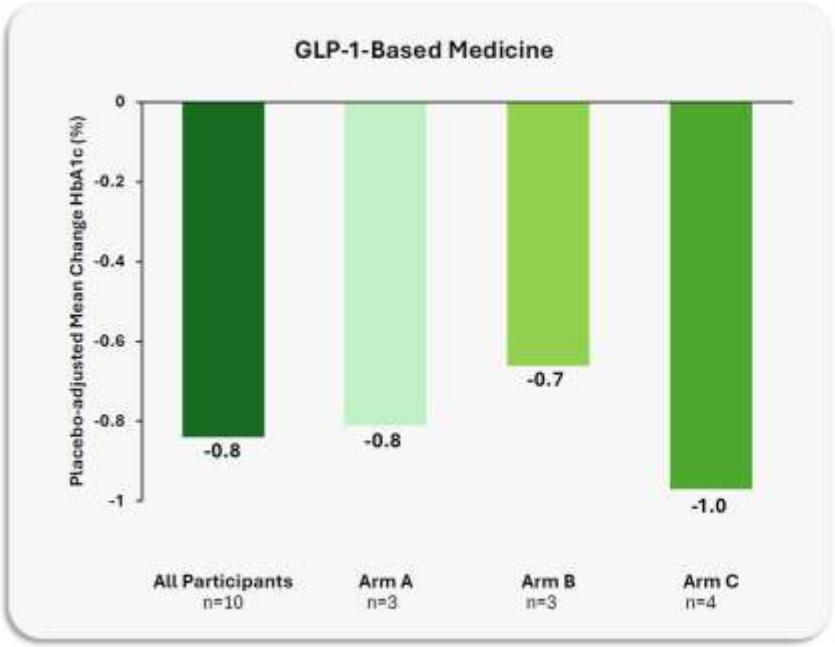
We are also seeing a new generation of drugs that impact insulin secretion such as the GIP inhibitor from Helicore. Our gut is that these emerging drugs would likely have the greatest effect in hyperinsulinemic patients rather than the hypo's as identified here by Biomea.

Source: https://investors.biomeafusion.com/static-files/246bcb3f-19b8-4f92-9c5b-a3d31c0766c5

Biomea Fusion Drug Associated with Improvement in HbA1c in Uncontrolled Users of GLP-1's

Change in HbA1c from Baseline to Week 26 in participants taking GLP1-RA at Baseline

Participants treated with GLP1-RA at baseline across all arms (N=10)



Arm A: 8 weeks of dosing 100mg QD;
Arm B: 12 weeks of dosing 100 mg QD;
Arm C: 8 weeks of 100 mg QD + 4 weeks of 100 BID

Icovamenib displayed **clinically meaningful 1.0% reduction in HbA1c** in participants **uncontrolled** on GLP-1-based therapies at Baseline

We also like what Biomea Fusion is doing here. They are testing whether their drug adds value to a GLP-1 agonist given that its MOA is orthogonal to GLP-1 MOA. Evidently it does. It would be of interest to evaluate HbA1c control on top of a GLP-1 RA in insulin deficient diabetics.

Our guess is that the Biomea drug would work nicely in this setting and this type of trial design could lead to a registrational program for the company's drug.

ADA guidelines indicate GLP-1's and SGLT's are the SOC for T2DM. It would be very interesting to test how well Icovamenib performs either on patients that can't be controlled on those therapies or on top of such therapies.

Source: https://investors.biomeafusion.com/static-files/246bcb3f-19b8-4f92-9c5b-a3d31c0766c5

Gan & Lee GLP-1 Agonist Delivers in T2DM

752-P
ADA 2025

Efficacy and Safety of Bofanglutide (GZR18), a Bi-weekly GLP-1 RA, Compared to Semaglutide in Chinese Patients with T2D

Haiya Wu[1], Ming Liu[2], Zhifeng Cheng[3], Li Lu[4], Hanqing Cai[5], Jingyu Liu[6], Jinling Liu[7], Yueyue Zheng[8], Su Wang[9], Jing Zhao[10], Wei Yang[10], Tian Xie[10], Yue Li[10], Anshun He[10], Spencer Carter[1], Wei Chen[10], Zhong-Ru Gan[10,*]

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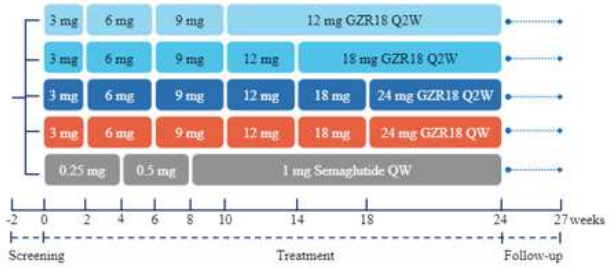
Introduction/Objective

- Bofanglutide (GZR18) is a GLP-1 RA that incorporates a C22 fatty di-acid moiety [1,2,3], which is currently in phase 3 clinical development.
- Another phase 2b trial in people with overweight or obesity demonstrated robust efficacy in body weight reduction following bi-weekly administration of GZR18 at target doses of 12 mg to 48 mg, with a mean percentage body weight change of -11.2% to -17.3% [4].
- This phase 2b trial was designed to compare the efficacy and safety of GZR18 across a wide dose range and dosing frequency (Q2W and QW) versus semaglutide (SEMA) in Chinese patients with T2D.

Methods

Study design

In this randomized, open-label, active comparator-controlled phase 2b trial, eligible adults with T2D (who were drug-naïve or with stable use of OADs, HbA1c of 7.0% to 11.0%) were randomized 1:1:1:1:1 to one of four GZR18 groups (12, 18, 24 mg Q2W and 24 mg QW) or the SEMA group (1 mg QW) for 24 weeks, including a dose escalation period.



Endpoints

Primary: Change in HbA1c from baseline to week 24.

Secondary: proportion of patients achieving HbA1c targets of <7.0% and ≤6.5%, and changes from baseline in FPG, body weight and lipid profiles.

GLP-1 RA= Glucagon-like peptide-1 receptor agonist; T2D= Type 2 diabetes; OADs= Oral anti-diabetic drugs; Q2W= Bi-weekly; QW= Once-weekly.

Results

Subject disposition

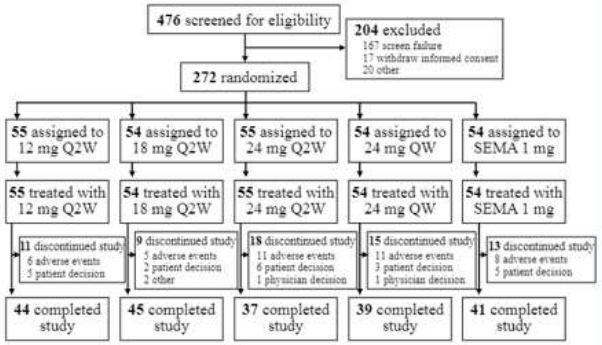


Table 1. Demographics and baseline characteristics

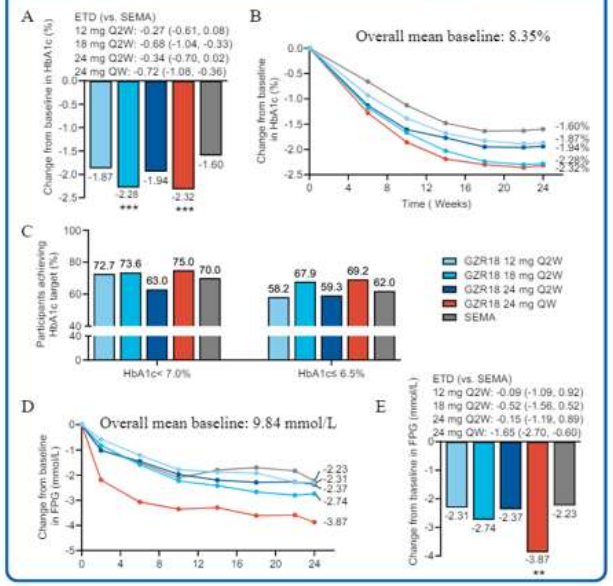
	GZR18				SEMA
	12mg Q2W N=55	18mg Q2W N=53	24mg Q2W N=54	24mg QW N=52	N=50
Age (years)	50.0 (11.1)	50.3 (9.2)	50.0 (10.6)	52.4 (11.4)	50.5 (10.5)
Sex (Male), n (%)	36 (65.5)	31 (58.5)	35 (64.8)	29 (55.8)	31 (62.0)
Race (Han), n (%)	55 (100)	51 (96.2)	54 (100)	51 (98.1)	48 (96.0)
Patients (drug-naïve), n (%)	26 (47.3)	23 (43.4)	25 (46.3)	24 (46.2)	22 (44.0)
HbA1c (%)	8.6 (1.1)	8.3 (1.0)	8.3 (0.9)	8.3 (1.1)	8.3 (0.9)
Diabetes duration (years)	4.3 (3.7)	3.7 (3.9)	4.0 (4.5)	4.7 (4.5)	4.5 (4.5)
FPG (mmol/L)	9.9 (2.2)	9.6 (2.0)	9.7 (2.2)	10.0 (2.5)	10.0 (2.7)
BW (kg)	78.4 (16.3)	77.9 (14.6)	79.0 (16.7)	71.3 (13.1)	79.1 (18.4)
BMI (kg/m^2)	28.4 (4.4)	28.1 (5.1)	28.3 (4.6)	26.3 (3.3)	28.5 (4.8)

Data were Mean (SD) or n (%). HbA1c= Glycated hemoglobin A1c; FPG= Fasting plasma glucose; BMI= Body mass index; BW= Body weight.

Figure legend

Figure 1. HbA1c change from baseline to week 24 (A) and over time (B), proportion of patients with HbA1c targets of <7.0% and ≤ 6.5% (C), change from baseline in FPG over time (D) and change from baseline to week 24 (E).
Figure 2. Change from baseline to week 24 in body weight (A) and lipid profiles (B).

GZR18 achieved significant HbA1c reductions (p< 0.001 for 18 mg Q2W and 24 mg QW vs. SEMA)



GZR18 achieved significant body weight reductions and improved blood lipid profiles

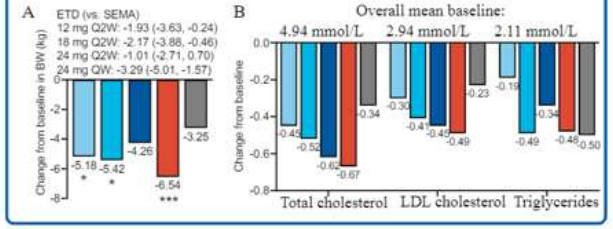


Table 2. Summary of adverse events (AEs)

Most AEs were GI in nature, mild to moderate in severity, primarily occurred during early dose-escalation period.
Two IP-related SAEs, vomiting and metabolic acidosis were reported, both resolved after management.

AEs, n(%)	GZR18 12mg Q2W N=55	GZR18 18mg Q2W N=53	GZR18 24mg Q2W N=55	GZR18 24mg QW N=54	SEMA N=54
AE	54 (98.2)	52 (98.1)	54 (98.2)	52 (96.3)	51 (94.4)
AE leading to study discontinuation	6 (10.9)	5 (9.4)	11 (20.0)	11 (20.4)	8 (14.8)
IP-related	5 (9.1)	4 (7.5)	10 (18.2)	10 (18.5)	8 (14.8)
SAE	5 (9.1)	3 (5.7)	2 (3.6)	4 (7.4)	0
IP-related	1 (1.8)	0	1 (1.8)	0	0
Death	0	0	0	0	0
GI AE	47 (85.5)	45 (84.9)	48 (87.3)	47 (87.0)	29 (53.7)
Nausea	35 (63.6)	26 (49.1)	37 (67.3)	31 (57.4)	14 (25.9)
Vomiting	26 (47.3)	25 (47.2)	33 (60.0)	26 (48.1)	6 (11.1)
Decreased appetite	25 (45.5)	25 (47.2)	22 (40.0)	30 (55.6)	15 (27.8)
Diarrhea	26 (47.3)	21 (39.6)	25 (45.5)	23 (42.6)	15 (27.8)
Hypoglycemia	0	2 (3.8)	0	1 (1.9)	1 (1.9)
Severe hypoglycemia	0	0	0	0	0
Injection site reaction	6 (10.9)	6 (11.3)	4 (7.3)	7 (13.0)	0

GI= Gastrointestinal; IP= Investigational product; SAE= Serious adverse event.

Conclusion

- In Chinese patients with T2D, GZR18 (Q2W or QW) demonstrated comparable or superior HbA1c and body weight reductions than semaglutide QW, along with an acceptable safety and tolerability profile.
- These findings suggest that GZR18 is a promising bi-weekly GLP-1 RA for the treatment of T2D and support advancement to phase 3 clinical development.

References

1. Zhang, M., et al. Eur J Pharmacol. 2022 Aug 5;928:175107.
2. Liu, Y., et al. Diabetes Obes Metab. 2025 May:27(5):2777-2789.
3. Li, W., et al. ADA 2025. 2025-A-4123-Diabetes.
4. Ji, L., et al. Obesity week 2024 (Oral-106). https://doi.org/10.1002/oby.24194.

Note: Data of all figure are least squares mean (LSM). Treatment differences versus SEMA are LSM (95% confidence interval). * p< 0.05, ** p< 0.01, *** p< 0.001 for GZR18 versus SEMA at week 24.

This work was supported by Gan & Lee Pharmaceuticals and was registered with clinicaltrials.gov (NCT06256549).

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/752-P/158836/752-P-Efficacy-and-Safety-of-Bofanglutide-GZR18-a

Kailera Data in T2DM at ADA

126-OR - Efficacy and Safety of a Novel Dual GLP-1/GIP Receptor Agonist in Participants with Type 2 Diabetes Mellitus Up to 32 Weeks

Introduction and Objective: HRS9531, a novel once-weekly (QW) dual GLP-1/GIP receptor agonist, showed preliminary efficacy with good tolerability in T2DM participants. This phase 2 study further evaluated the efficacy and safety of HRS9531 in Chinese T2DM participants with treatment to 32 weeks which consisted of a 20-week (W) core treatment followed by a 12W extension treatment.

Methods: In this randomized, double-blind phase 2 trial, participants with T2DM, HbA1c 7.5%-10.5%, inadequately controlled with lifestyle or stable metformin, were randomized to receive QW subcutaneous HRS9531 (1, 2, 3 and 4.5 mg) and corresponding placebo. During extension, HRS9531 doses remained unchanged while participants in placebo group were added HRS9531 1 mg QW (placebo-HRS9531 1 mg/W group). Primary endpoint was change from baseline in HbA1c at 20W. The efficacy and safety in 32W were also observed.

Results: Of 199 randomized participants, 186 received and 180 completed the extension treatment. At 20W, mean HbA1c changes from baseline were from -2.1% to -2.7% in HRS9531 groups. HRS9531 maintained efficacy over 32 weeks. Mean changes in HbA1c were -2.1%, -2.5%, -2.7% and -2.4% in the 1, 2, 3 and 4.5 mg groups, respectively, with 91.7% of participants in the 4.5 mg group achieving HbA1c ‹ 7.0%. The change in HbA1c of the placebo-HRS9531 1 mg/W group was -2.0%. HRS9531 induced a continuous dose-dependent body weight loss ranging from -4.0% to -8.9%. At 32W, HRS9531 was associated with improvement in systolic blood pressure, TG levels and UACR up to -9.5 mmHg, -25.7% and -61.8%, respectively. Most emergent-treatment adverse events (TEAEs) were mild or moderate. The most common TEAEs were diarrhea, decreased appetite and nausea. No clinically significant hypoglycemia or severe hypoglycemia was reported.

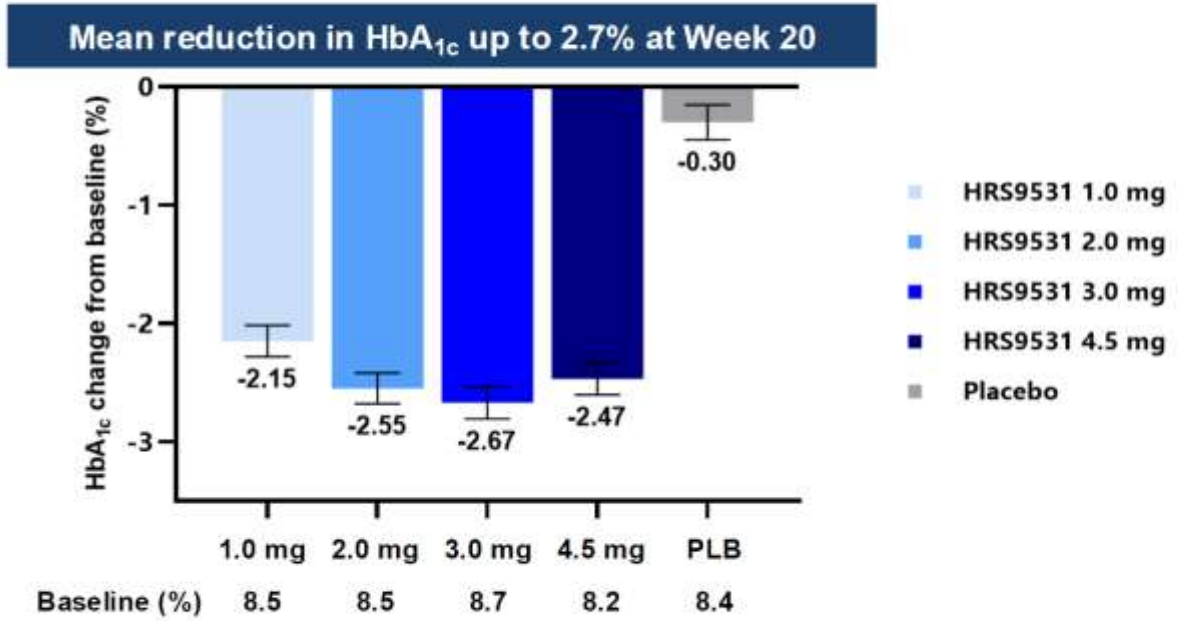
Conclusion: HRS9531 demonstrated improved and sustained glycemic control and weight loss over 32 weeks treatment, with a favorable safety and low risk of hypoglycemia.

Source: https://www.kailera.com/wp-content/uploads/2025/06/Phase_2_clinical_trial_of_HRS9531_in_participants_with_type_2_diabetes_up_to_32_weeks_ADA2025.pdf

Reductions in HbA1C on HRS9531 Quite Impressive

Primary Endpoint: HbA_{1c} Reduction at Week 20

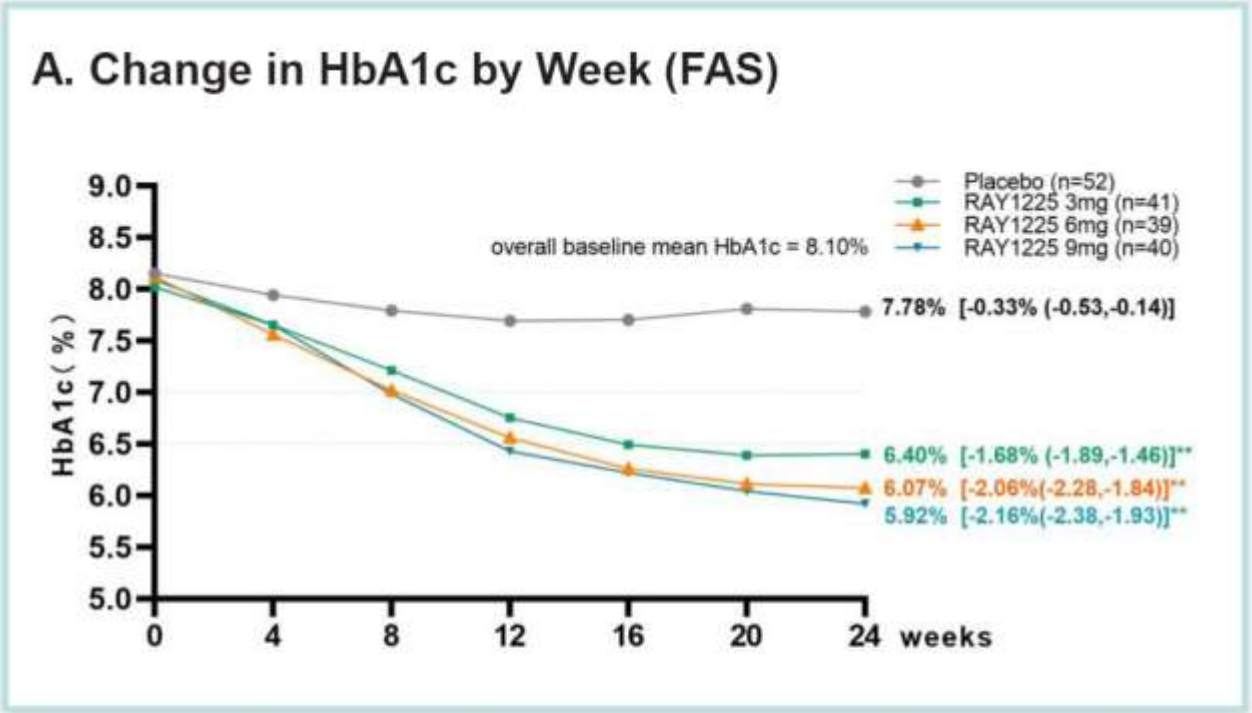
At Week 20, HbA_{1c} reductions in the 4 doses group of HRS9531 were all greater than that in the placebo group (p<0.0001 for all comparisons with placebo).



Data presented are LSMean and error bars indicate SEM.
The analysis was performed using a mixed-effects model for repeated measures (MMRM). Hypothetical strategy estimated data after permanent discontinuation of study drug and/or initiation of recue therapy and/or the use of prohibited treatment were excluded.
LSMean, Least Squares Mean; SEM, standard error.

Source: https://www.kailera.com/wp-content/uploads/2025/06/Phase_2_clinical_trial_of_HRS9531_in_participants_with_type_2_diabetes_up_to_32_weeks_ADA2025.pdf

Raynovent's RAY-1225 Data (GLP-1/GIP agonist) in T2DM



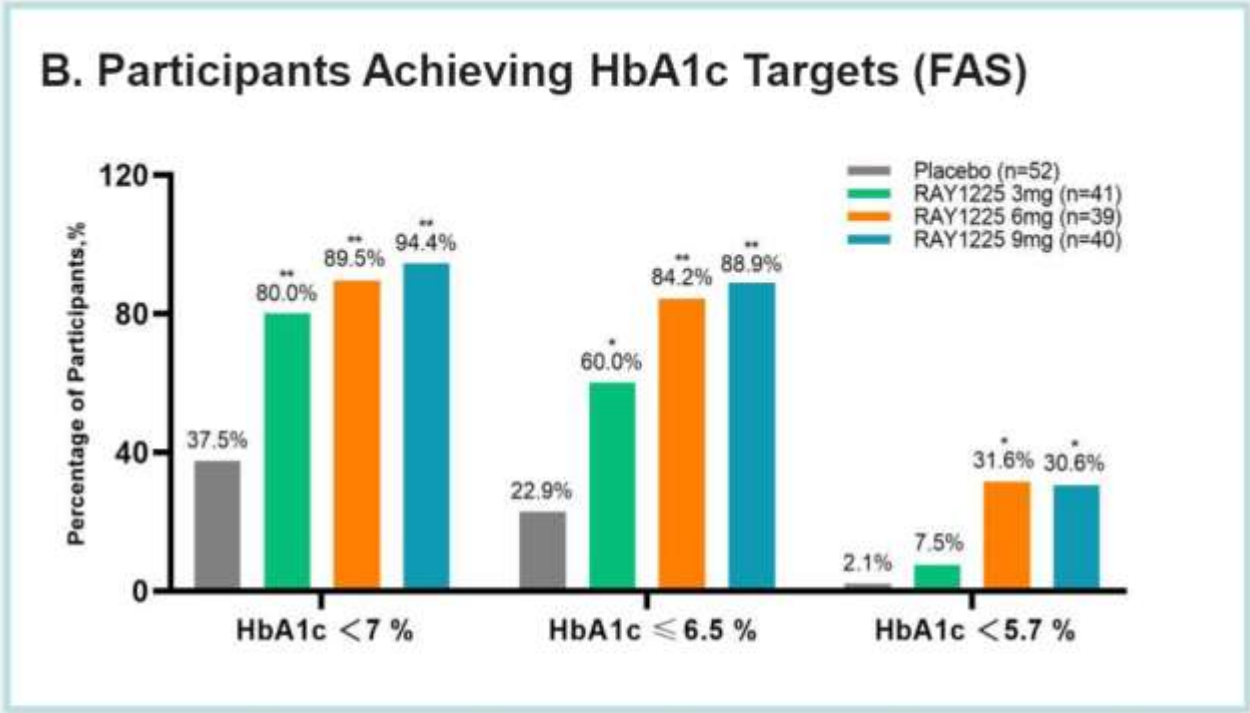


Figure 1. Effect of Biweekly RAY1225, as Compared with Placebo, on HbA1c.

- **Panel A shows the change in HbA1c according to weeks since randomization, derived from a mixed model for repeated measures (MMRM) analysis; Mean[Least-squares means(95% CI)] are presented.**
- **Panels B shows the percentages of participants who achieving HbA1c targets of <7%, ≤6.5%, and <5.7%, from baseline to week 24.**
- *** $p < 0.001$, ** $p < 0.0001$. FAS, full analysis set.**

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/795-P/158960/795-P-Efficacy-and-Safety-of-RAY1225-Once-Every

Verdiva / SciWind Data in T2DM for Ecnoglutide / VrB-101

727-P
ADA 2025

A Phase 3 evaluation of cAMP-biased GLP-1 analog ecnoglutide versus dulaglutide in adults with type 2 diabetes

Xiaoying Li [1], Yang He[1], Nianrong Mi[2], Huihui Wang[3], Shuping Zhao[4], Feifei Jiang[5], Ming Yang[4], Shaohui Bing[6], Qing Zheng[5], Jing Ning[5], Mengying Guo[4], Yue Bu[4], Lei Guan[5], Yao Li[6], Liu Yang[5], Wanjun Guo[6], Susan Xu[4] for the EECOH-2 Investigators

[1]Zhong Shan Hospital, Fudan University, Shanghai, China, [2]Central Hospital Affiliated to Shandong First Medical University, Jinan, China, [3]The First Hospital of Qiqihar, Qiqihar, China, [4]Tonghua Central Hospital, Tonghua, China, [5]Sciwind Biosciences, Hangzhou, China, [6]Sciwind Biosciences, San Ramon, USA

Background

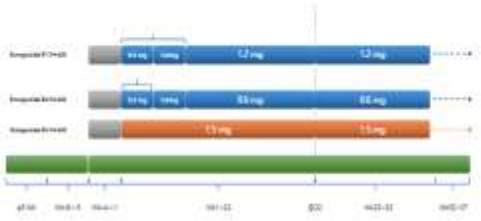
Ecnoglutide is a novel, cAMP-biased long-acting GLP-1 analog being developed for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Ecnoglutide once weekly subcutaneous injection has been shown to be safe and well tolerated in Phase 1 through Phase 3 clinical studies, with a safety profile similar with approved GLP-1 receptor agonists[1,2]. In these studies, ecnoglutide treatment resulted in reductions in HbA1c and body weight in participants with T2DM or overweight/obesity.

Methods

EECOH-2 (NCT05680129) is a randomized, open-label, active-controlled, phase 3 study of ecnoglutide, enrolling 623 adults with T2DM and inadequate glycemic control with metformin, at 52 sites across China. Participants were randomized in a 1:1:1 ratio to receive once-weekly ecnoglutide (0.6 mg or 1.2mg) or dulaglutide (1.5mg) for a total of 52 weeks, including dose escalation. The primary endpoint of this study was mean change in HbA1c at week 32.

Changes in mean bodyweight and body mass index, as well as safety and tolerability were also evaluated.

Study Design



Results

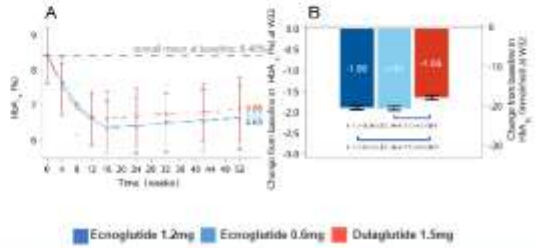
Trial Profile

Baseline Demographics and Characteristics

	Ecnoglutide 1.2 mg (N=208)	Ecnoglutide 0.6 mg (N=206)	Dulaglutide 1.5 mg (N=207)
Gender (M/F, %)	54.3/45.7	58.3/41.7	55.1/44.9
Age (year)	54.1 (10.11)	54.2 (10.89)	53.4 (9.28)
HbA1c (%)	8.4 (0.78)	8.4 (0.79)	8.4 (0.78)
Fasting glucose (mmol/L)	9.6 (1.82)	9.5 (1.96)	9.6 (1.93)
Fasting insulin (μU/mL), median (IQR)	9.4 (6.32, 15.19)	9.6 (5.62, 15.80)	9.2 (5.46, 14.73)
Body weight (kg)	74.2 (12.27)	73.7 (12.90)	72.9 (14.15)
Body mass index (kg/m²)	27.2 (3.59)	26.9 (3.45)	26.6 (3.65)
Diabetes duration (month), median (IQR)	76.1 (39.65, 122.70)	64.8 (39.30, 113.40)	63.3 (39.10, 119.10)

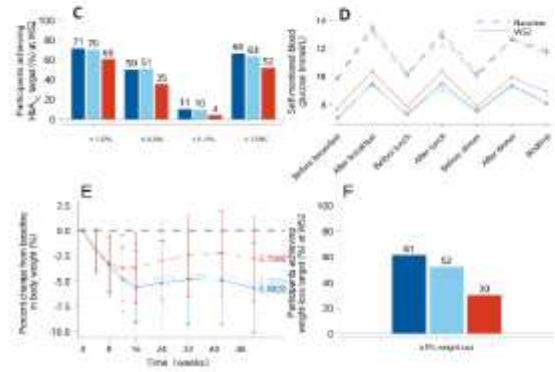
Data represent mean (SD), unless otherwise stated. IQR=interquartile range

Ecnoglutide treatment resulted in greater HbA1c decline



Results - continued

- Ecnoglutide resulted in significantly greater reduction in mean HbA1c, fasting glucose, postprandial blood glucose and body weight.
- Ecnoglutide also resulted in significantly higher proportion of participants achieving HbA1c targets as well as weight reduction targets.



Least-squares mean and standard error are shown. P<0.05 for all ecnoglutide doses vs dulaglutide at Week 32 and Week 52.

*The composite endpoint of HbA1c<7.0%, no severe or lab-confirmed symptomatic hypoglycemia and no weight gain.

Summary of treatment-emergent adverse events (TEAEs)

	Ecnoglutide 1.2 mg (N=208)	Ecnoglutide 0.6 mg (N=206)	Dulaglutide 1.5 mg (N=207)
Any TEAE	193 (92.8)	174 (84.5)	181 (87.4)
TEAE ≥ Grade 3	27 (13.0)	23 (11.2)	18 (8.7)
Serious TEAE	20 (9.6)	23 (11.2)	16 (7.7)
TEAE leading to study discontinuation	9 (4.3)	3 (1.5)	6 (2.9)
TEAE leading to treatment discontinuation	8 (3.8)	6 (2.9)	6 (2.9)
TEAE leading to death	1 (0.5)	1 (0.5)	0

Data represent number of participants (percent)

Results - continued

TEAEs ≥10% incidence in any treatment group

	Ecnoglutide 1.2 mg (N=208)	Ecnoglutide 0.6 mg (N=206)	Dulaglutide 1.5 mg (N=207)
Decreased appetite	91 (43.8)	65 (31.6)	49 (23.7)
Diarrhea	63 (30.3)	62 (30.1)	29 (14.0)
Nausea	56 (26.9)	38 (18.4)	29 (14.0)
Vomiting	40 (19.2)	20 (9.7)	22 (10.6)
Lipase elevated	38 (18.3)	23 (11.2)	30 (14.5)
Hyperuricemia	23 (11.1)	24 (11.7)	26 (12.6)
Urinary tract infection	16 (7.7)	22 (10.7)	19 (9.2)
Upper respiratory infection	14 (6.7)	26 (12.6)	22 (10.6)

Data represent number of participants (percent)

Conclusions

- Once-weekly ecnoglutide was superior to dulaglutide in improving glycemic control and reducing bodyweight in adults with T2DM inadequately controlled with metformin.
- Ecnoglutide treatment resulted in sustained glycemic control as well as bodyweight reduction.
- More participants receiving ecnoglutide achieved HbA1c target of ≤6.5% and weight loss target of ≥5.0% than participants receiving dulaglutide (51% vs 35% and 61% vs 30%, respectively).
- Ecnoglutide was safe and well tolerated. The most frequently reported TEAEs were decreased appetite, diarrhea and nausea, which were mostly mild to moderate in severity and self-limiting.

References

1 Guo et al Molecular Metabolism 2023; 75 101762
2 Zhu et al. Nature Communications 2024 15 8408

Reset Zoom + Zoom -

Strong BrightGene Data in T2DM at ADA

303-OR: Efficacy and Safety of BGM0504 in Chinese Patients with Type 2 Diabetes—A Multicenter, Randomized, Double-Blind, Placebo-Controlled and Semaglutide Positive-Controlled Phase 2 Trial

Introduction and Objective: BGM0504 is a dual agonist targeting the glucagon-like peptide-1 receptor (GLP-1R) and glucose-dependent insulinotropic polypeptide receptor (GIPR). This study aimed to evaluate the safety and efficacy of BGM0504 in Chinese adults with type 2 diabetes mellitus (T2DM) and compare its performance to Semaglutide through multiple subcutaneous injections.

Methods: This multicenter, randomized, placebo-controlled, and Semaglutide positive-controlled trial included 64 Chinese adults with T2DM. Participants were randomized into five groups: BGM0504 5 mg (n=12), 10 mg (n=12), 15 mg (n=12), placebo (n=12), and Semaglutide 1.0 mg (n=16). The study consisted of a titration phase (2-6 weeks), 12 weeks of once-weekly treatment, and a 2-week follow-up. The trial was registered with the Chinese NMPA (CTR20232464).

Results: Changes in HbA1c from baseline to week 12 relative to placebo were as follows (LSM, 95% CI): 5 mg group: −1.82% (−2.83 to −0.8110 mg group: −2.05% (−3.27 to −0.82); 15 mg group: −2.56% (−3.58 to −1.54); Semaglutide 1.0 mg: −1.86% (−2.83 to −0.90).

The 15 mg dose was superior to Semaglutide (p=0.0327). Improvements in FPG and 2h-PPG relative to placebo ranged from −3.18 to −1.63 mmol/L and −6.16 to −4.76 mmol/L, respectively ($p < 0.05$). The percentage of participants achieving HbA1c <7.0% was: 5 mg group: 76.9%; 10 mg group: 81.8%; 15 mg group: 91.7% Semaglutide 1.0 mg: 75.0% Placebo: 16.7%

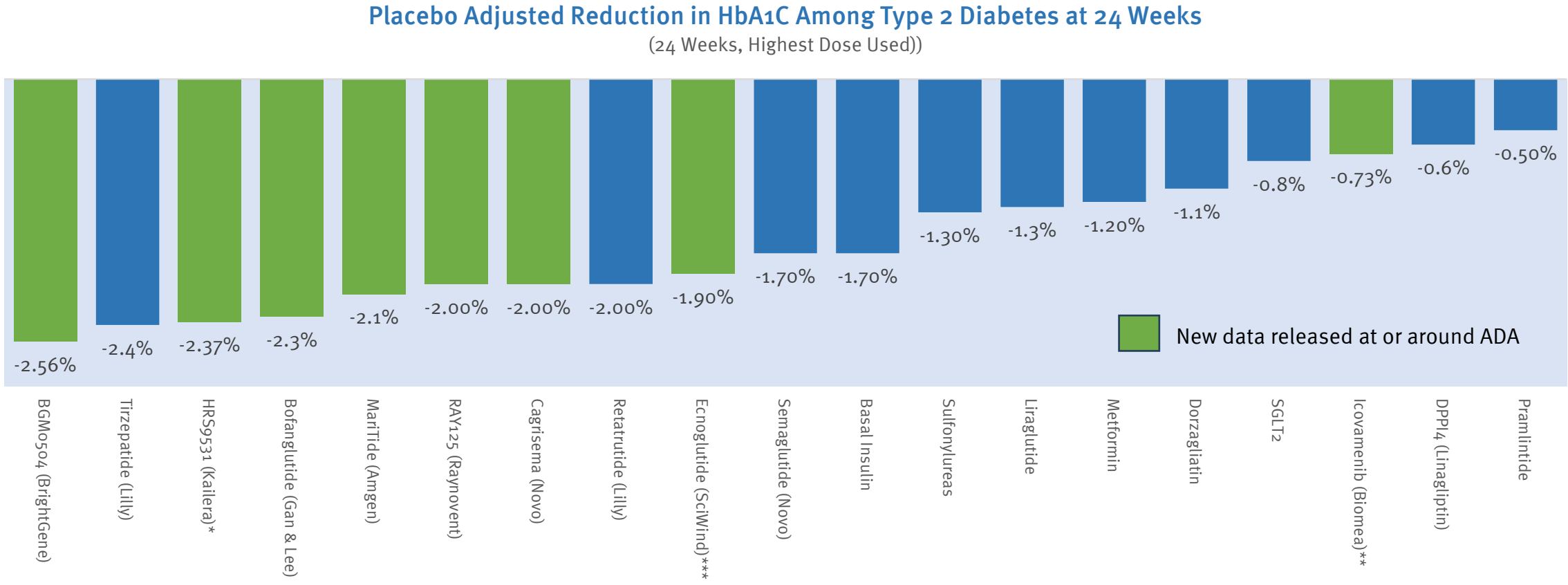
All BGM0504 doses were superior to placebo in achieving this target ($p < 0.05$). The 15 mg group also demonstrated significantly greater weight reduction compared to Semaglutide ($p < 0.001$). All doses of BGM0504 were well tolerated, with common adverse events.

Conclusion: BGM0504 was safe and well-tolerated, with the 15 mg dose showing the most substantial effects. It is a promising treatment option for improving glycemic control and achieving weight reduction in patients with T2DM.

Source: https://diabetesjournals.org/diabetes/article/74/Supplement_1/303-OR/158743/303-OR-Efficacy-and-Safety-of-BGM0504-in-Chinese

Update: HbA_{1c} Improvements at 24-Weeks in T2DM

Tirzepatide is the current market leader for improvement in HbA1c in patients with Type 2 diabetes. Brightgene and Kailera have developed molecules with the same MOA and have shown very similar improvements in HbA1c. Amgen's MariTide comes close to matching these results with a once monthly antibody approach. One thing that is interesting here is that retatrutide does not seem to add value in HbA1c control to tirzepatide. The window is obviously open for competition in this area – particularly for companies that wish to take a precision approach by adding on a molecule such as icovamenib or dorzagliatin to a GLP-1/GIP agonist.



* These data are for 20 weeks of treatment; ** patients were dosed for only 12 weeks but assessed at 26 weeks; these patients were dosed for 26 weeks. No placebo arm was used in the study.

Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context. Differences exist in study designs and conditions, and caution should be exercised when comparing data across studies.

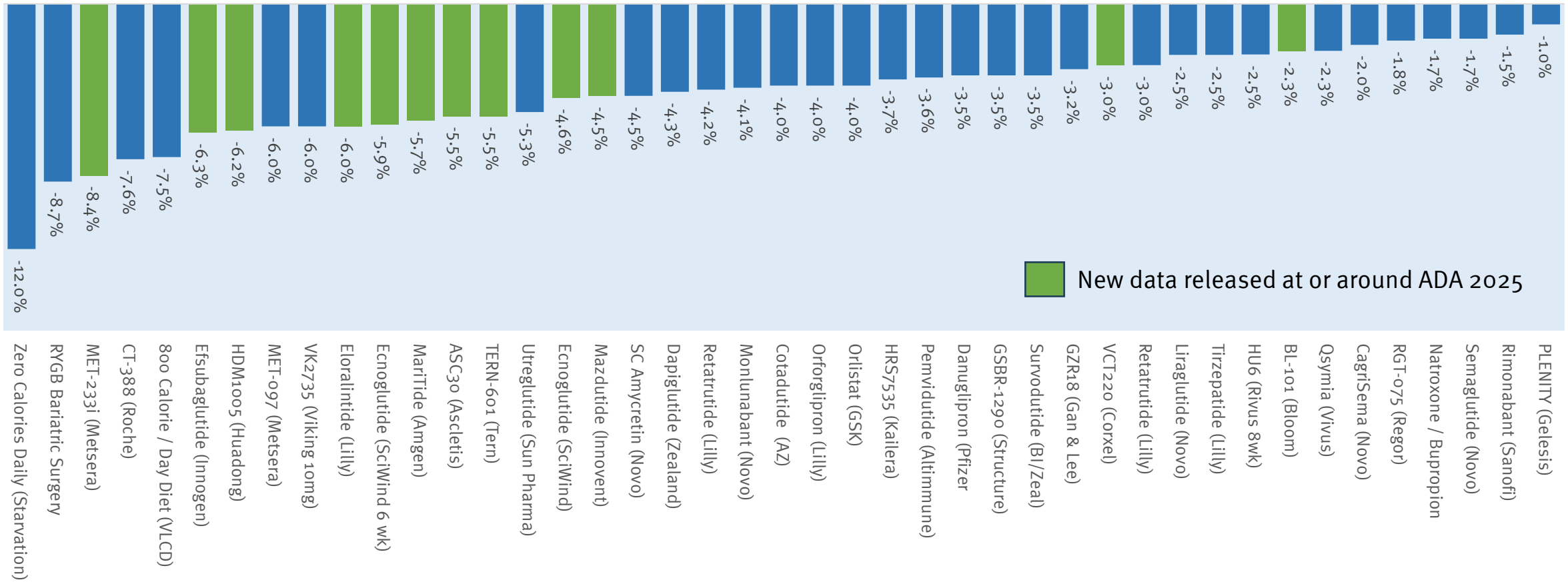
Contextualizing Weight Loss Data From ADA

Update: 4-Week Weight Loss Leaders After ADA

Metsera's MET-233, Eloralintide (Lilly)and Efsubaglutide (Innogen) are strong new competitors at four weeks. Amgen's MariTide has fallen off with new data while Roche's CT-388 remain a key efficacy leader at four weeks. Not shown is new and impressive 6-week data from GumAMY (AbbVie). In practice, 4-week data is not that meaningful because weight loss can be induced by avoiding a run in and using drugs with low tolerability.

Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

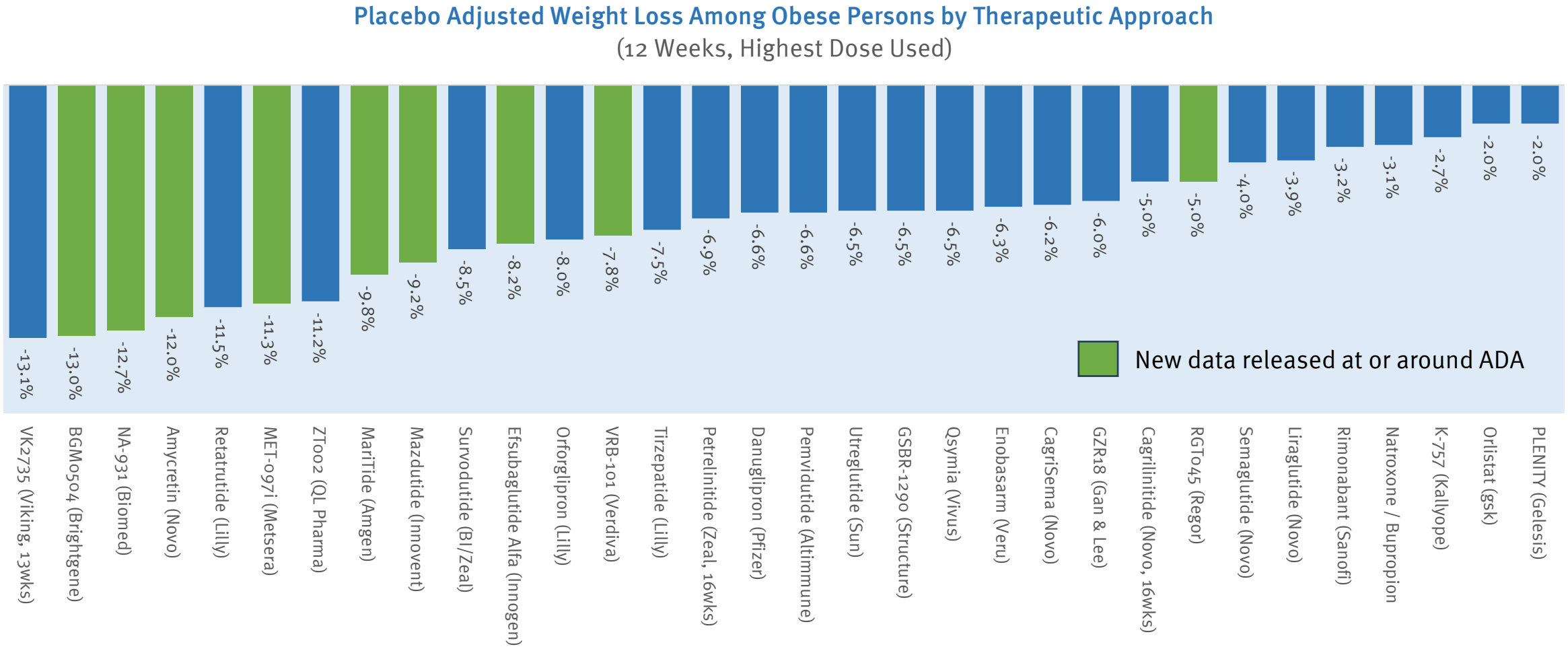
(4 Weeks, Highest Dose Used))



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context. Differences exist in study designs and conditions, and caution should be exercised when comparing data across studies.

Update: 12-Week Weight Loss Leaders After ADA 2025

We are seeing multiple new contenders show their data this year. Particularly notable weight loss has been displayed by GBM0504 (Brightgene) and NA-931 (Biomed Industries). Brightgene ran a multi-center study and has indicated that they have a favorable tolerability profile but did not show the data in their recent ADA poster. Biomed showed data for their quad incretin molecule which had excellent tolerability in a five-center study. Novo's amycretin also looks good but was generated from a single center. We have seen how much results can change going from Phase 2a to Phase 2b in recent studies from Amgen (MariTide) and CagriSema (Novo).



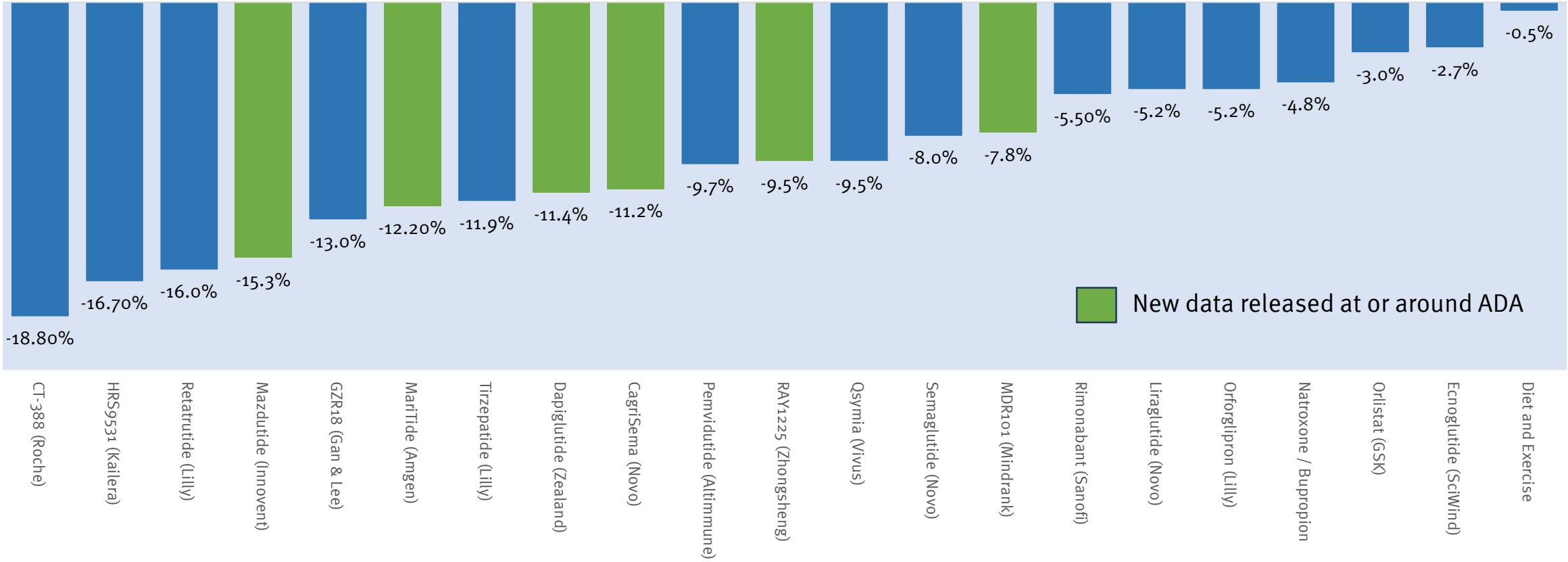
Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context. Differences exist in study designs and conditions, and caution should be exercised when comparing data across studies.

Update: 24-Week Weight Loss Leaders After ADA 2025

What's so interesting here is that there is much less change this year than last at 24-weeks. The new datasets from Innovent on mazdutide and Amgen on MariTide are impressive but both agents involved some tolerability challenges. There appear to be three serious contenders in this category today - CT-388 (Roche), HRS9531 (Kailera) and retatrutide (Lilly). Tolerability and Phase 3 strategy for each will likely be determinative of the medium-term future of the obesity drug market.

Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(24 Weeks, Highest Dose Used)



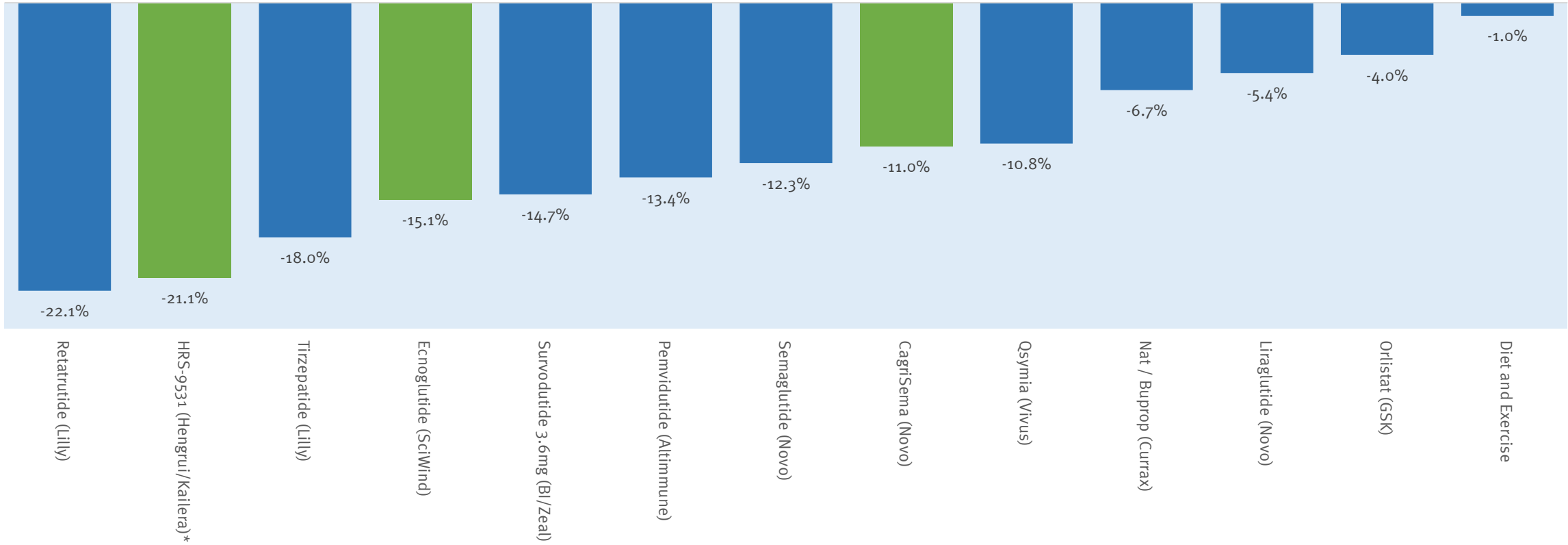
Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Update: 48-Week Weight Loss Leaders After ADA 2025

Also notable was the absence of practice-changing data at 48-weeks at this year's ADA. The one-year benchmarks for weight loss owned by retatrutide and tirzepatide have not yet been disrupted. SciWind ecnoglutide is looking good. The updated CagriSema data from Novo in the last year appears far from competitive. It will be interesting to see what a better GLP-1/amylin (DACRA) type drug such as amycretin can do. Lilly is obviously positioning for this potential competition by developing a standalone amylin analogue.

Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

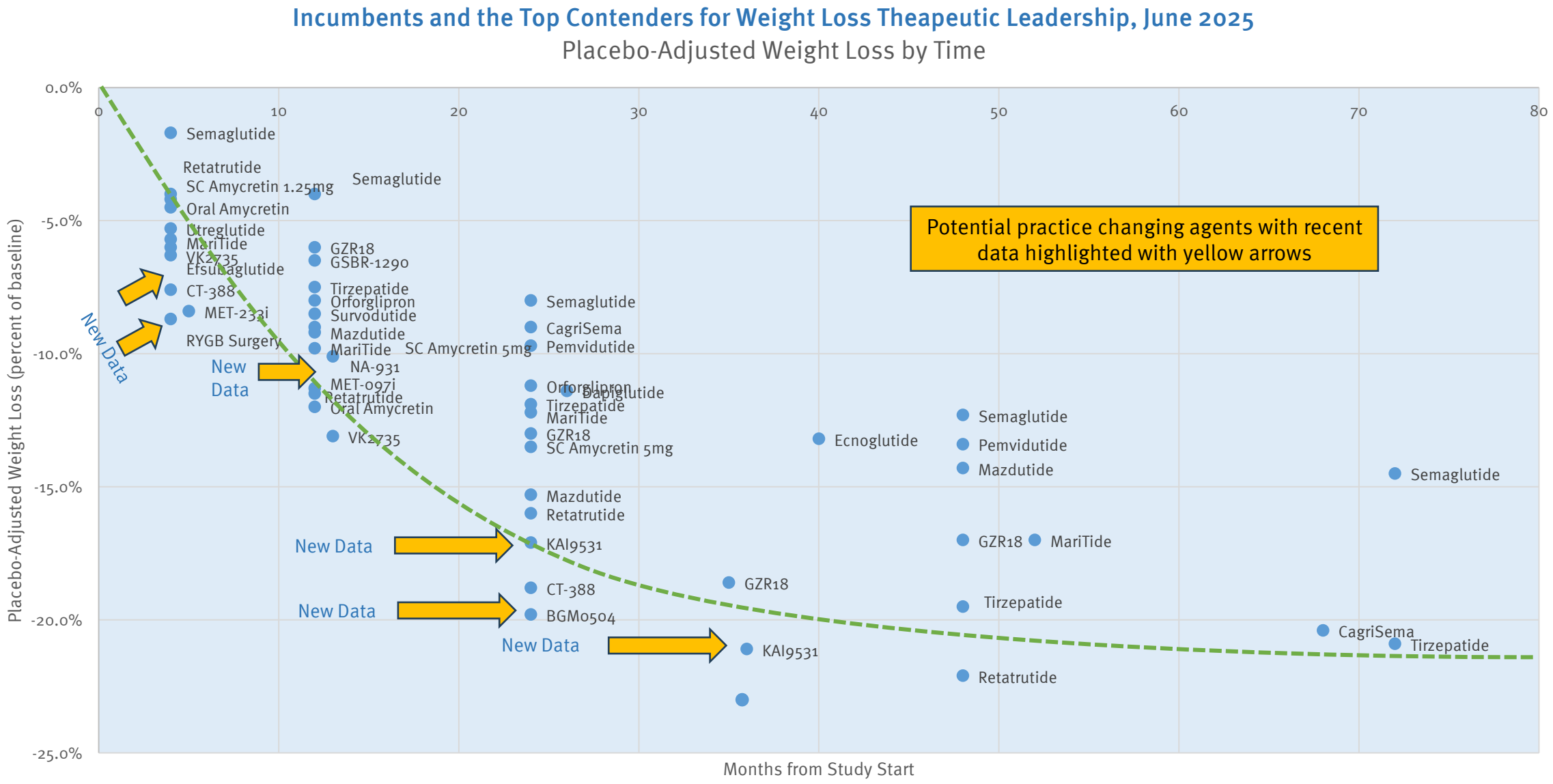
(48 Weeks, Highest Dose Used)



* 32 week data.

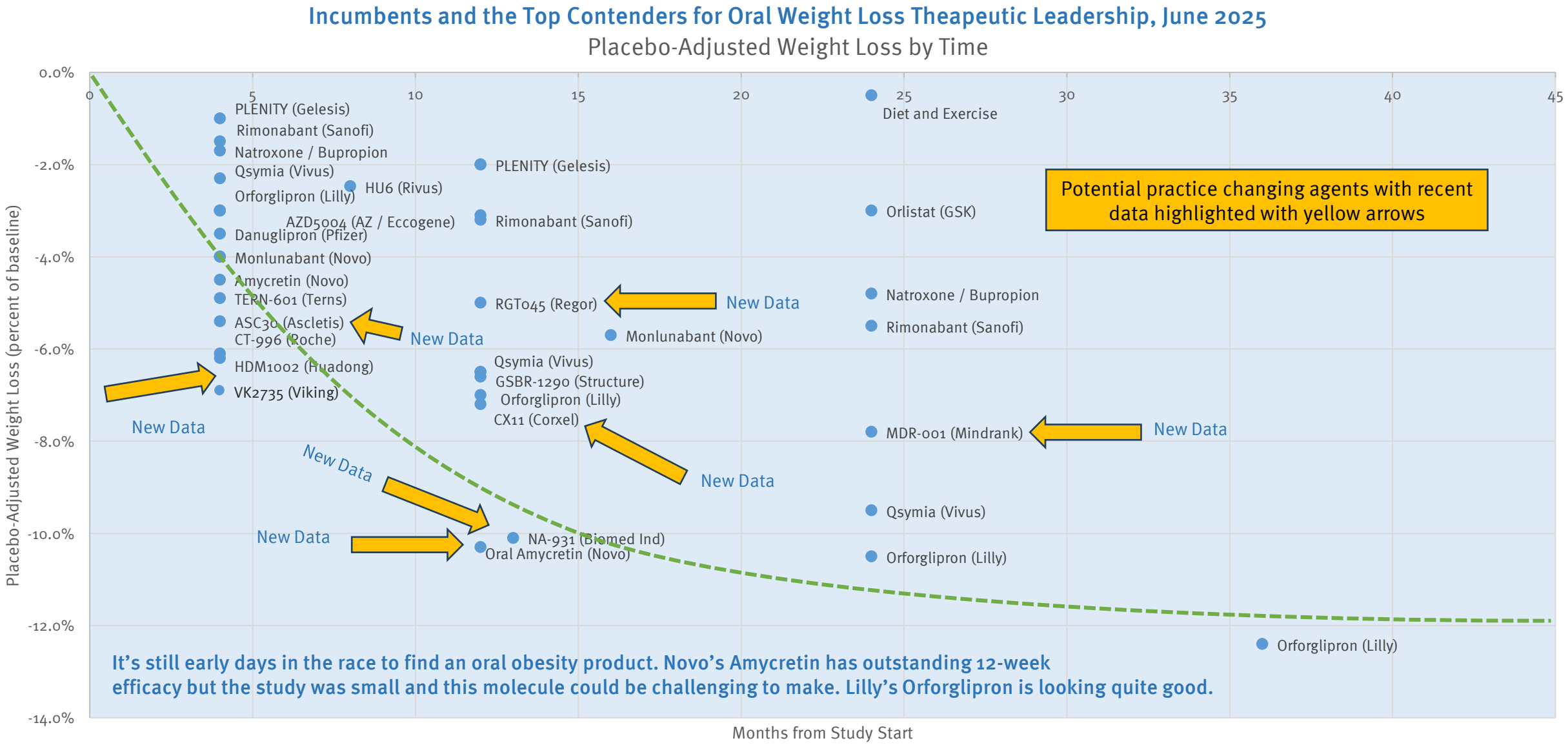
Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Summary: Weight Loss Difference Makers after ADA 2025



Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

Summary: Oral Contenders for Weight Loss Leadership

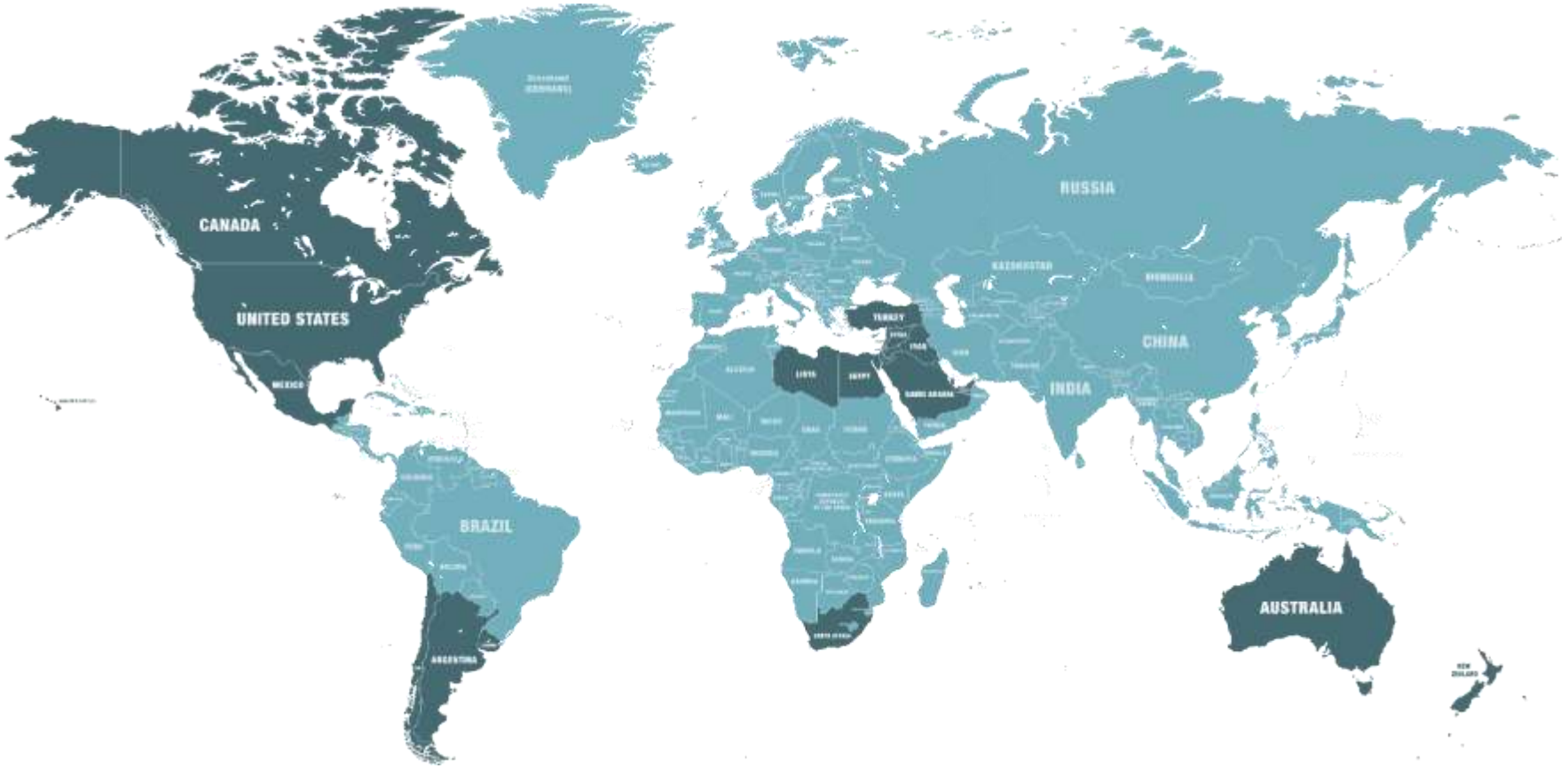


Source: Stifel analysis of various company presentations and press releases. Please note that these are not results from head-to-head studies and would likely be different in such a context.

The Obesity Epidemic

The Global Obesity Epidemic

Top 20 Countries With The Highest Obesity Rates



36%

Rate of adult obesity in the US

25%

Estimated rate of obesity worldwide by 2035

2+

Lost years of average US life expectancy relative to peer countries

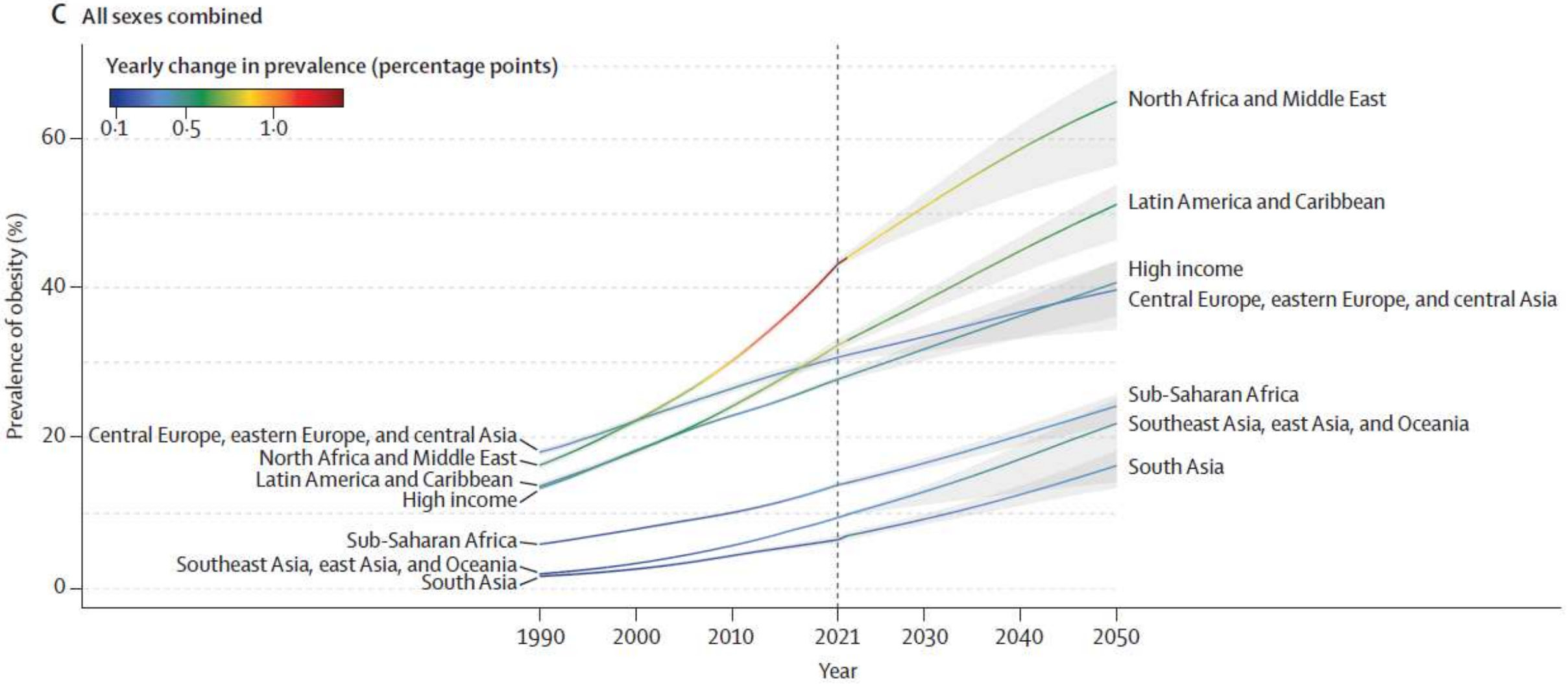
30%

Higher overall mortality for each 5 kg/m2 higher BMI

Source: FactMaps, The World Factbook (Central Intelligence Agency).

Global Obesity Prevalence Going Through the Roof

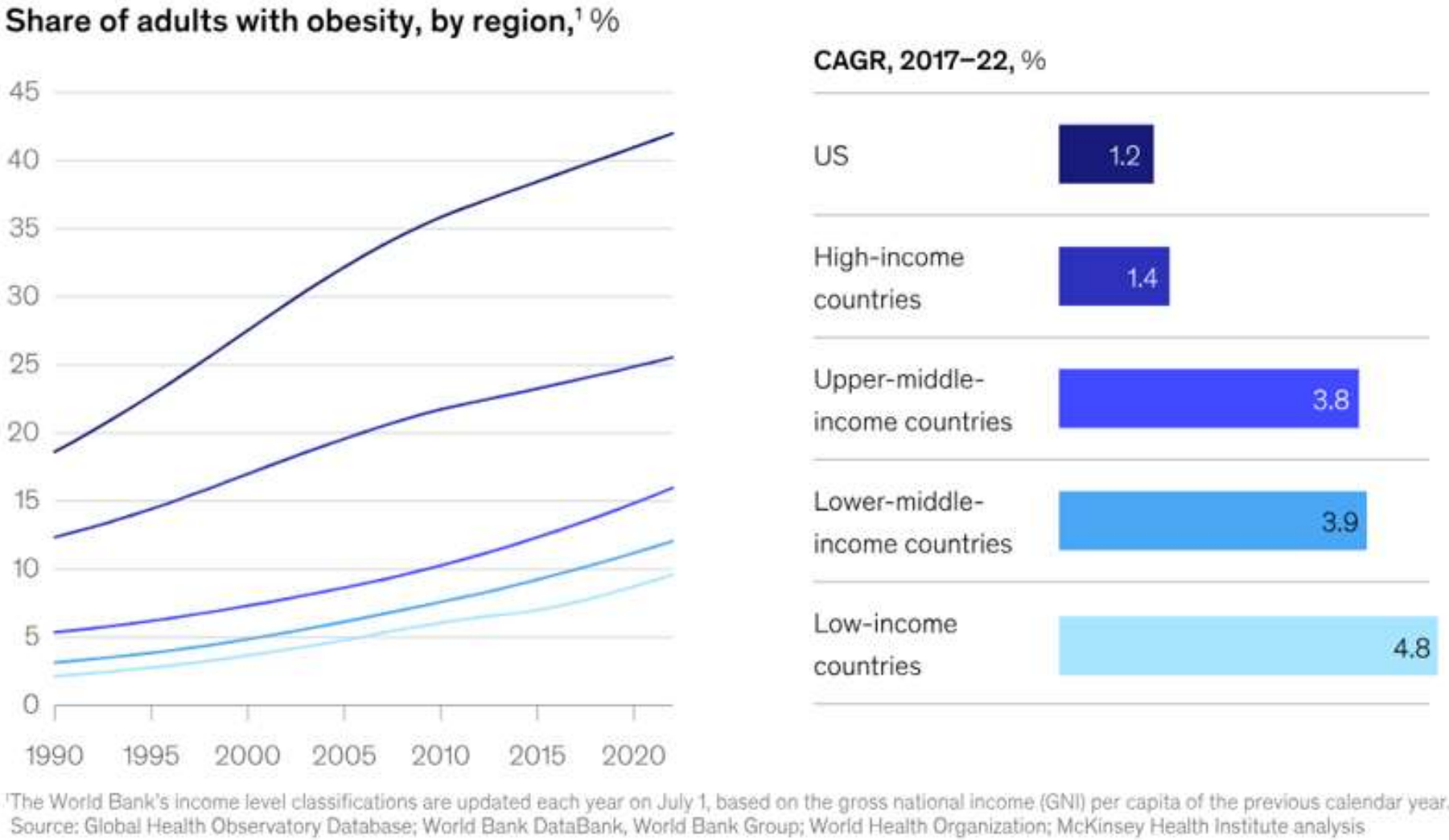
Thorkild I A Sørensen, "Forecasting the global obesity epidemic through 2050," Lancet, March 8, 2025



Source: https://www.sciencedirect.com/science/article/pii/S0140673625003551

Burden of Obesity in Future to Hit Emerging World Most

McKinsey Health Institute, *The path toward a metabolic health revolution*, Report, May 20, 2025

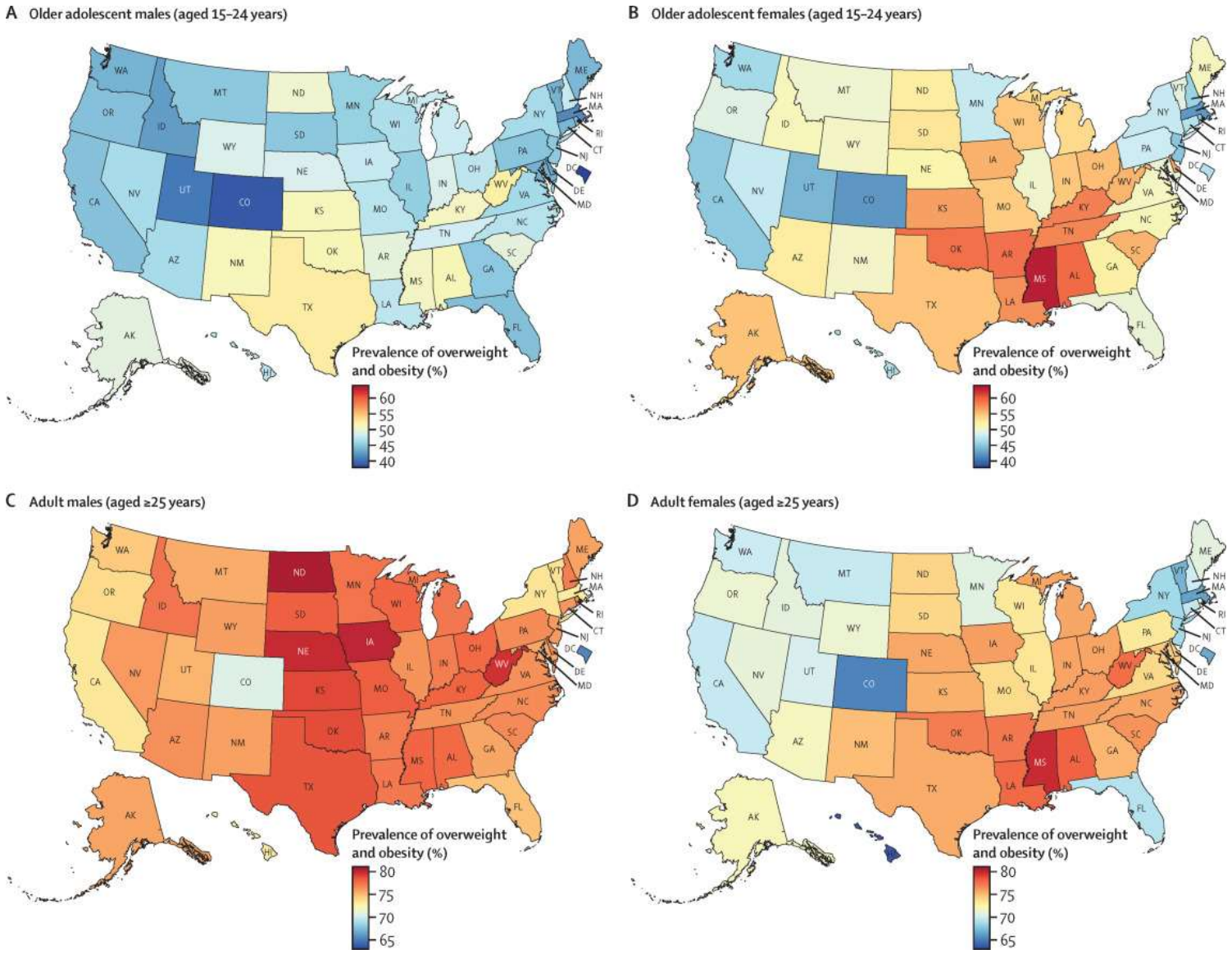


Source: https://www.mckinsey.com/featured-insights/sustainable-inclusive-growth/charts/obesitys-growing-but-unequal-burden

Obesity Prevalence By State in the USA

Lancet, Dec 7, 2024

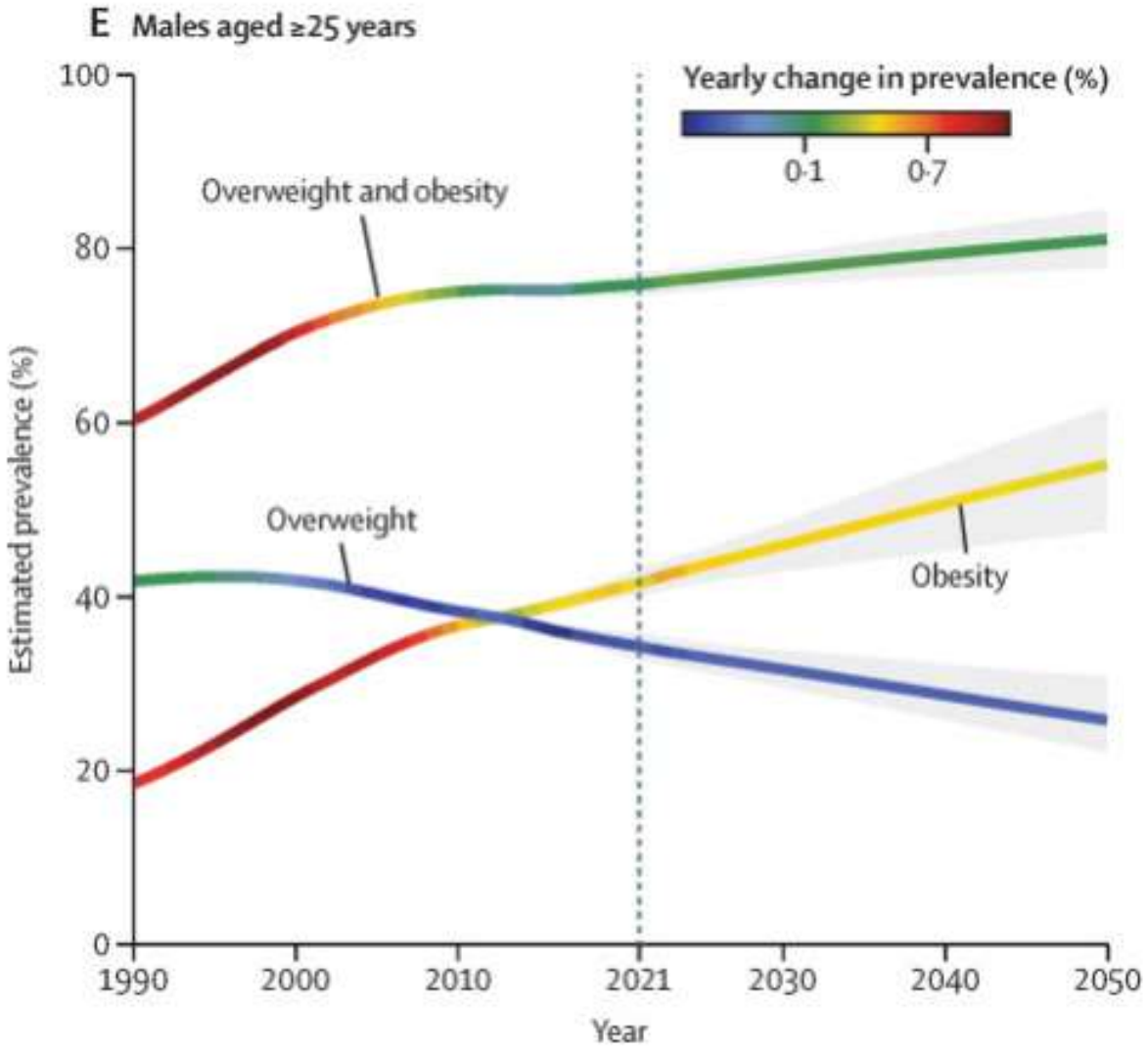
To our knowledge, our study is the first to report the historical and projected trends in overweight and obesity for older adolescents (aged 15–24 years) and adults (aged ≥25 years) from 1990 to 2021, with forecasts to 2050 for total number and prevalence at the national level and across all 50 states and Washington, DC. Additionally, we provide past, current, and forecasted national-level prevalence for children and younger adolescents (aged 5–14 years). In our analysis, we used all available national and subnational data in the USA and applied systematic adjustments to reconcile differences between self-reported and measured anthropometric data. We examined the differential surges of prevalences of overweight and obesity across age, sex, and state-level geography in the past three decades, and analysed how, if the current pattern holds, the future trajectory will affect the US population across the country.

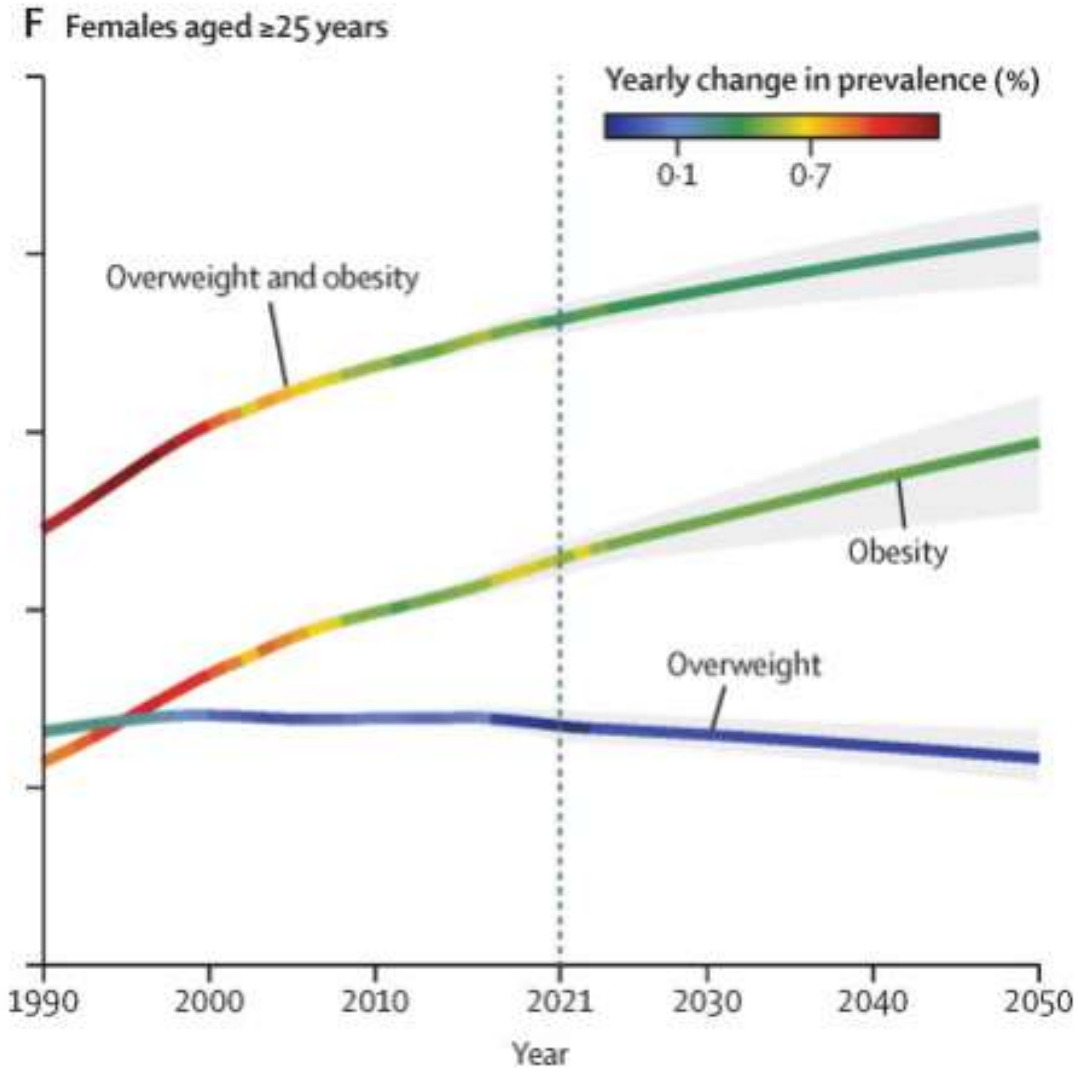


Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01548-4

GBD Study: Prevalence of Obesity in the U.S. Headed North Indefinitely

Lancet, Dec 7, 2024





Source: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(24)01548-4

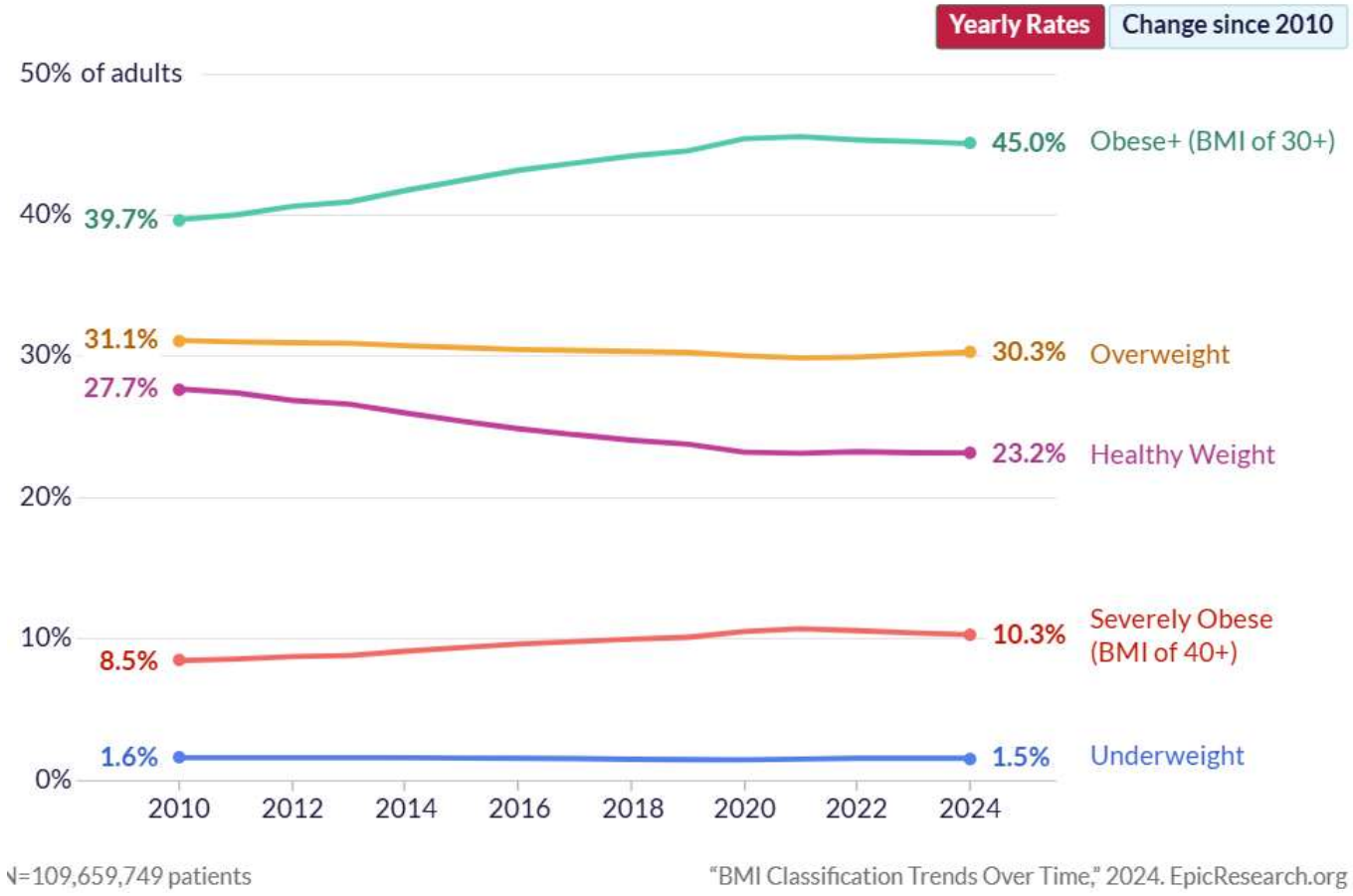
Epic Data Tell a Different Story on Direction of U.S. Obesity

Dual Team Study, Epic Research, Feb 4, 2025

Recently, there have been conflicting reports on the trends in obesity rates in the U.S., with some reporting a peak in the rate of obesity and others reporting the rate of obesity will continue to climb through at least 2025. The U.S. Centers for Disease Control and Prevention (CDC) reports that obesity increases the risk of high blood pressure, diabetes, and heart disease among patients as well as increased medical expenditure.

We aimed to understand the trends in adult BMIs since 2010. **We studied the BMI classification of more than 109 million patients who had an outpatient visit between Q1 2010 and Q3 2024.**

We found that the percentage of adults classified as obese (BMI of 30 or greater) increased from around 40% in 2010 to around 45% in 2020, a 13.6% increase, and this rate remained fairly stable through 2024. **The rate of severe obesity (BMI of 40 or greater) increased from 8.5% of patients in 2010 to 10.7% in 2021, followed by a downward trend to 10.3% in 2024.**The rate of patients with a healthy weight dropped from 27.7% to 23.2% between 2010 and 2024.

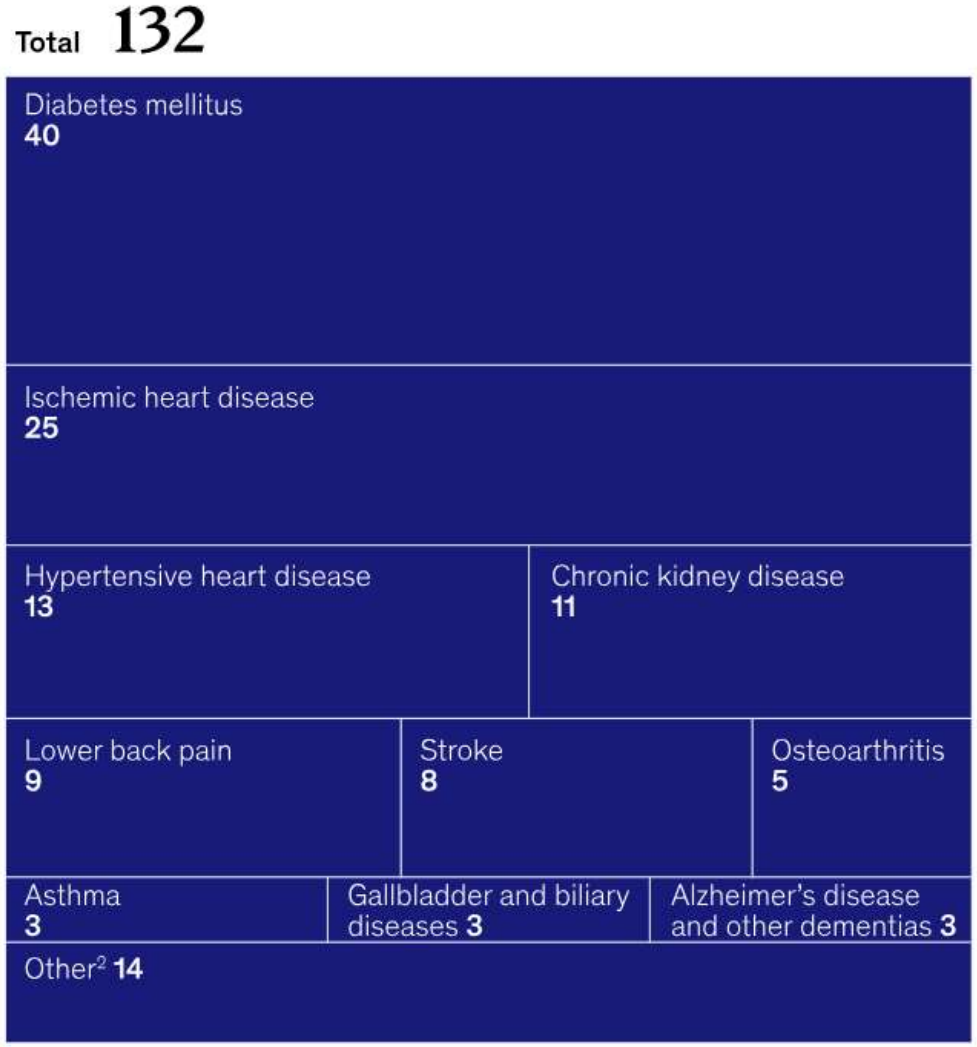


Source: https://www.epicresearch.org/articles/after-a-decade-of-increase-obesity-and-severe-obesity-have-trended-back-down

McKinsey: Obesity is a Known Risk Factor for Disease

McKinsey Health Institute, *The path toward a metabolic health revolution*, Report, May 20, 2025

Annual disability-adjusted life years (DALYs) attributable to high body mass index, global, 2022, million DALYs[1]



The disease burden of obesity on individuals with the condition and on society at large is substantial. A typical adult living with obesity today can expect to live approximately 35 years with the condition, in addition to common comorbidities. In total, more than 132 million DALYs annually are attributable to high BMI, equivalent to the annual burden of all chronic respiratory diseases (108 million DALYs) and about half of the annual burden for all cancers (252 million DALYs). For context, this is equivalent to three times the estimated DALYs burden of the global COVID-19 pandemic (43 million DALYs between January 2020 and April 2021). **If obesity were to be eliminated as a global public health concern, an extra 6.5 billion years of life could be gained globally.**

Source: https://www.mckinsey.com/mhi/our-insights/the-path-toward-a-metabolic-health-revolution#/

Large-Scale Analysis Highlights Obesity as a Risk Factor for Disease

Mousavi S. et. al., "Large-scale analysis highlights obesity as a risk factor for chronic, non-communicable inflammatory diseases," ***Front Endocrinol*** **(Lausanne). 2025 Feb 3;16:1516433.**

A large-scale cohort study of over 3 million individuals with overweight or obesity compared to an equal number of controls found that excess weight significantly increases the risk of developing chronic inflammatory diseases (CIDs). **Overall, 28.48% of overweight/obese individuals developed a CID versus 17.55% of non-overweight individuals, with a hazard ratio of 1.52.** Elevated risks were observed for most CIDs studied, though results varied for some conditions. Sex- and race-stratified analyses revealed that overweight and obesity posed higher risks for certain CIDs in women and in White individuals, highlighting the need to address sex and racial disparities in research and prevention.

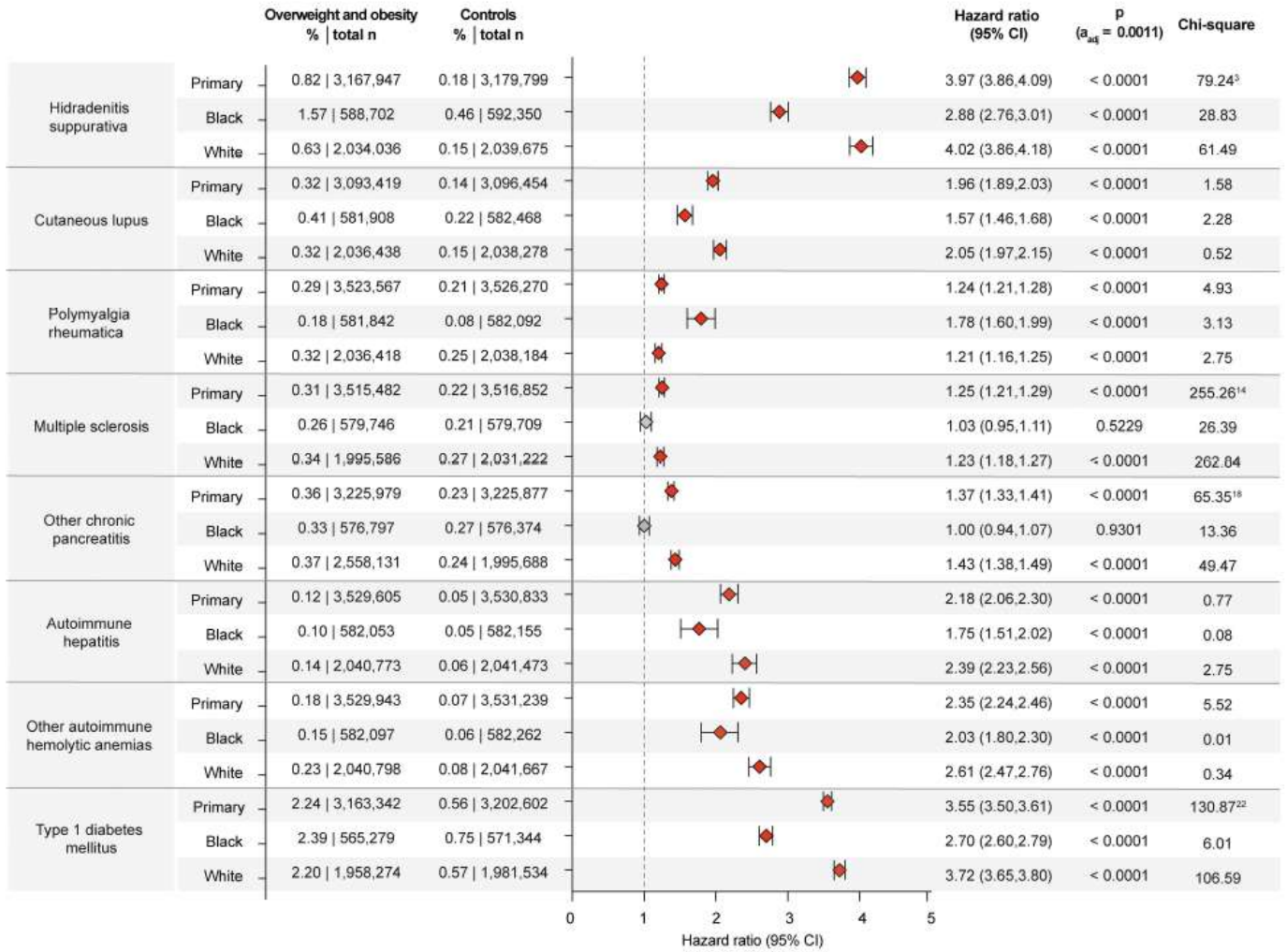


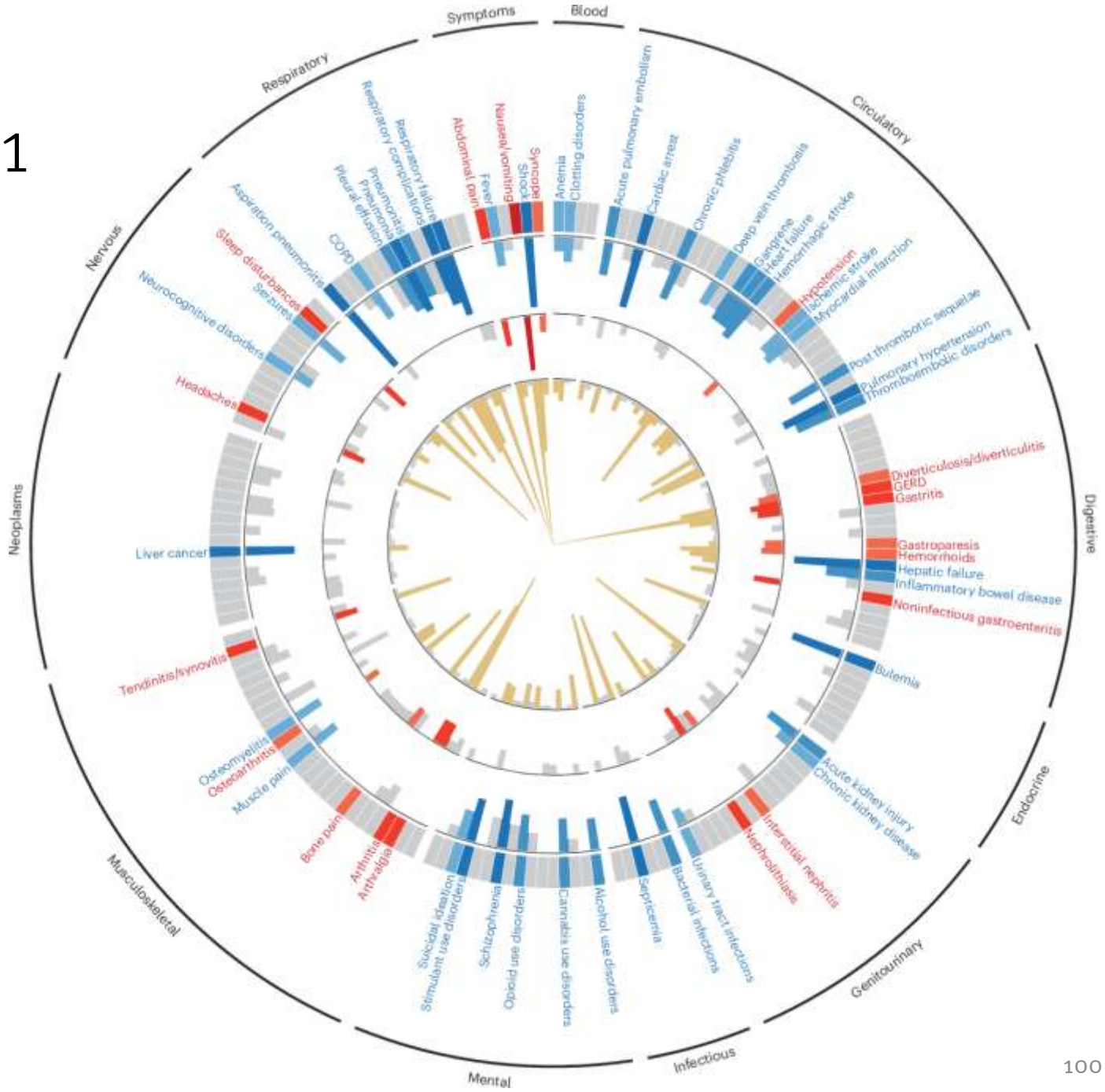
FIGURE 4
Chronic non-communicable inflammatory diseases with racial disparities in obesity and overweight-related risks. Risk of those chronic non-communicable inflammatory diseases that demonstrated racial disparities relating to the risk imposed by obesity and overweight. For comparisons with a highly violated proportionality assumption in the primary analysis, the odds ratio (OR) that also excludes outcomes prior to the index event, its' 95%-confidence interval and p-value are provided in the footnotes: [3]OR 4.558 (4.43,4.69) p<0.0001, [14]OR 1.412 (1.371,1.454) p<0.0001, [18]OR 1.871

Source: https://pubmed.ncbi.nlm.nih.gov/39963282/

Dozens of Diseases Positive Affected by GLP-1 Drug Usage

Xie, Y., Choi, T. & Al-Aly, Z. Mapping the effectiveness and risks of GLP-1 receptor agonists. *Nat Med* 31, Jan 20, 2025, 951–962

This circos plot shows an atlas of associations between GLP-1RAs and 175 health outcomes across 12 outcome categories. From outermost to innermost ring: (1) 12 outcome categories, (2) outcome names with decreased risks (blue), increased risks (red), and nonsignificant associations (grey), (3) heatmap of risk magnitudes, (4) reduced risk magnitudes, (5) increased risk magnitudes, and (6) statistical significance (negative log-transformed *P* values; yellow = significant, gray = nonsignificant). The figure highlights the systemic effects of GLP-1RAs — revealing decreased risks for many health conditions and increased risks for several adverse outcomes.



Source: https://www.nature.com/articles/s41591-024-03412-w

The Idea that Obesity is Linked to Disease is Not New

1872

ON CORPULENCE

IN

RELATION TO DISEASE:

WITH SOME REMARKS ON DIET.

BY

WILLIAM HARVEY,

FELLOW OF THE ROYAL COLLEGE OF SURGEONS, ASSIST.-SURGEON TO THE GREAT NORTHERN HOSPITAL, AND SURGEON TO THE ROYAL DISPENSARY FOR DISEASES OF THE EAR.

LONDON:
HENRY RENSHAW, 356, STRAND.
1872.

The sufferers from this disease are found most frequently among those on whom fortune has smiled, whose incentives to physical exertion are in abeyance, while the inducements of the table are in excess. Nevertheless, among the out-patients of hospitals we occasionally notice cases in which Corpulence has been the cause of a variety of subjective symptoms which have made life wretched.

1815

Cursory Remarks
ON
CORPULENCE;
OR
OBESITY
CONSIDERED AS A DISEASE:
WITH A
CRITICAL EXAMINATION
OF ANCIENT AND MODERN OPINIONS,
RELATIVE TO ITS
CAUSES AND CURE.

THIRD EDITION,
CONTAINING A REFERENCE TO THE MOST REMARKABLE CASES THAT HAVE OCCURRED IN THIS COUNTRY.

BY
WILLIAM WADD, SURGEON.

London:
PRINTED FOR J. CALLOW, MEDICAL BOOKSELLER, NO. 10, CROWN COURT, PRINCES STREET, SOHO.
1816.

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Obesity Pharmaceuticals Market Review

Unprecedented Impact Of GLP-1 Obesity Drugs

The advent of semaglutide and tirzepatide has been transformative for the obesity market:

Weight loss affecting consumer industries

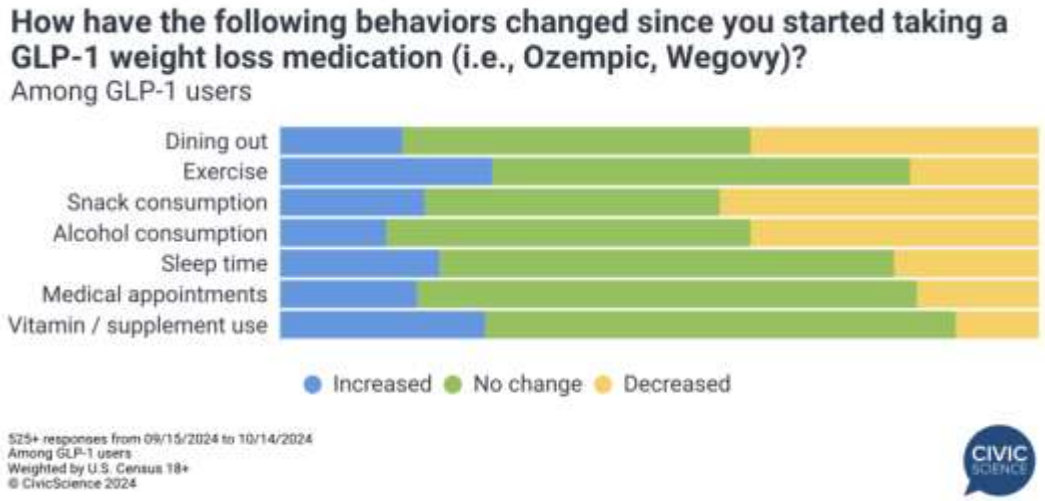
Highest valuations in pharma's history

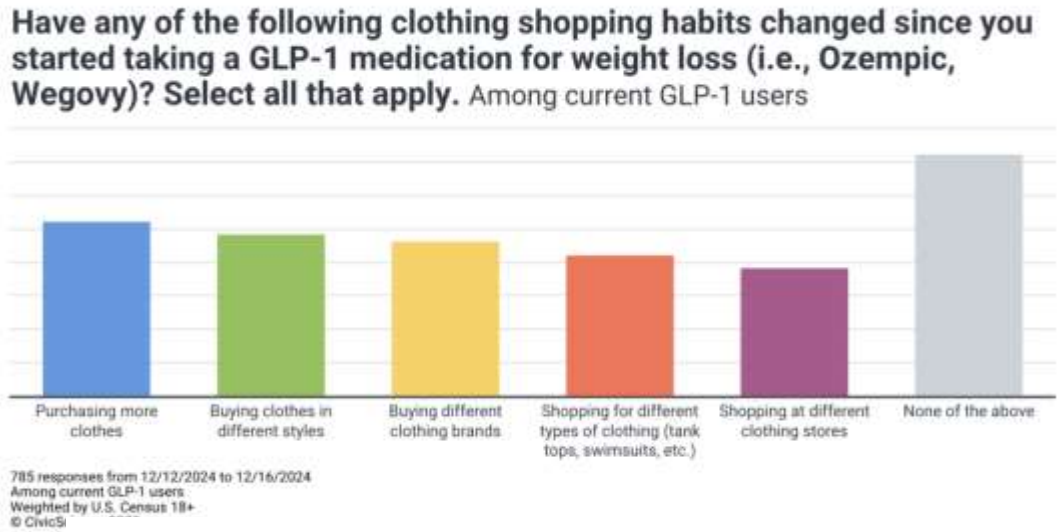
Highest revenue forecasts in pharma's history. $78 billion run rate in Q1 2025 (up from $54bn a quarter before)

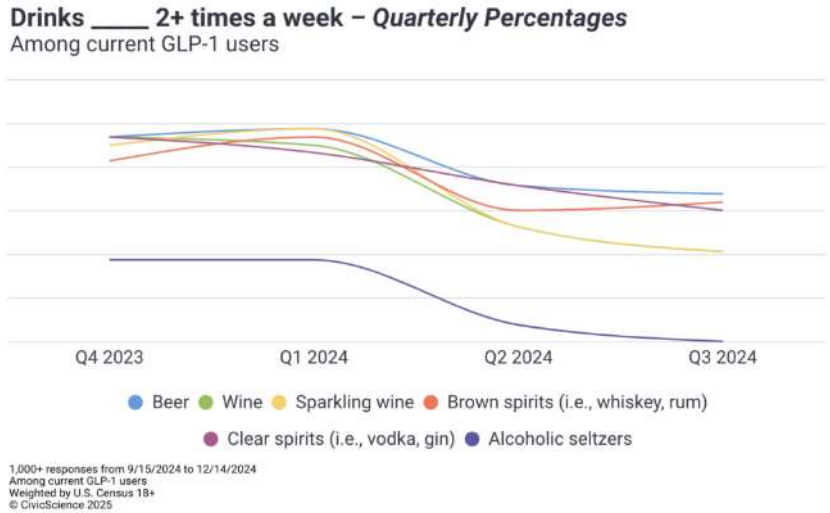
Highest consumer interest in pharmaceuticals

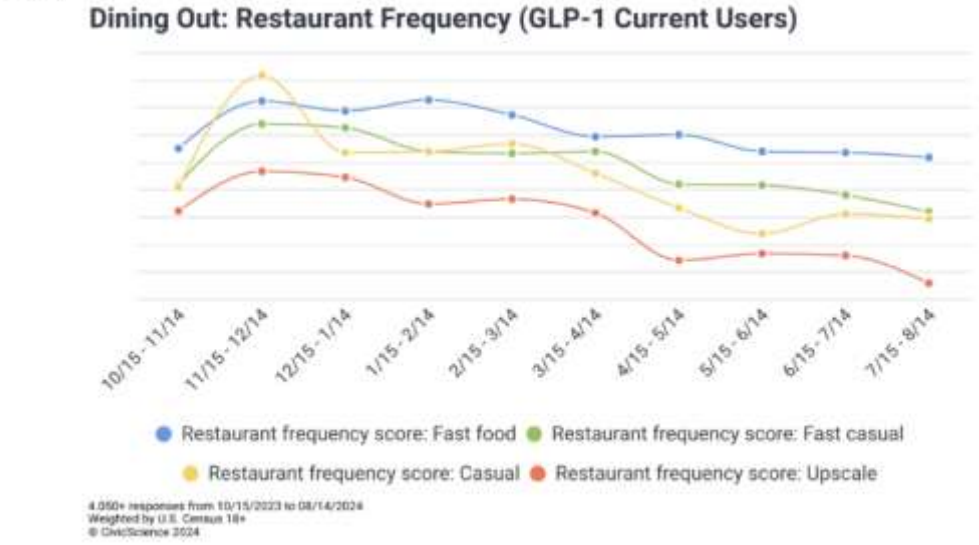
Unparalleled competition emerging

Effect of Weight Loss Drugs on Consumer Behavior









Source: https://info.civicscience.com/glp-1-trends-by-civicscience

Why Is The Market Opportunity So Large?

Chronic Treatment

Obesity Not Going Away

Pays For Payors

Multiple Needs & Market Niche

Powerful Aesthetic Driver

Definition Of Obesity Will Broaden

Key Unmet Needs in Obesity Therapeutics Development

For all the progress that has been made, there is ample room for new entrants to gain footing by addressing unmet needs that remain with existing therapies.

Key unmet market needs include:

Avoidance of Nausea Side Effect

Avoidance of the "Rebound Effect"

Reduction in Drug Cost

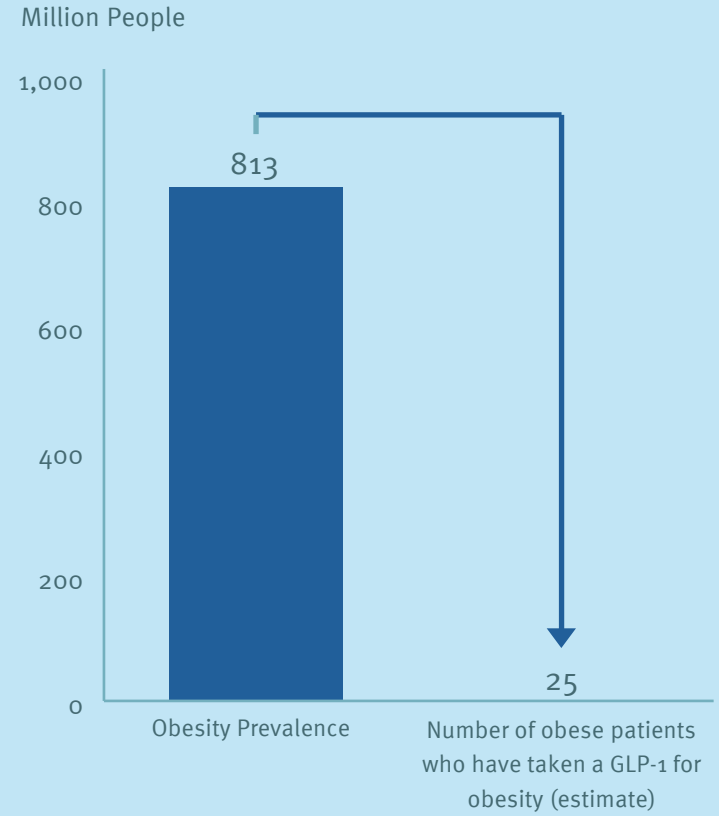
Oral Delivery

Avoidance of Muscle Loss/Enhancement of Muscle

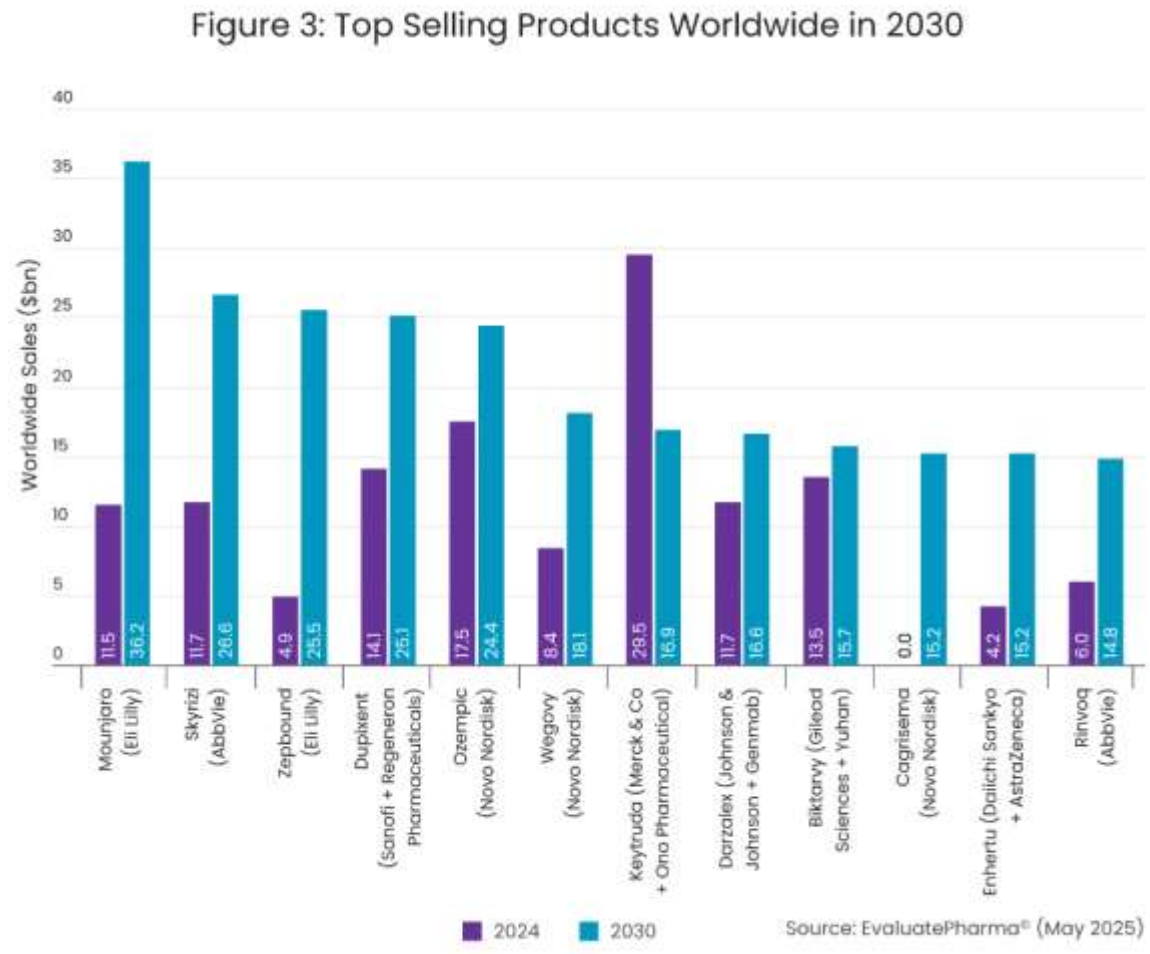
Less Frequent Dosing

Drugs That Can be Safely Provided Direct to the Patient

Few People are Treated for Obesity Today



Evaluate: Analysts Forecast that Tirzeptatide Hits $62 Billion by 2030



Top12 included due to semaglutide and tirzepatide-based brands appearing twice each.

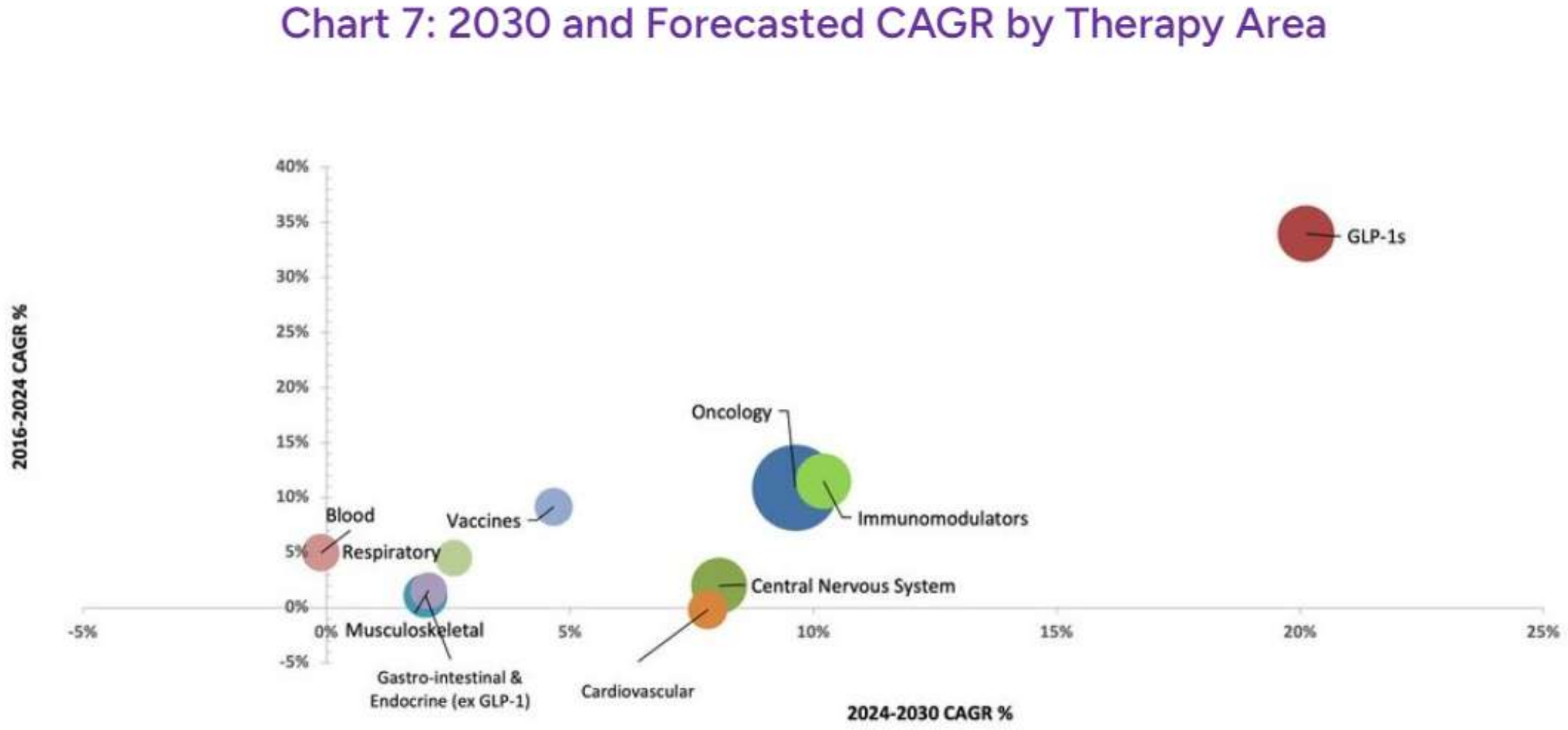
Glucagon-like peptide-1 (GLP-1)- based drugs are now a category apart, projected to reach hitherto unseen sales peaks. Tirzepatide, sold by Eli Lilly & Co. as Mounjaro for diabetes and Zepbound for obesity, will be worth close to $62 billion by 2030. That's three times larger than the peak reached by AbbVie's auto-immune disease blockbuster Humira, and double 2024 sales of Merck & Co Inc.'s cancer behemoth Keytruda, now on the brink of generic competition.

GLP-1 based drugs will make up five of the top ten best-sellers in 2030, and account for four of the top ten most promising pipeline candidates.

Lilly's supremacy in this battle is already apparent. Mounjaro and Zepbound will be the best- and third-best sellers, respectively, by the end of the decade, and Lilly's oral GLP-1 orforglipron and triple-G agonist retatrutide are in the top three most valuable pipeline contenders. First-mover Novo Nordisk lost ground due to its sluggish response to manufacturing shortages of Wegovy (semaglutide), which led to a flood of compounded (pharmacy-mixed) drug. Then a

Source: https://www.evaluate.com/thought-leadership/2025-world-preview/

Evaluate Pharma: GLP-1 Category is the Fastest Growing in the Entire Pharma Sector

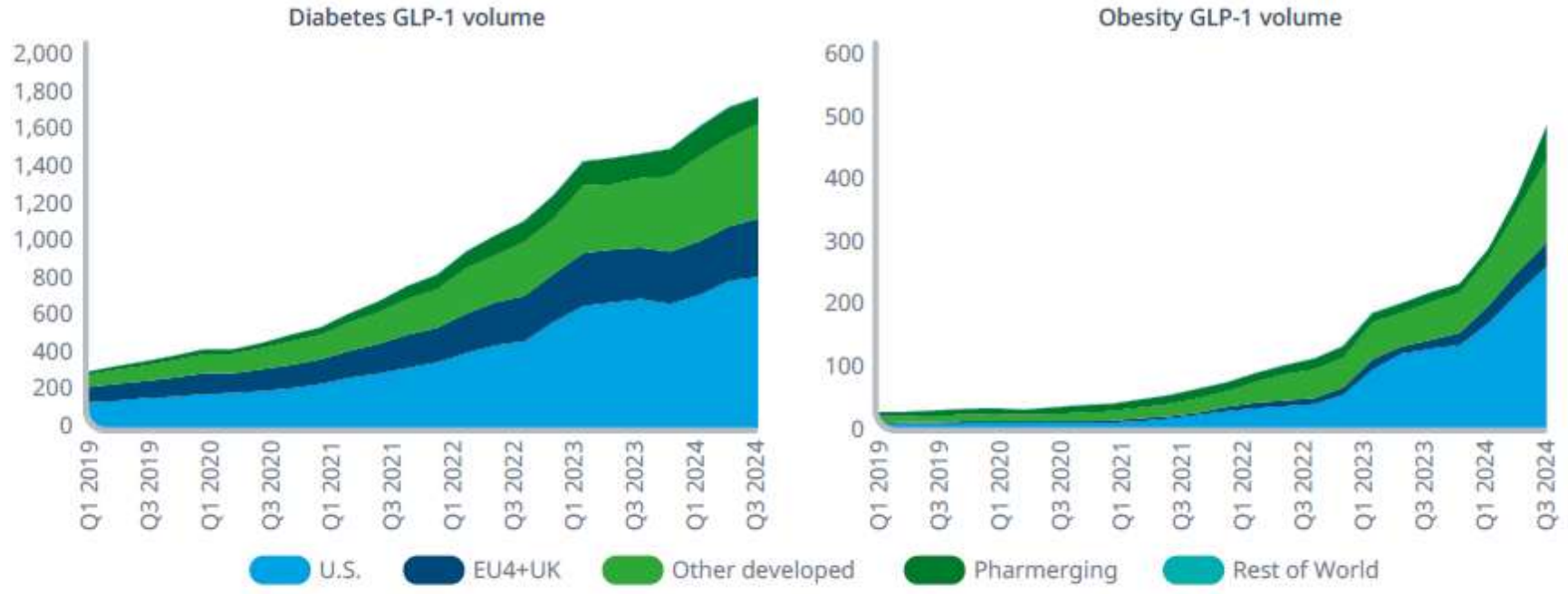


Source: https://www.evaluate.com/thought-leadership/2025-world-preview/

IQVIA Institute (June '25): GLP-1 Uptake for Obesity Exploding

GLP-1 agonists have seen rapid uptake in both diabetes and obesity, predominantly in the U.S. and other developed markets

Exhibit 14: Quarterly GLP-1 agonist volume, defined daily doses (DDD) in millions, Q1 2019–Q4 2024



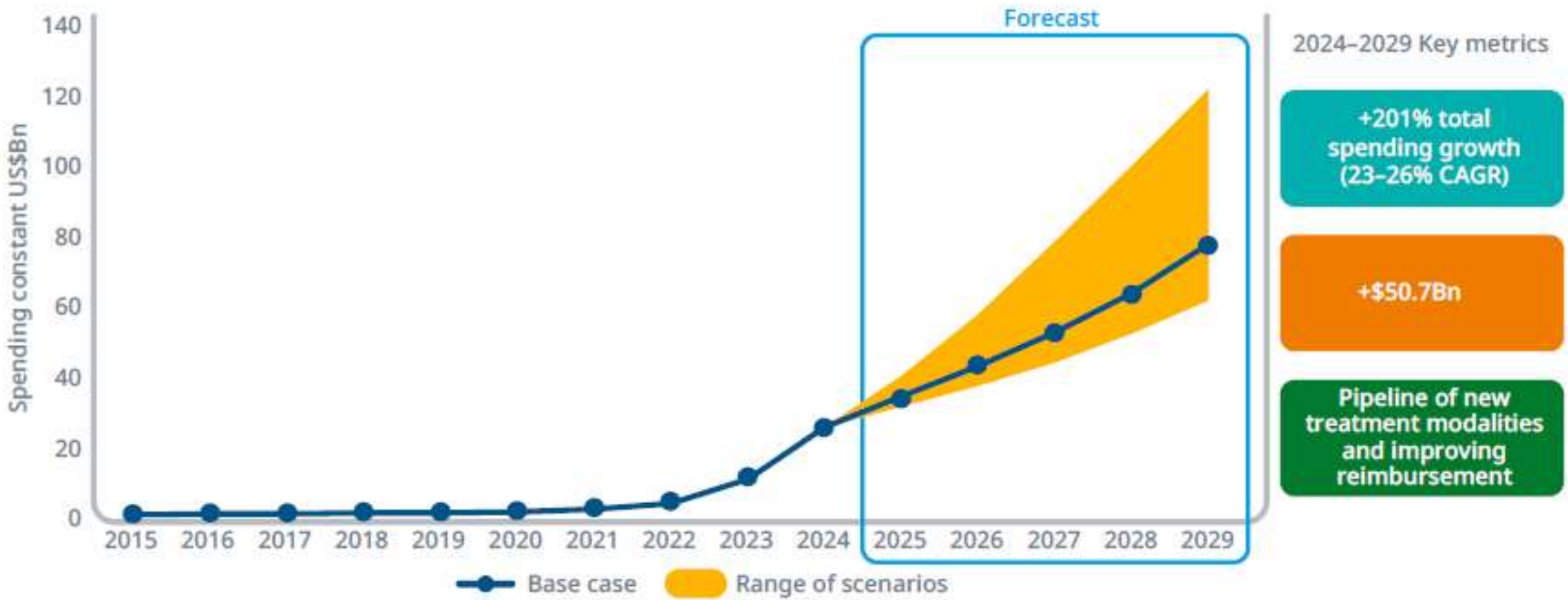
Source: IQVIA MIDAS, Dec 2024; IQVIA Institute, Jun 2025.

"The dramatic growth of therapies based on glucagon-like peptide-1 (GLP-1) has accelerated in the past 18 months, primarily through wider usage for treating obesity. The inflections in volume observed coincide with the obesity indication approval in the U.S. in 2021 for semaglutide (Wegovy) and 2023 for tirzepatide (Zepbound). While the U.S. has been the largest area of growth to date, manufacturing constraints experienced in 2023 and resolved in 2024 resulted in less volume available to countries outside the U.S. and especially for the obesity formulations."

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-outlook-through-2029

Global obesity spending has accelerated in the past 2 years from novel drugs with upside if more widely reimbursed

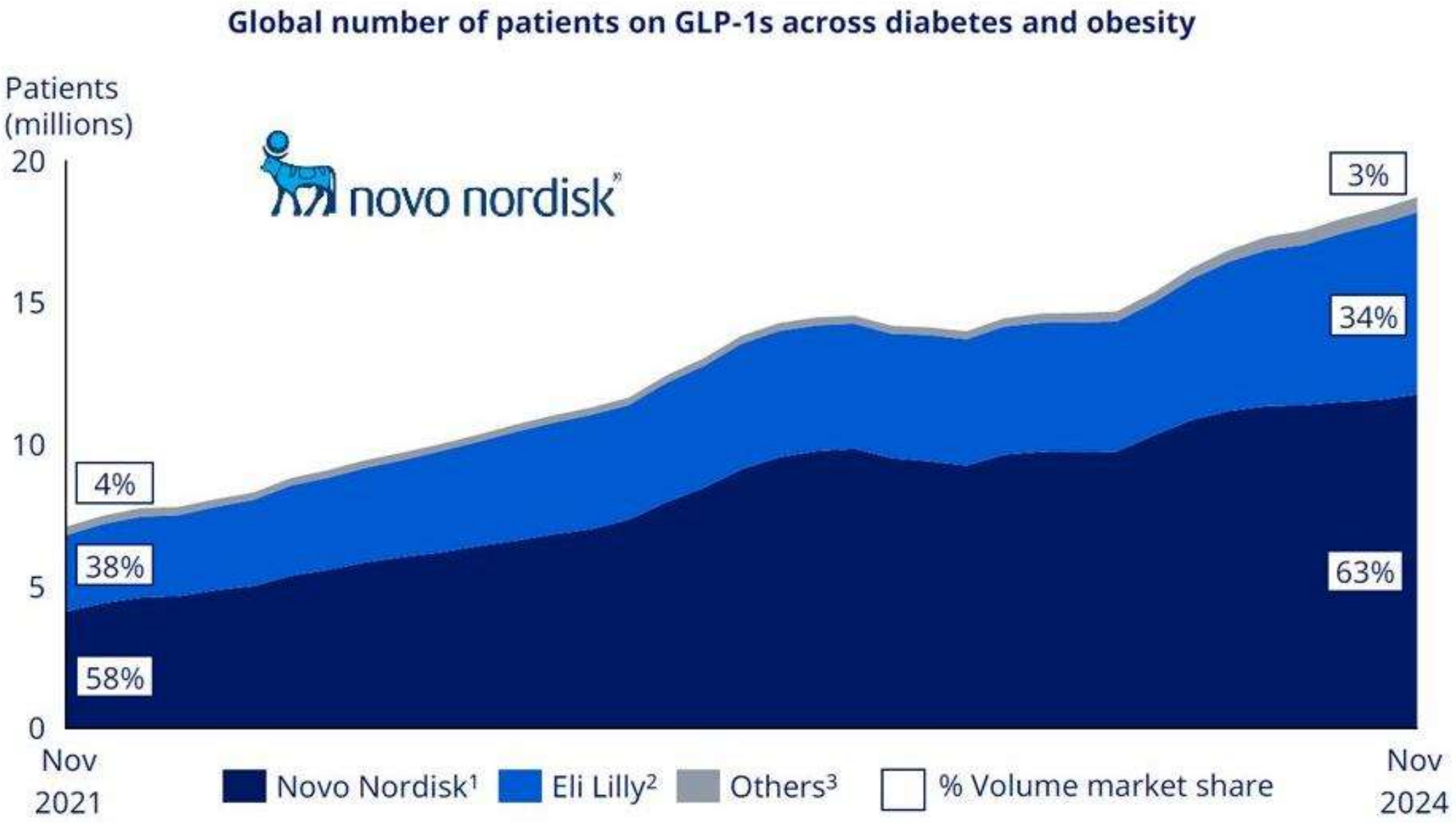
Exhibit 49: Global obesity spending and growth



Source: IQVIA Forecast Link, IQVIA Institute, May 2025.

Source: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-outlook-through-2029

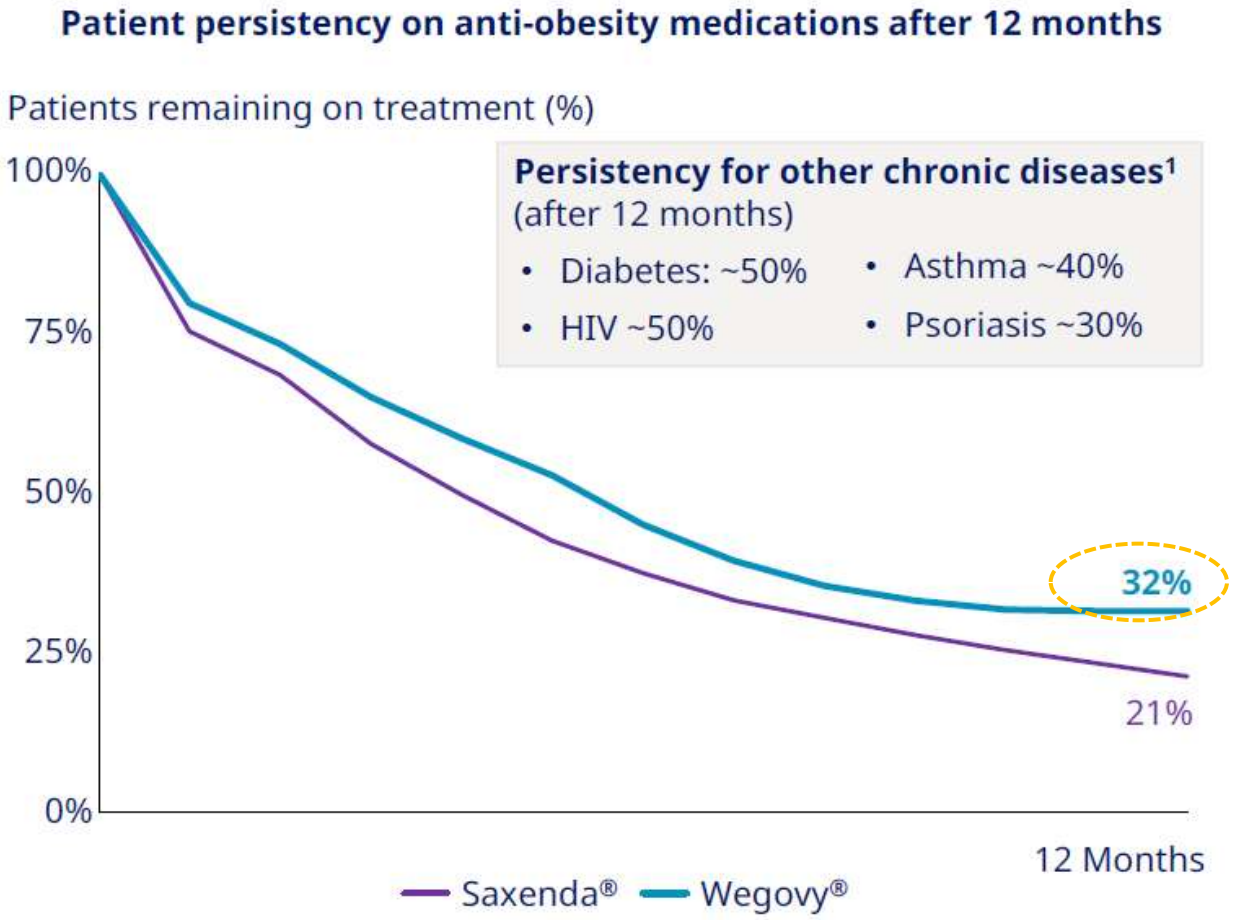
Key Aspects of the Market: 15mm+ Users of GLP-1's

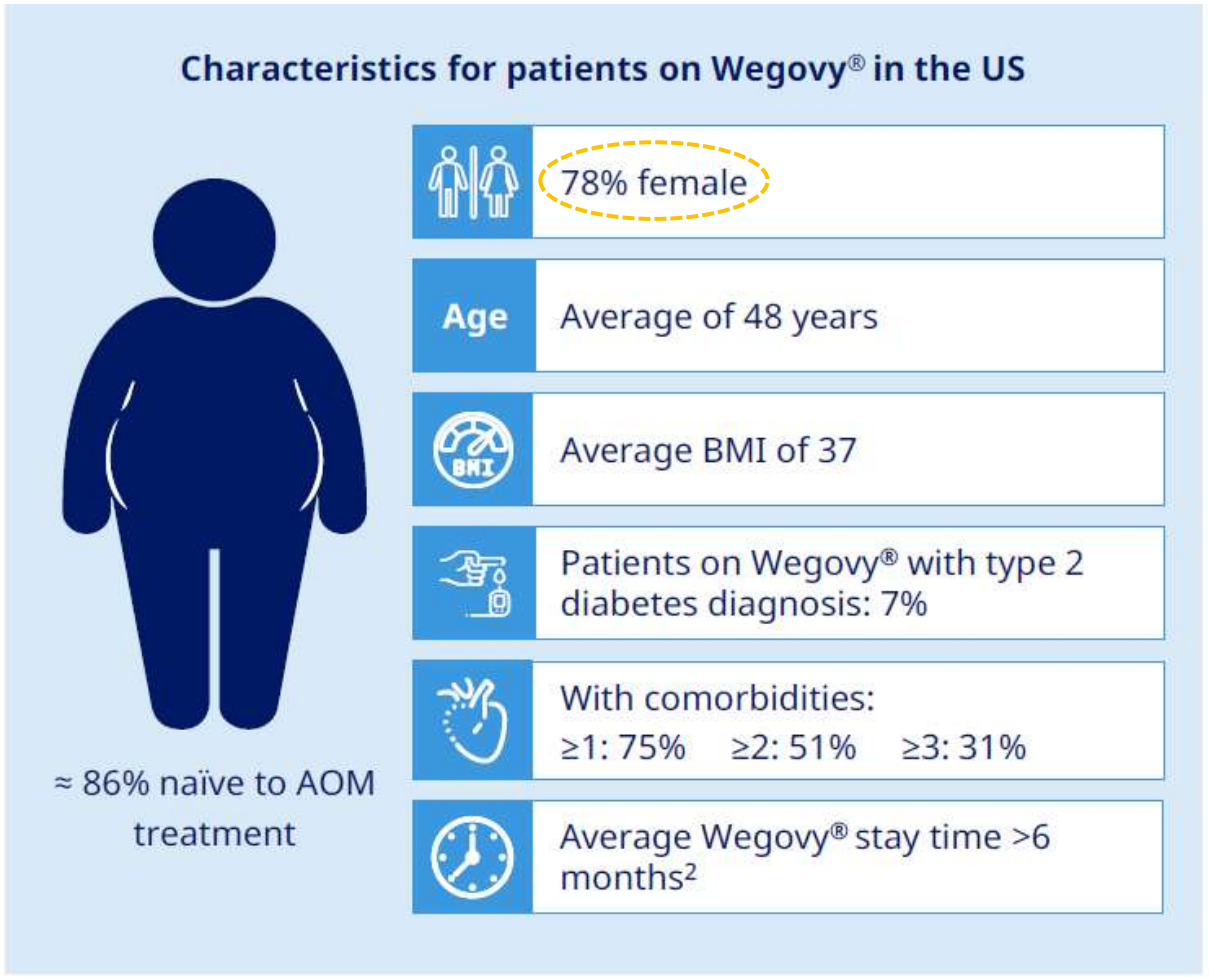


Source: Novo Nordisk Investor Presentation, Jan 2025

Key Aspects of the GLP1 Market: Low Persistence and Female Predominant Patient Base

Novo Nordisk, Q1 Investor Presentation, 2025





[1]Hichborn, et al. (2018). Improving patient adherence through data-driven insights. McKinsey & Company; [2] Average Wegovy® stay time >6 months despite supply constraints based on real world data, patient cohort included those initiating therapy between Oct '21 and Mar '22, followed for 1 year;
AOM: Anti-obesity medications; BMI: Body mass index; HbA1c: Haemoglobin A1c; HIV: Human Immunodeficiency Virus; US: United States
Source: IQVIA LAAD, AOM Rx, 12 months ending November 2024; Real world evidence based on prescription data

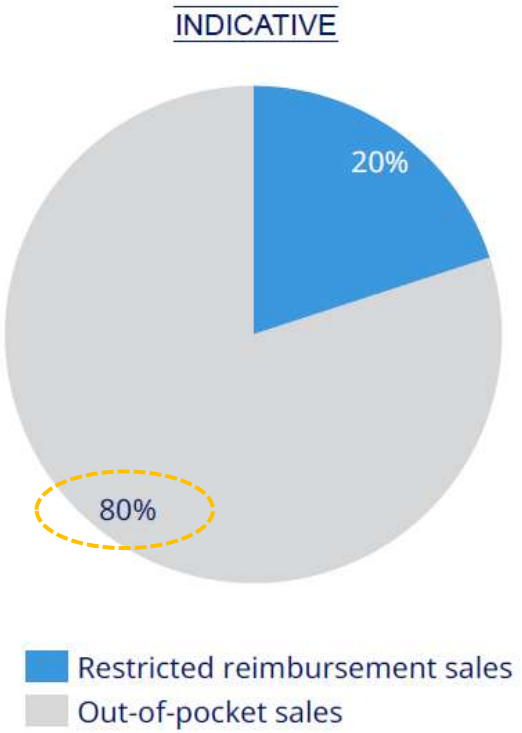
Source: https://investor.novonordisk.com/q1presentation2025/

Key Aspects of the Market: Heavy Out of Pocket Spend

Novo Nordisk, Q1 Investor Presentation, 2025

Anti-obesity medications are expected to be mostly out-of-pocket, with SELECT as key lever to improve reimbursement

Majority of IO AOM sales are currently OOP



Current AOM reimbursement examples

wegovy® semaglutide injection 2.4 mg

UK	**BMI ≥35** or BMI ≥ 30 with ORC

Saxenda® liraglutide injection

COL	**BMI ≥30** with two ORCs
CH	**BMI ≥28 with ≥1 ORC** or BMI ≥35

15 countries have selected reimbursement for Saxenda®

SELECT could improve access to Wegovy®

Wegovy® reimbursed
Leverage SELECT to expand or improve market access

Wegovy® not reimbursed
Use SELECT to open or re-open reimbursement negotiations

Out-of-pocket
Increase willingness to pay in out-of-pocket markets

AOM: Anti-obesity medication; BMI: Body mass index; CH: Switzerland; COL: Columbia; IO: International Operations; OOP: Out-of-pocket; ORC: Obesity-related comorbidity; UK: United Kingdom
Note: Break-down of IO AOM sales is an estimate and cover both Saxenda® and Wegovy®

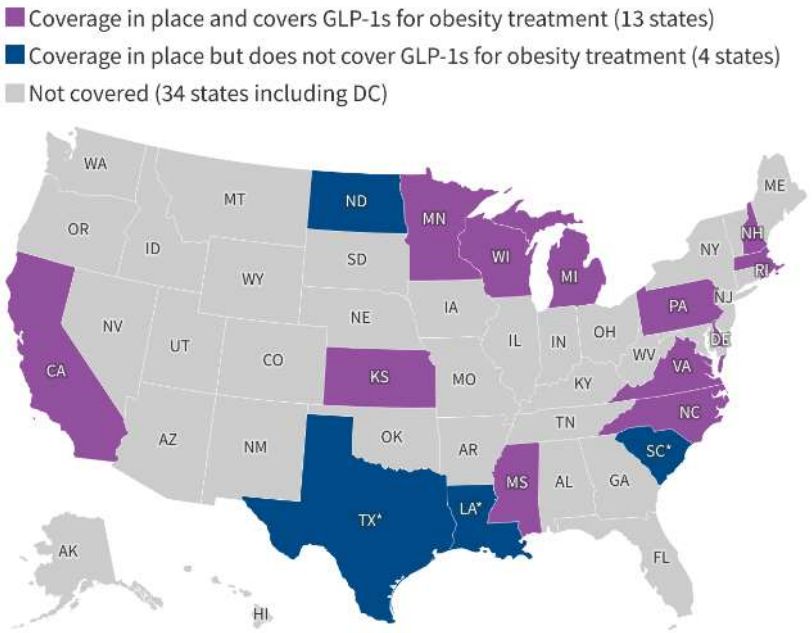
Source: https://investor.novonordisk.com/q1presentation2025/

Key Aspects of the Market: U.S. Medicaid Coverage for GLP-1's Growing but Still Spotty

Elizabeth Williams, Robin Rudowitz, and Clea Bell, KFF Brief, November 4, 2024

Figure 1

Thirteen States Covered GLP-1s for Obesity Treatment as of August 2024



Note: GLP-1 = glucagon-like peptide-1. Coverage is under fee-for-service as of August 2024. FL did not respond to the 2024 survey; publicly available data used to verify status. NC reported adding coverage of obesity drugs in August 2024 and is included here. *These states, either in survey responses or publicly available data, noted coverage was limited to one drug (Orlistat).

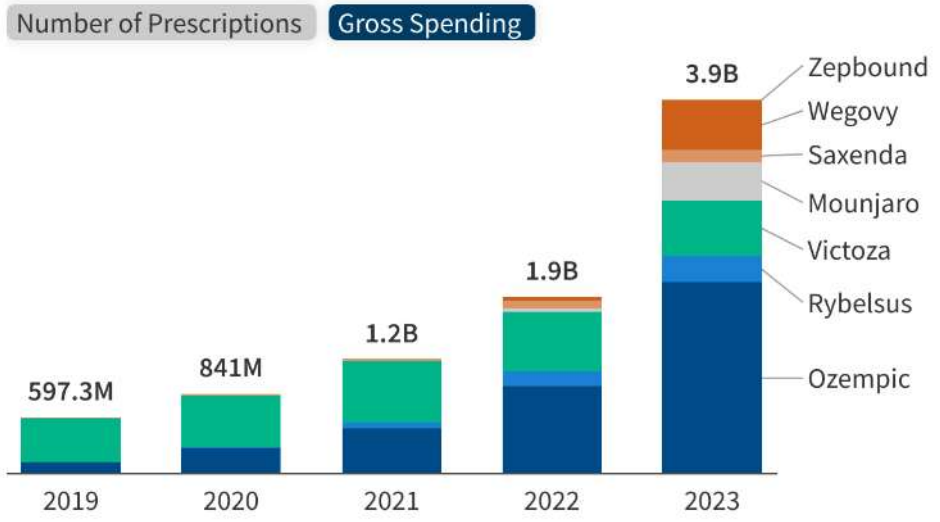
Source: Annual KFF survey of state Medicaid officials conducted by Health Management Associates, October 2024

KFF

Figure 2

Medicaid Prescriptions and Gross Spending on GLP-1s has Increased Rapidly in Recent Years

Gross Medicaid spending on select GLP-1s (glucagon-like peptide-1s)



Note: Gross spending is Medicaid spending before rebates. This includes GLP-1s approved for obesity treatment (Saxenda, Wegovy, and Zepbound) and corresponding formulations approved to treat type 2 diabetes (Ozempic, Rybelsus, Victoza, and Mounjaro). State Medicaid coverage of obesity medications is limited, but drugs to treat type 2 diabetes would be covered by Medicaid in all states (see "Medicaid Coverage of and Spending on GLP-1s" for more information).

Source: KFF analysis of 2019-2023 State Drug Utilization Data, accessed October 2024.

KFF

GLP-1 (glucagon-like peptide-1) drugs have been used as a treatment for type 2 diabetes for over a decade, but newer forms of these drugs have gained widespread attention for their effectiveness as a treatment for obesity. While these drugs have provided new opportunities for obesity treatment, they have also raised questions about access to and affordability of these drugs. These drugs are expensive when purchased out of pocket, and coverage in Medicaid, ACA Marketplace plans, and most large employer firms remains limited, though a number of state Medicaid programs and other payers are re-evaluating their coverage policies. Expanding Medicaid coverage of these drugs could increase access for the almost 40% of adults and 26% of children with obesity in Medicaid. At the same time, expanded coverage could also increase Medicaid drug spending and put pressure on overall state budgets. In the longer term, however, reduced obesity rates among Medicaid enrollees could also result in reduced Medicaid spending on chronic diseases associated with obesity, such as heart disease, type 2 diabetes, and types of cancer.

Source: https://www.kff.org/medicaid/issue-brief/medicaid-coverage-of-and-spending-on-glp-1s/

Key Aspects of the Market: No Medicare Coverage of GLP-1's for Obesity

Melissa MacCalla, Senior Healthcare Solutions, April 9, 2025

If you're enrolled in Medicare and have diabetes or heart disease along with obesity, you may already qualify for coverage of GLP-1 medications. Currently, Medicare does pay for these drugs when they're prescribed to treat specific health conditions. For instance, if your doctor has diagnosed you with type 2 diabetes, Medicare might cover Ozempic, which contains the active ingredient semaglutide.

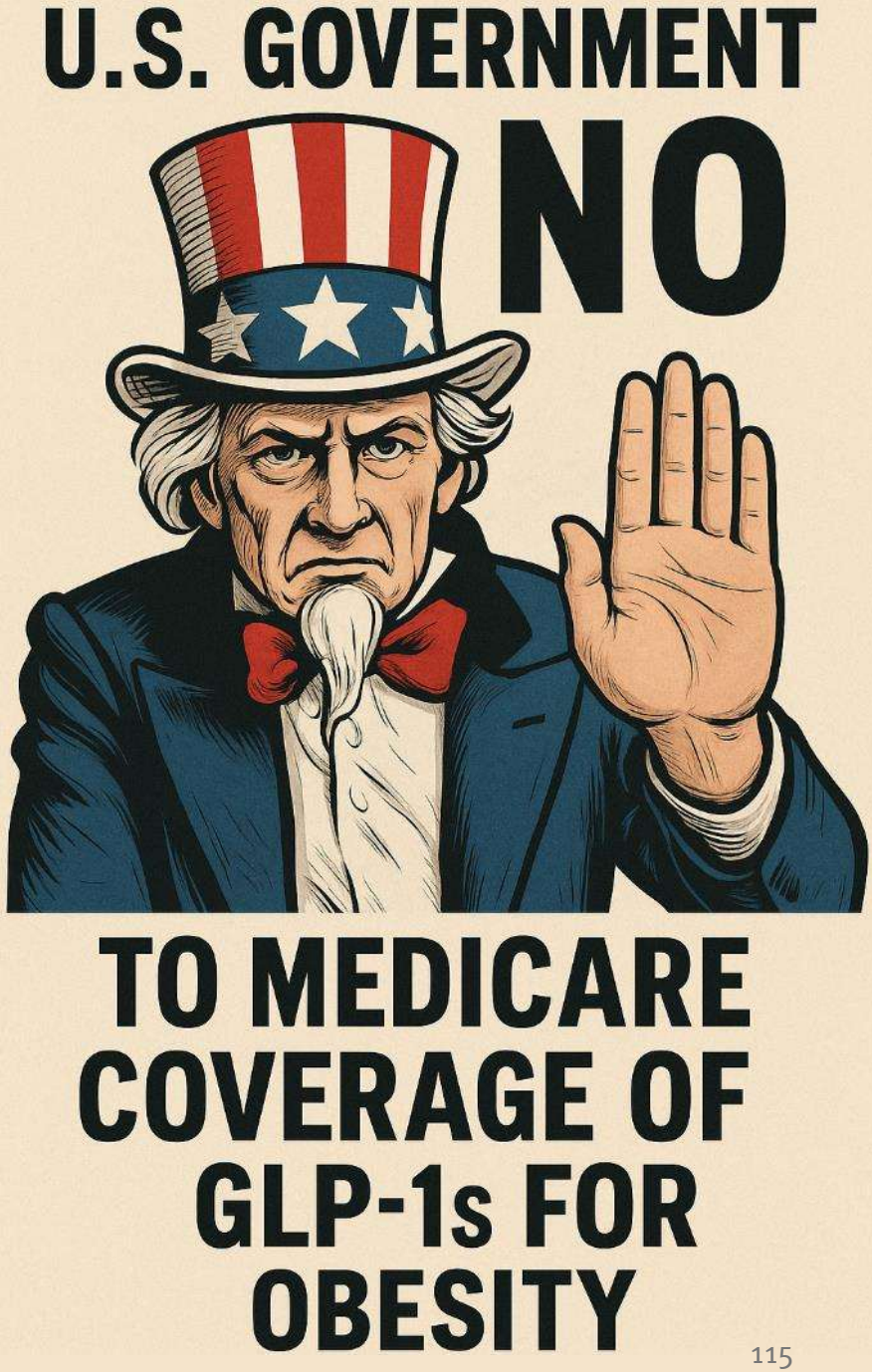
You should know that the coverage rules draw a clear line between using these medications for treating diseases versus using them purely for weight management. If you're hoping to get a prescription just to lose weight without having a qualifying condition like diabetes or heart disease, Medicare won't currently cover the cost. This distinction matters because these medications aren't cheap and can run up to $1,000 per month when paid for out-of-pocket.

Before leaving office, the Biden administration had put forward a plan that would have significantly changed how you access these weight loss medications. Their proposal aimed to expand Medicare Part D prescription drug coverage to include GLP-1 drugs specifically when prescribed for weight loss. This would have meant that even if you don't have diabetes or heart disease, you could have received these medications at your regular prescription drug copay rate rather than paying the full price out-of-pocket.

The Trump administration has now reversed this proposed expansion, deciding that Medicare and Medicaid won't cover GLP-1 drugs when they're prescribed solely for weight loss. If you were hoping to access medications like Wegovy or Zepbound through your Medicare coverage without having diabetes or heart disease, you'll need to adjust your expectations. The decision means the current, more limited coverage policy will remain in place.

Health Secretary Robert F. Kennedy Jr. has been particularly vocal in his opposition to these medications. Rather than expanding drug coverage, he's proposed alternative approaches to weight management for seniors. He's advocating for Medicare to cover organic food and gym memberships as a healthier and more cost-effective solution. According to Kennedy, these preventative measures would benefit beneficiaries while also saving the government money compared to the estimated $35 billion price tag of expanding drug coverage.

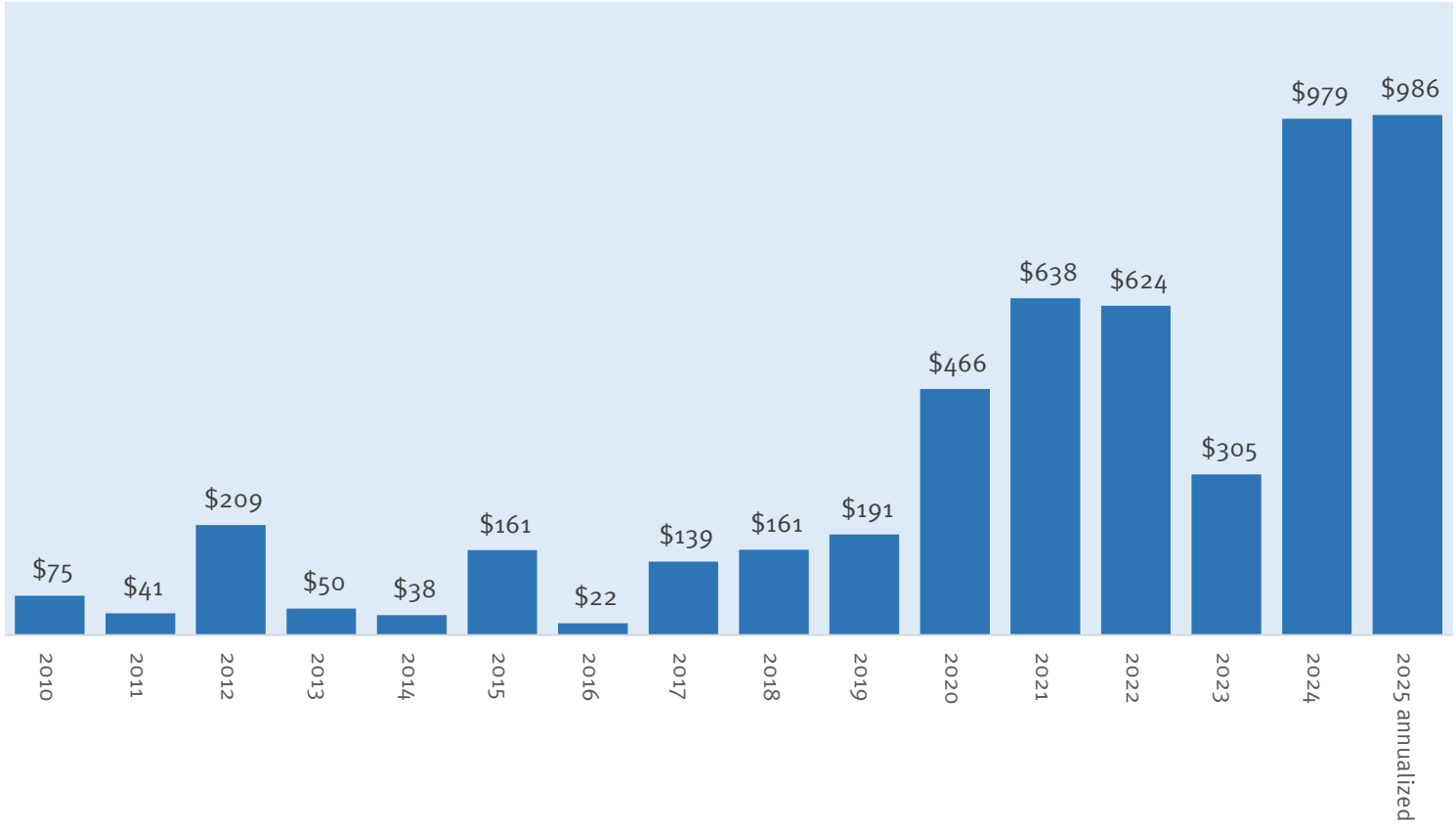
Source: https://seniorhealthcaresolutions.com/blog/trump-blocks-glp-1-weight-loss-medicare-coverage/



Private Market: Venture Dollars Pour Into the Obesity Field

A key metric of interest is the volume of venture dollars flowing into companies in a given therapeutic area. The chart above shows that investment is up tenfold between 2025 and 2019 and that investments over the last years are up quite substantially from prior years.

Venture Dollars Invested in Obesity Private Biotech Companies Jan 20210 to Jun 2025

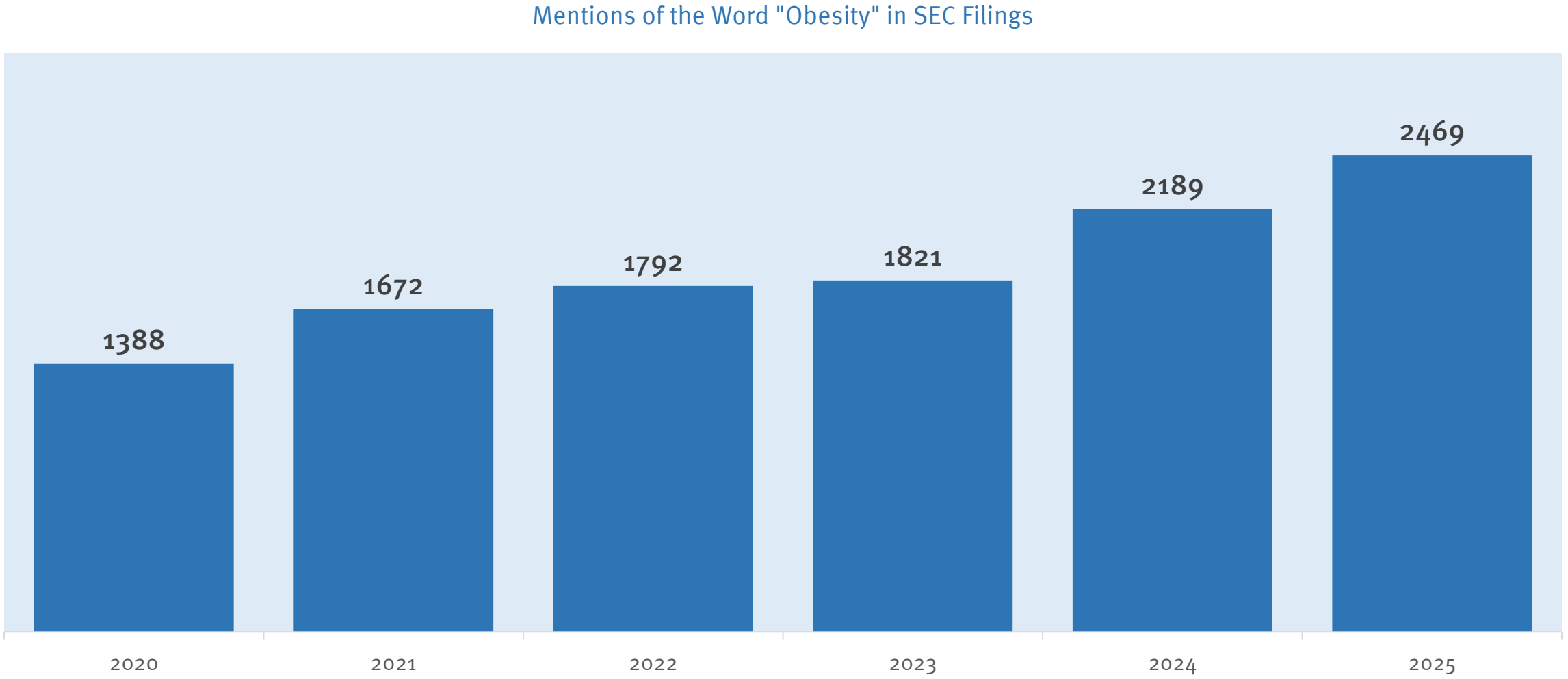


Top Venture Rounds in Obesity, 2022 to 2025

Verdiva Bio	$410mm Jan 2025
kailera	$400mm Oct 2024
Metsera	$290mm Apr 2024
KALLYOPE	$236mm Feb 2022
CARMOT THERAPEUTICS	$160mm Feb 2022
CARMOT THERAPEUTICS	$150mm May 2023

Source: DealForma. Investments through June 30, 2025 annualized to derive 2024 estimate.

Public Market: The Word “Obesity” Has Become Quite Popular in SEC Filings



Source: https://www.sec.gov/edgar/search/

Robust Strategic Deal Activity in Obesity

Pharma interest in accessing obesity drugs remains high with activity from AbbVie, Merck, Novo Nordisk and Roche in the last year and a half. Ongoing conversations lead us to expect that this level of activity will continue in the year ahead.

Date	Transaction Type	Licensee	Licensor	Lead Product/ Platform of Interest				Geography	Consideration (in $mm)			Royalties
				Asset	MoA/ Target	RoA	Phase		Upfront	Contingent	Total	
3/12/2025	Licensing	Roche	ZEALAND PHARMA	Petrelintide	Amylin	Injectable	Phase 2	U.S. and EU	$1,650	$3,250	$4,900 (1)	Co/Co; Tiered DD High-Teens
3/3/2025	Licensing	abbvie	gubra	GUB014295	Amylin	Injectable	Phase 1	W.W.	$350	$1,875	$2,225	Tiered
3/24/2025	Licensing	novo nordisk	联邦制药	UBT251	GLP-1/ GIP/ Glucagon	Injectable	Phase 2 (China)	W.W. (ex. China)	$200	$1,800	$2,000	Tiered
12/18/2024	Asset Acq.	MERCK	HANSOH PHARM	HS-10535	GLP-1	Oral	Preclinical	W.W.	$112	$1,900	$2,012	Tiered; HSD to LDD
11/4/2024	Licensing	novo nordisk	ascendis pharma	TransCon Platform	GLP-1	Injectable	Preclinical	W.W.	$100	$185	$285	Tiered; MSD
5/17/2024	Licensing	kailera	HENGRUI	KAI-9531	GLP-1/ GIP	Injectable	Phase 2	W.W. (ex. China)	$100	$5,935	$6,035	LSD to LDD
3/28/2025	Licensing	novo nordisk	Lexicon pharmaceuticals	LX9851	ACSL5	Oral	Preclinical	W.W.	$75	$925	$1,000	Tiered
1/10/2025	Licensing	Verdiva Bio	SCIWIND	XW004	GLP-1	Oral	Phase 2 Ready	W.W. (ex. China & SK)	$70	$2,400	$2,470	Tiered
11/12/2024	Licensing	APOLLO	Sunshine Lake	APL-18881	FGF21/ GLP-1	Injectable	Phase 2 (China)	W.W. (ex. China)	$12	$926	$938	Tiered; HSD to LDD
1/23/2024	Licensing	novo nordisk	eracal	Era-379	Appetite Suppressor	Oral	Preclinical	Undisclosed	nd	nd	$255	nd

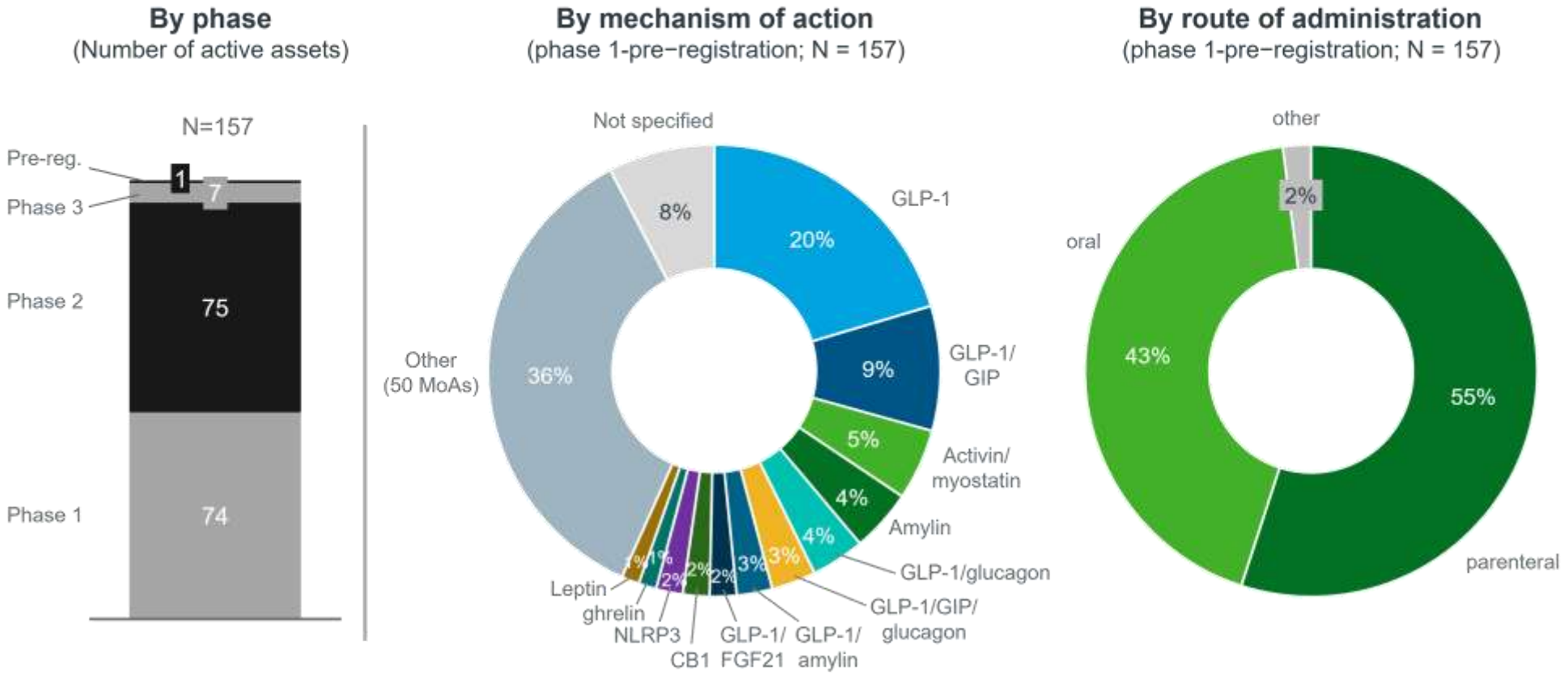
Sources: Company filings and press releases. Note: Only includes collaborations since 2024 focusing on a product or program for obesity with geographic scope of W.W., or at least the U.S. Excludes collaborations between large-cap pharmaceutical companies. Excludes amendments or exercise of options based on prior collaboration, unless otherwise noted. "na" means not available. "nd" means not disclosed. LSD = Low-single digits, MSD = Mid-single digits, HSD = High-single digits, DD = Double-digits, LDD = Low-double digits. Transactions sorted on total upfront (high to low).

(1) Upfront includes two anniversary payments equaling a total of $250mm. Contingent includes a $350mm payment paid by Zealand to Roche, offsetable against the development milestone payments.

IQVIA: 157 Drugs in Pipeline

IQVIA counted 124 drugs in the pipeline in January 2024. The pipe is growing fast. Our own estimate of the pipeline size is far higher.

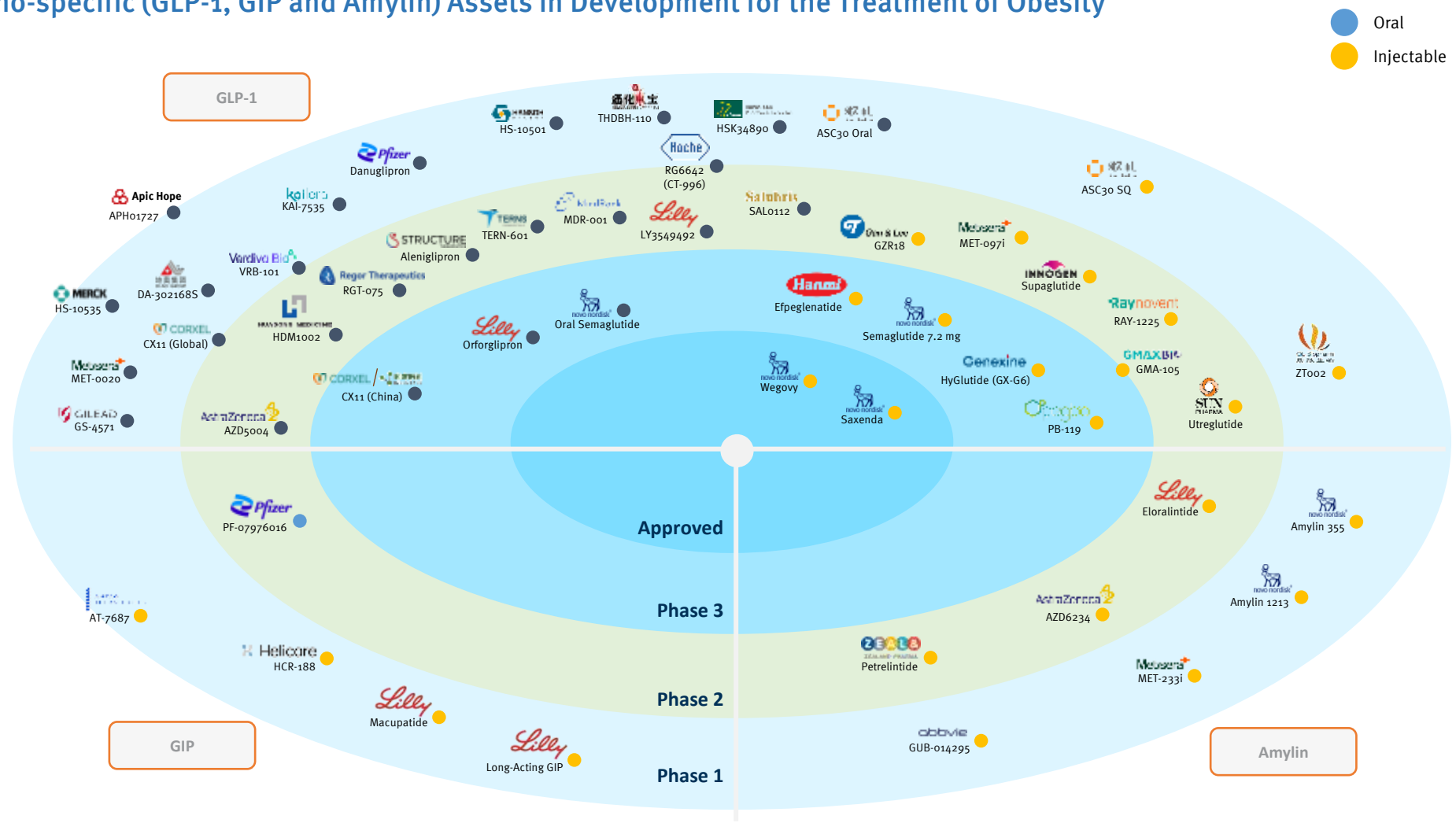
Figure 2
Pipeline of obesity assets



Source: IQVIA Analytics Link; Clinicaltrials.gov; company reports, press releases, desk research; IQVIA EMEA Thought Leadership analysis; December 2024

Obesity Market Landscape

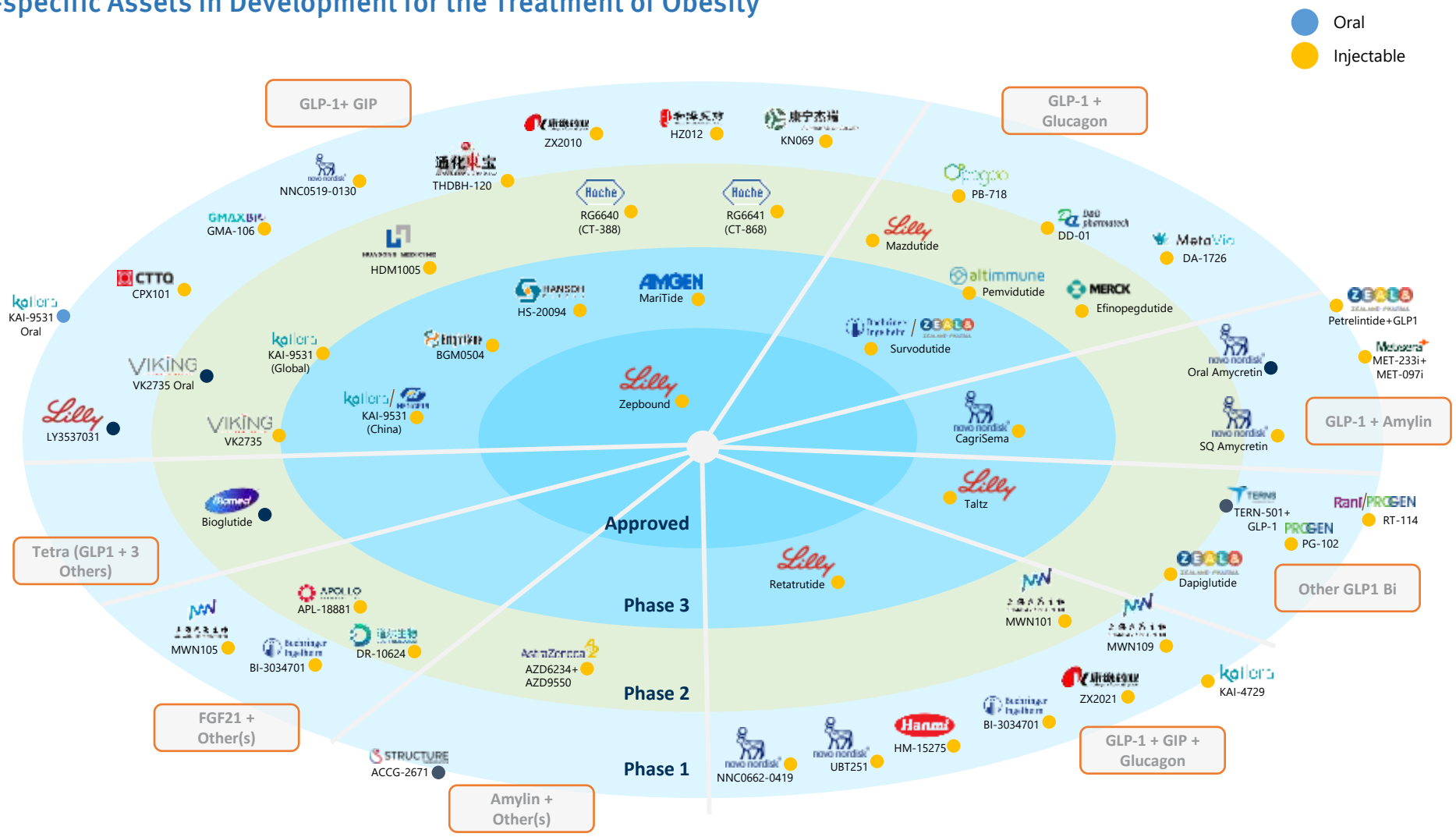
Selected Mono-specific (GLP-1, GIP and Amylin) Assets in Development for the Treatment of Obesity



Sources: Company websites, press releases, presentations, filings, Wall Street Research and BioMedTracker.

Obesity Market Landscape

Selected Multi-specific Assets in Development for the Treatment of Obesity

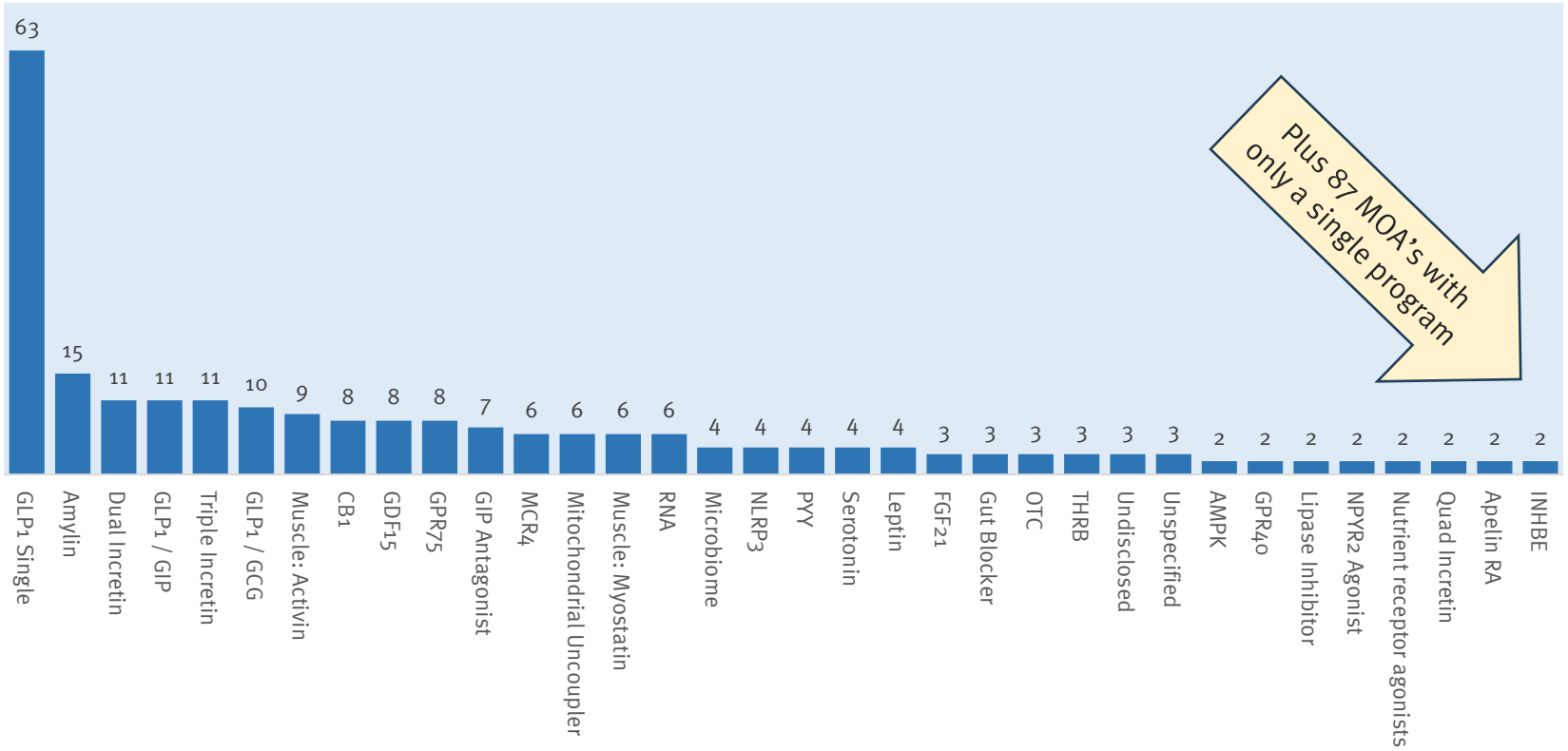


Sources: Company websites, press releases, presentations, filings, Wall Street Research and BioMedTracker.

MOA Crowding as of July 2025

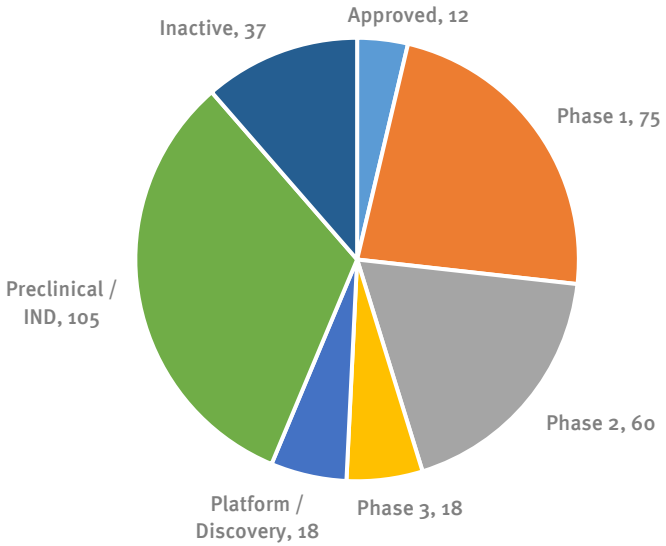
The GLP-1 agonist space is very crowded. Other MOA's with more than three or more programs in development include amylin, dual incretins, GLP/GIPs, GLP/GCGs, Activins, CB1 and GDF15. Compared to other fields like immuno-oncology and immunology, the obesity drug development area is relatively uncrowded – except in the GLP-1 space and, increasingly, in the dual and amylin fields.

Number of Obesity Programs by MOA (Pipeline or Approved, July 2025, 2 or more programs only included)



Status of Obesity Drug Pipeline,

(count of drugs by stage of development, July '25)



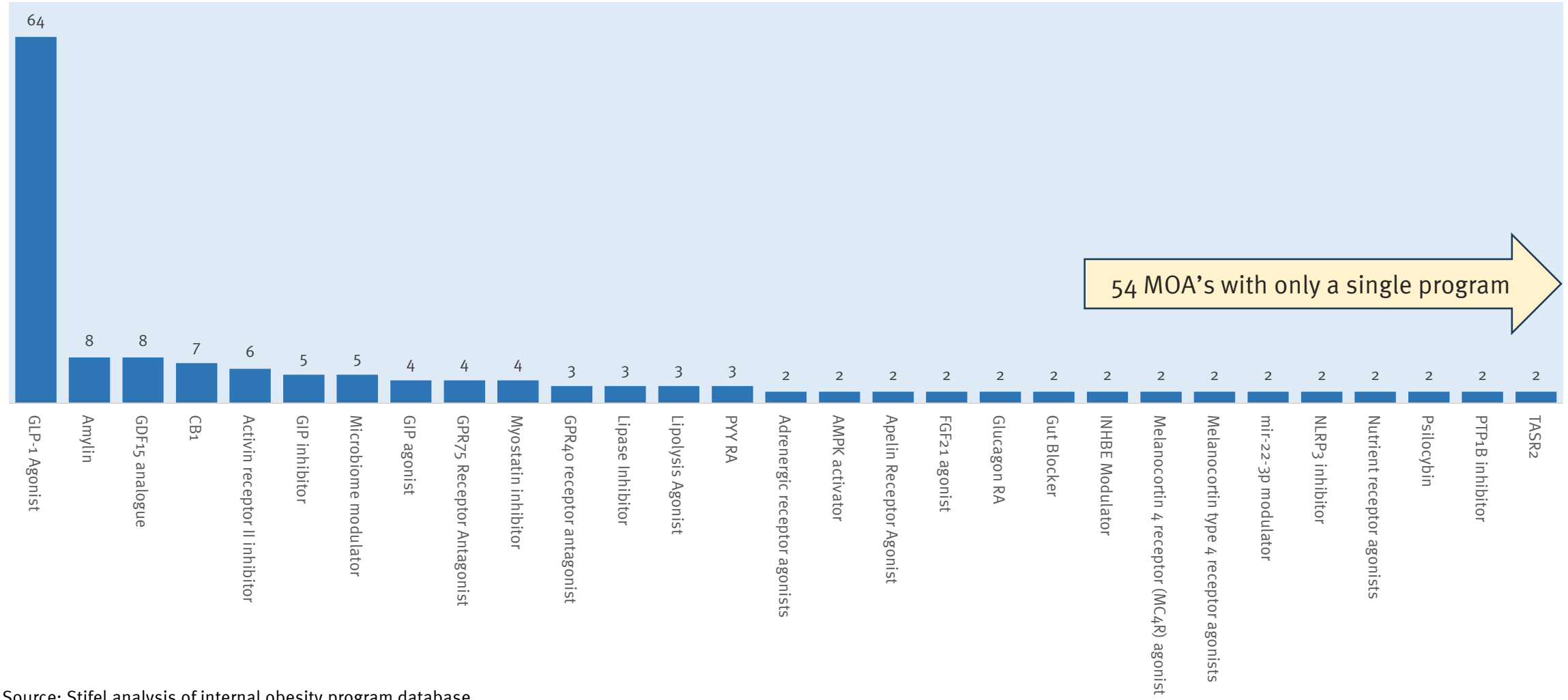
We count 277 programs for obesity in development as of early July 2025. There are an additional eleven approved drugs and 37 programs that are no longer in development. There are undoubtedly dozens of other programs in "stealth mode". A year ago, we counted 202 programs in development. The pipeline has grown by 37% in a year.

Source: Stifel analysis of internal obesity program database.

Comparison: MOA Counts in June 2024

We saw big growth in the amylin and muscle fields year on year.

Number of Obesity Programs by MOA (Pipeline or Approved, June 2024, 2 or more programs only included)



Source: Stifel analysis of internal obesity program database.

Public Company Obesity Data Catalyst Calendar: 2025

Company	Program	Modality	Trial / Milestone	Timing
Eli Lilly	Orforglipron	Oral non-peptide GLP-1	Phase 3 results (ATTAIN-1/2) in obese patients	Q3 2025
Metsera	MET-097I	Monthly GLP-1a	Phase 2b obesity data (VESPER-1)	Q3 2025
Aardvark Therapeutics	ARD-101	Gut-restricted TAS2R agonist	Phase 2 obesity data	Q4 2025
Altimmune	Pemvidutide	GLP-1/glucagon dual agonist	Phase 2 MOMENTUM-2 obesity data	Q4 2025
Arrowhead Pharma	ARO-INHBE	INHBE Inhibitor	Phase 1/2a data (Part 1)	Q4 2025
Ascletis	ASC30	Oral GLP-1	Phase 2a obesity data	Q4 2025
AstraZeneca	AZD6234	LA amylin	Phase 2 data (APRICUS study)	H2 2025
BioAge Labs	BGE-102	NLRP3	Phase 1 data	Q4 2025
Corbus	CRB-913	Oral CB1 antagonist	Phase 1b MAD CB1 Readout	Nov 2025
Eli Lilly	Orforglipron	Oral non-peptide GLP-1	Phase 3 obesity results (ACHIEVE-2) vs SGLT2 in T2DM	H2 2025
Eli Lilly	Orforglipron	Oral non-peptide GLP-1	Phase 3 obesity results (ACHIEVE-5) in T2DM	H2 2025
Eli Lilly	Tirzepatide	Triple GLP-1/GIP/glucagon	Post-marketing study in CV outcomes (SURPASS-CVOT)	H2 2025
Hengrui (Kailera)	HRS9531	Dual GLP-1/GIP agonist	Phase 3 data (540 subject China study – 6mg peak dose)	H2 2025
Huadong Medicine	HDM1005	Dual GLP-1/GIP agonist	Phase 2 obesity data	H2 2025
MetaVia Pharma	DA-1726	GLP-1/GCG	Phase 1 data	H2 2025
Metsera	MET-233i	Monthly Amylin Agonist	Phase 1b obesity data (12 weeks)	Q4 2025
Metsera	MET-0970/MET-2240	Oral GLP-1	Phase 1 obesity data	Q4 2025
Novo Nordisk	NN-9662	Triple incretin drug	Phase 1 data	H2 2025
Pfizer	PF-07976016	GIP Inhibitor	Phase 2 obesity data	Q4 2025
Skye Biopharma	Nimacimab	CB1 antibody	Phase 2 CB1 Readout	Q4 2025
Structure Therapeutics	Aleniglipron	Oral small molecule GLP-1	Phase 2 obesity data from two studies	Q4 2025
Terns Pharmaceuticals	TERN-601	Oral GLP-1	Phase 2 data	Q4 2025
Viking Therapeutics	VK2735 (oral)	Dual GLP-1/GIP agonist	Phase 1 data for the oral formulation	Q4 2025
Wave Life Sciences	INHBE-GALNAC	INHBE Inhibitor	Phase 1 data	Q4 2025

Source: Stifel research

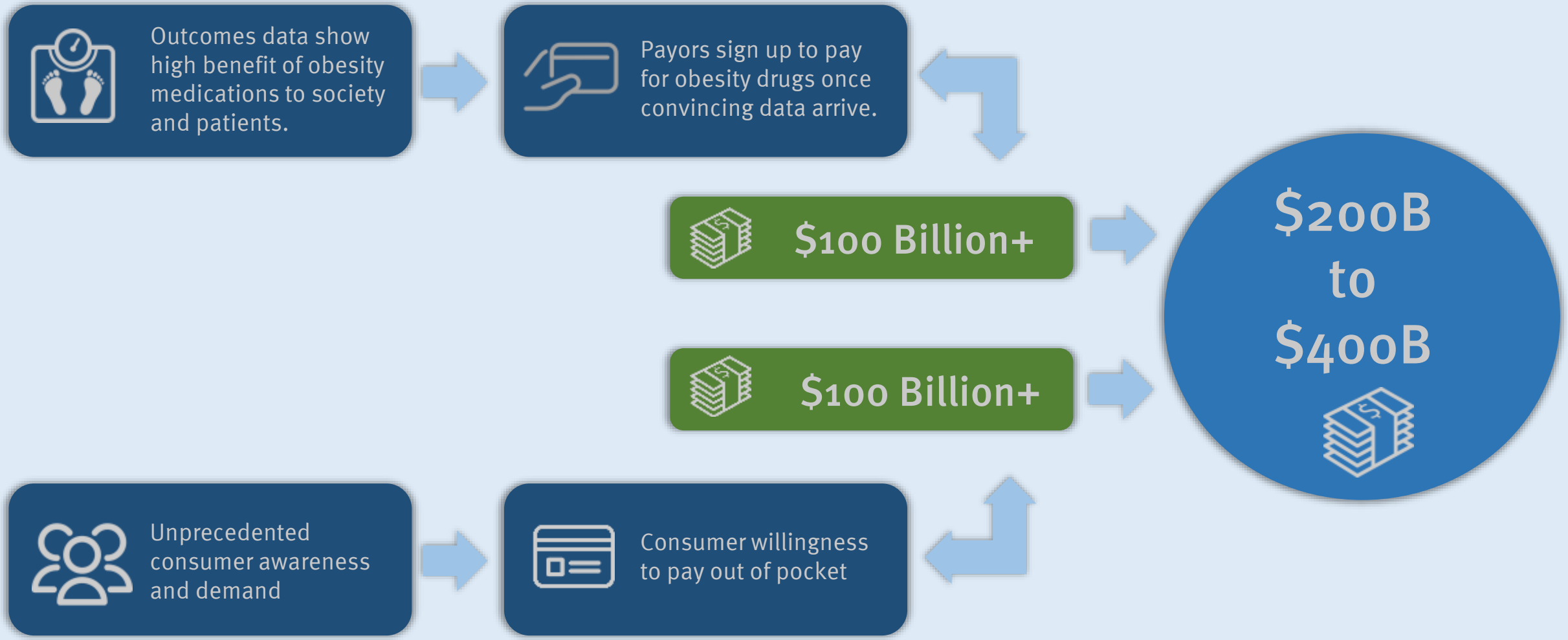
Public Company Obesity Data Catalyst Calendar: 2026

Company	Program	Modality	Trial / Milestone	Timing
AstraZeneca / Eccogene	AZD5004	Oral GLP-1	Phase 2 data (VISTA / SOLSTICE studies)	Q1 2026
Roche	CT-388	Biased GLP-1 + GIP Dual Agonist	Phase 2 data	Q1 2026
Roche	CT-868	Biased GLP-1 + GIP Dual Agonist	Phase 2 data	Q1 2026
Aldeyra	ADX-743	RASP Modulator	Phase 1 obesity data	H1 2026
Eli Lilly	Retatrutide	Triple GLP-1/GIP/glucagon	Phase 3 obesity results	H1 2026
Gan & Lee	Bofanglutide (GZR18)	GLP-1	Phase 2 head-to-head with tirzepatide	H1 2026
Hansoh	HS-10501	Oral small molecule GLP-1	Phase 1 data	H1 2026
Structure Therapeutics	ACCG-2671	Oral small molecule agonist	Phase 1 obesity data	H1 2026
Zealand / Roche	Petrelintide	Amylin Agonist	Phase 2b ZUPREME-1 data	H1 2026
Zealand Pharma	Dapiglutide	Dual GLP-1/GIP peptide	Phase 2 obesity data	H1 2026
Zealand Pharma/BI	Survodutide	GLP-1/GCG	Phase 3 readouts (SYNCHRONIZETM-1/2)	H1 2026
Amgen	MariTide (AMG 133)	GLP-1/GIP antibody-peptide	Phase 3 obesity data	H2 2026
Eli Lilly	Orforglipron	Oral non-peptide GLP-1	Phase 3 obesity results in OSA	Q4 2026
Eli Lilly	Retatrutide	Triple GLP-1/GIP/glucagon	Phase 3 data in OA of the knee (TRIUMPH-4)	Q4 2026

Source: Stifel research

We Think the U.S. Obesity Drug Market Grows to Over $200 Billion

This is the just for the United States. We see at least another $100bn in likely revenue from outside the U.S.



Four Key Trends that Are Shaping the Obesity Drug Market in 2025

We believe that the obesity drug market is and will continue to be shaped by four large trends:

#1

EXPLODING SELF-PAY MARKET

Revenue in the self-pay / DTC part of the obesity drug market is growing at well over 100% a year. The consumer is reshaping (literally) what pharma marketing means. The active consumer interested in weight loss will continue to drive the obesity drug market given that governments largely do not reimburse these drugs.

#2

OBESITY DRUG CRAZE IS GOING GLOBAL

We have been struck by the fact that tirzepatide hit a billion-dollar run rate in its first three months on the India market in 2025. In the same way we were all surprised by how big Ozempic® and Mounjaro® became in the U.S., we are going to be shocked again as sales skyrocket globally as the obesity drug craze goes global in the next 24 months.

#3

LILLY OBESITY PORTFOLIO SET TO DOMINATE MARKET

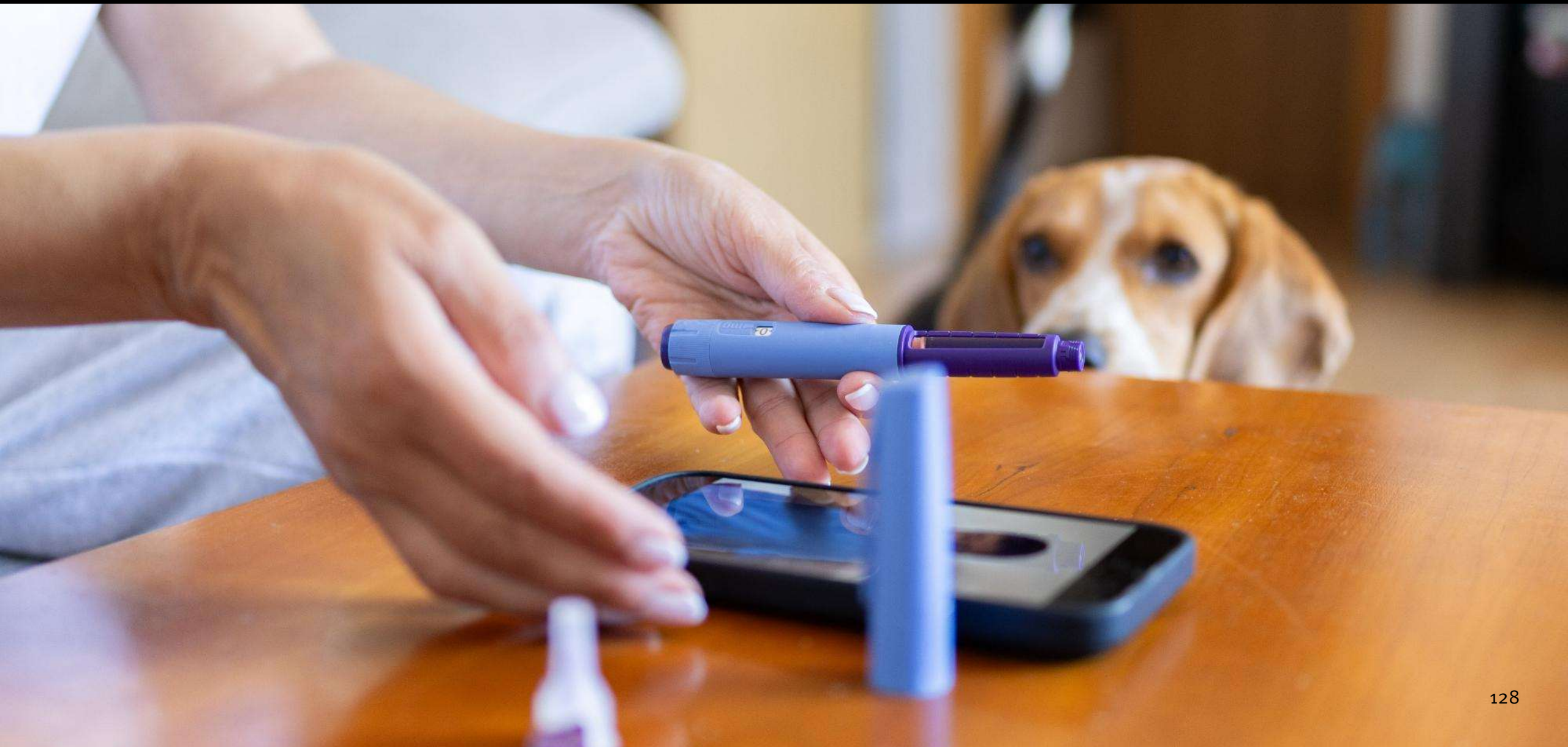
Lilly's strategy in the obesity market has been to place a big bet on every square of the strategic chess board. This strategy is paying off with excellent data for both bima and elora shared at this year's ADA conference. The reality of a dominant Eli Lilly has negative implications for many emerging competitors whose portfolios are incremental.

#4

OPPORTUNITIES REMAIN TO DISRUPT THE MARKET

We are not optimistic about the prospects for many pipeline projects in today's emerging obesity market. This is because (1) Lilly has a dominant portfolio and (2) semaglutide, a very good drug, will be generic in roughly five years. But, the good news is that many opportunities remain to upend the market with new approaches.

Trend #1: The Exploding U.S. Self Pay Market for Obesity Drugs



Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Americans Want to Lose Weight

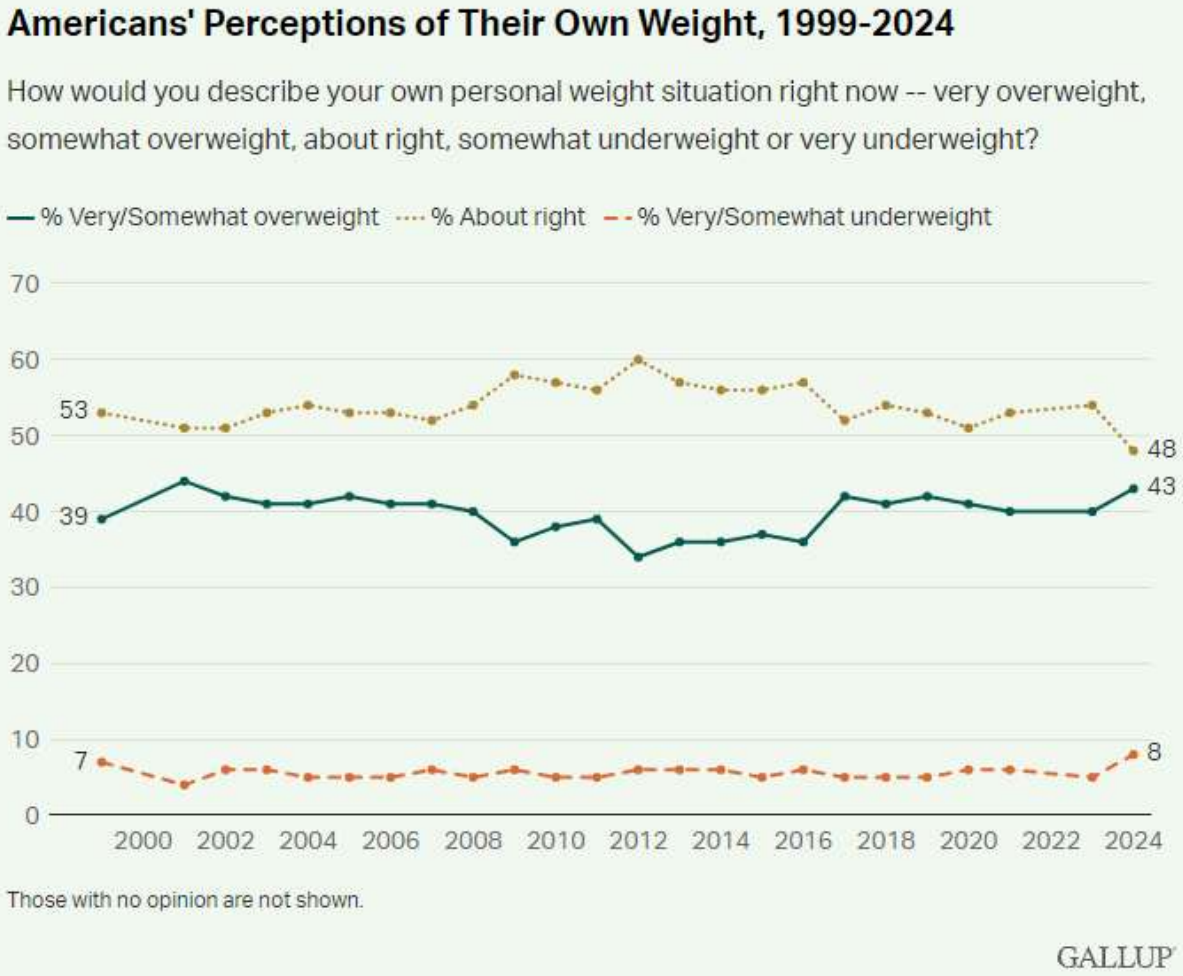
Megan Brenan, Gallup Poll Summary, "43% of Americans Say They Are Overweight; 55% Want to Slim Down," Dec 26, 2024

WASHINGTON, D.C. -- As the new year approaches and Americans consider their resolutions for 2025, losing weight may be on the minds of many. More than four in 10 U.S. adults, 43%, view themselves as overweight -- and even more, 55%, say they want to lose weight. However, only 27% report they are actively working toward that goal. Women continue to be more likely than men to say they are overweight and to express a desire to trim down.

Meanwhile, 30% of Americans report having lost a significant amount of weight in the past two years, with 4% attributing the reduction to prescription medication.

In their effort to achieve better health, about one-quarter of U.S. adults use fitness trackers, such as smartwatches or smart rings, or monitor their health statistics using an app on their smartphone or tablet.

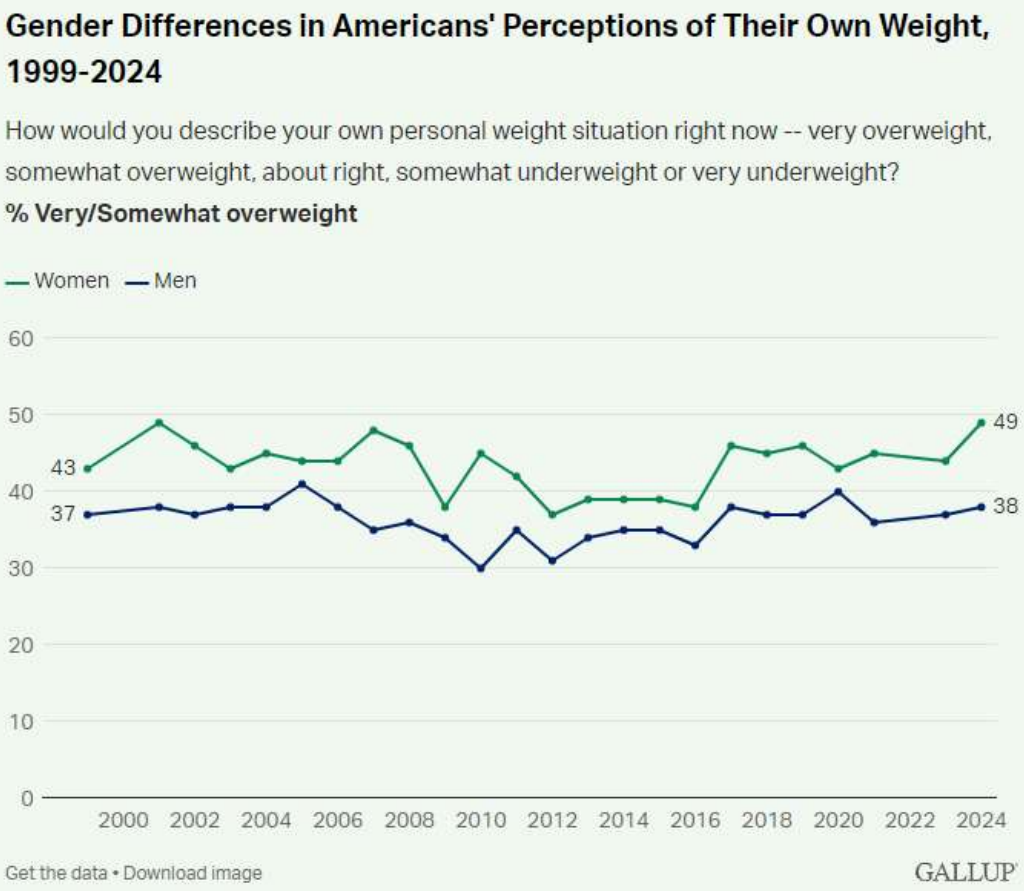
These findings are from Gallup's annual Health and Healthcare survey, conducted Nov. 6-20.

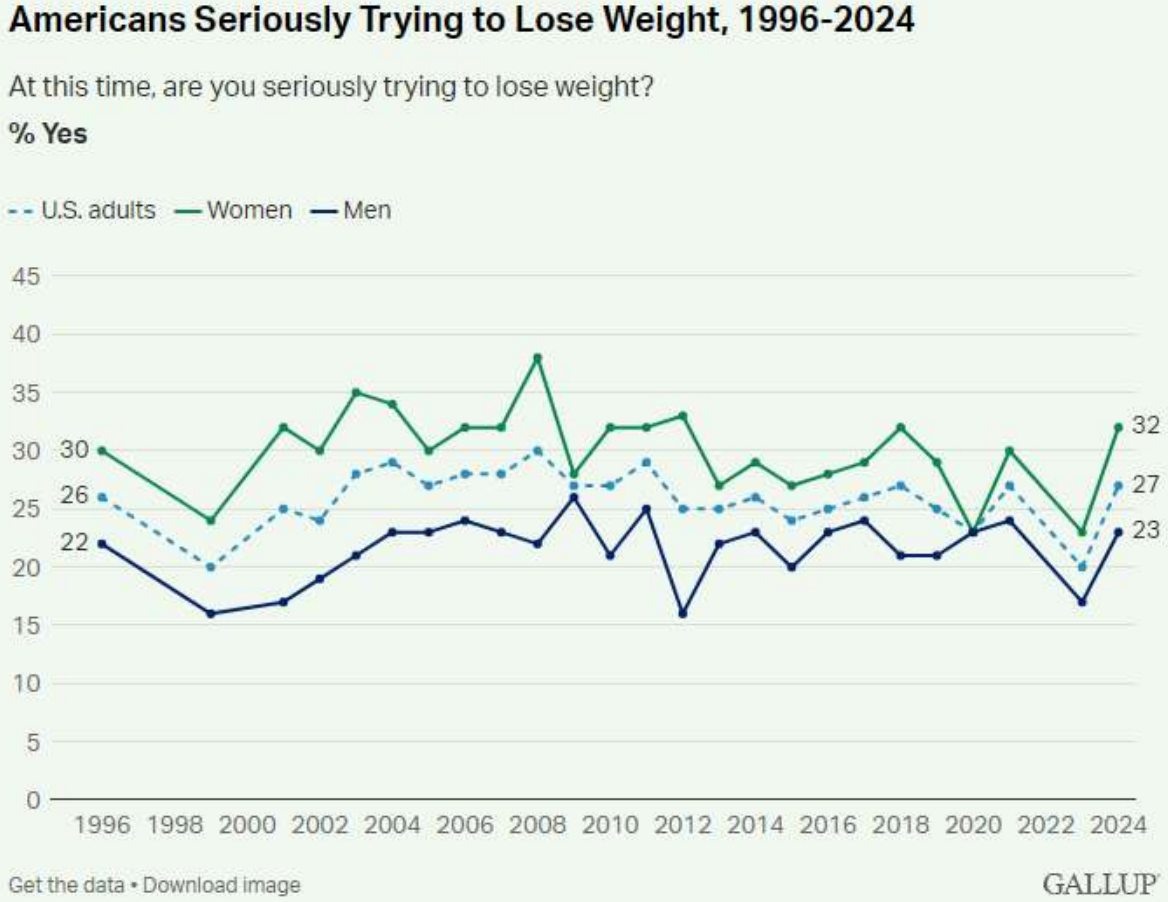


Source: https://news.gallup.com/poll/654425/americans-say-overweight-slim-down.aspx

More Gallup Poll Data Showing High Interest in Weight Loss

Megan Brenan, Gallup Poll Summary, "43% of Americans Say They Are Overweight; 55% Want to Slim Down," Dec 26, 2024





Source: https://news.gallup.com/poll/654425/americans-say-overweight-slim-down.aspx

GLP-1 Demand Related to Core Societal Views of Ideal Female Form

For better or worse, women in many Western countries are willing to spend substantial money to look thinner.

Garner et.al., *Psychological Reports*, 1980

The current study attempts to document and quantify the shift toward a thinner ideal shape for females in our culture over the last 20 years. Data from Playboy centerfolds and Miss America Pageant contestants indicated a **significant trend toward a thinner standard**. Over the same period there was a significant increase in diet articles in six popular women's magazines. These changes occurred within the context of increasing population weight norms for young women.

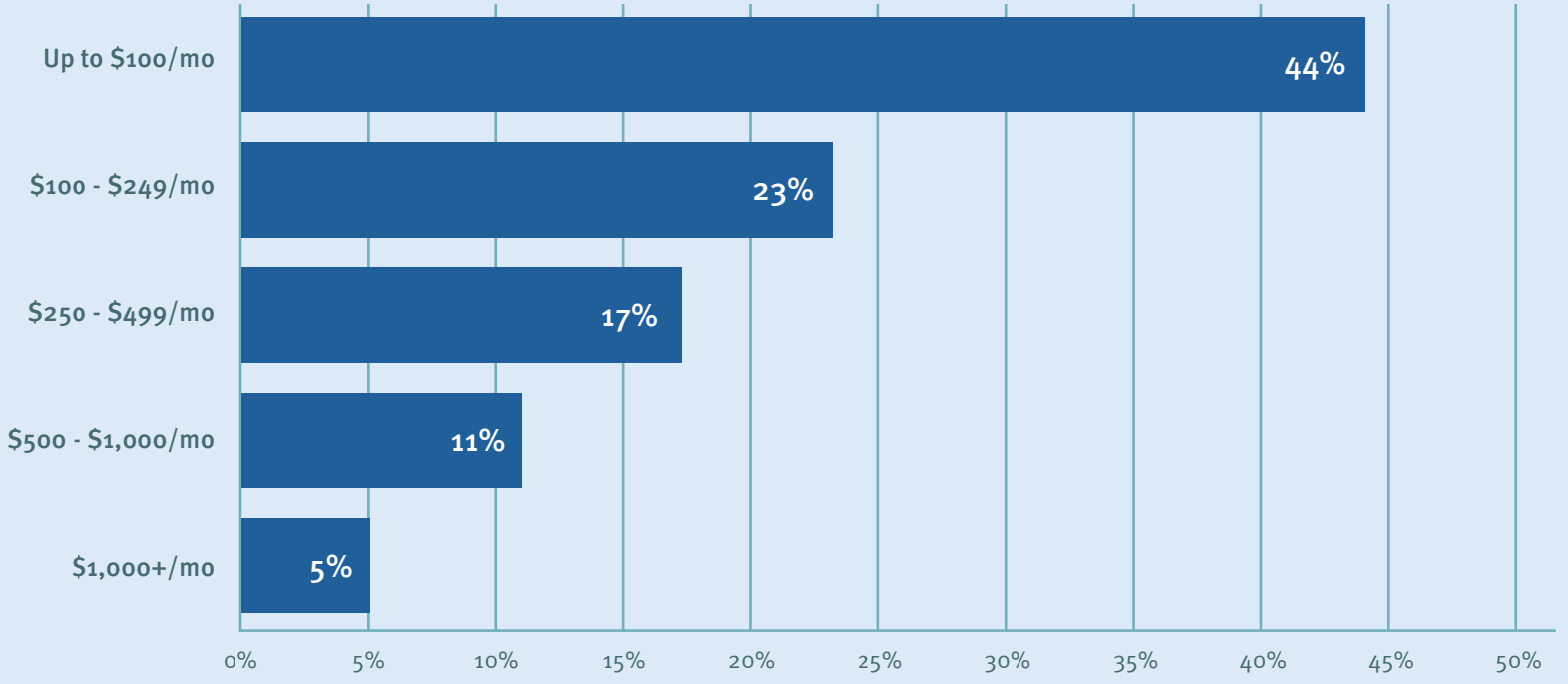
Source: https://www.yahoo.com/lifestyle/how-the-ideal-miss-universe-body-has-morphed-over-195703448.html, https://journals.sagepub.com/doi/epdf/10.2466/pro.1980.47.2.483

The Consumer Obesity Drug Market Will Likely Exceed the Insured Market

We believe that the consumerization of obesity products will be the main driver of obesity market size in the next three to five years – not insurer behavior. Governments largely are not reimbursing these drugs which limits uptake.

STAT-HARRIS POLL: OBESITY AND WEIGHT LOSS MEDS

Almost Half of Americans Would Spend Up To $100/Month; 5% $1,000/Month



Source: https://www.statnews.com/wp-content/uploads/2023/06/STAT-Harris-Poll_Obeisity-and-Weight-Loss-MedsSent_21Jun2023-1-1.pdf

Consumer Needs

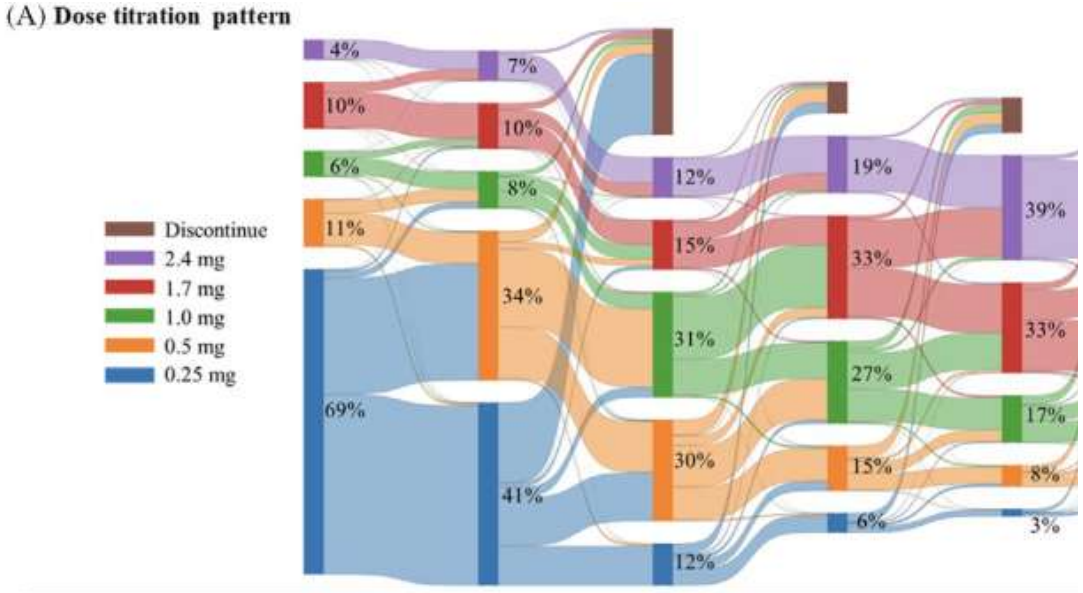
Affordability

Aesthetic

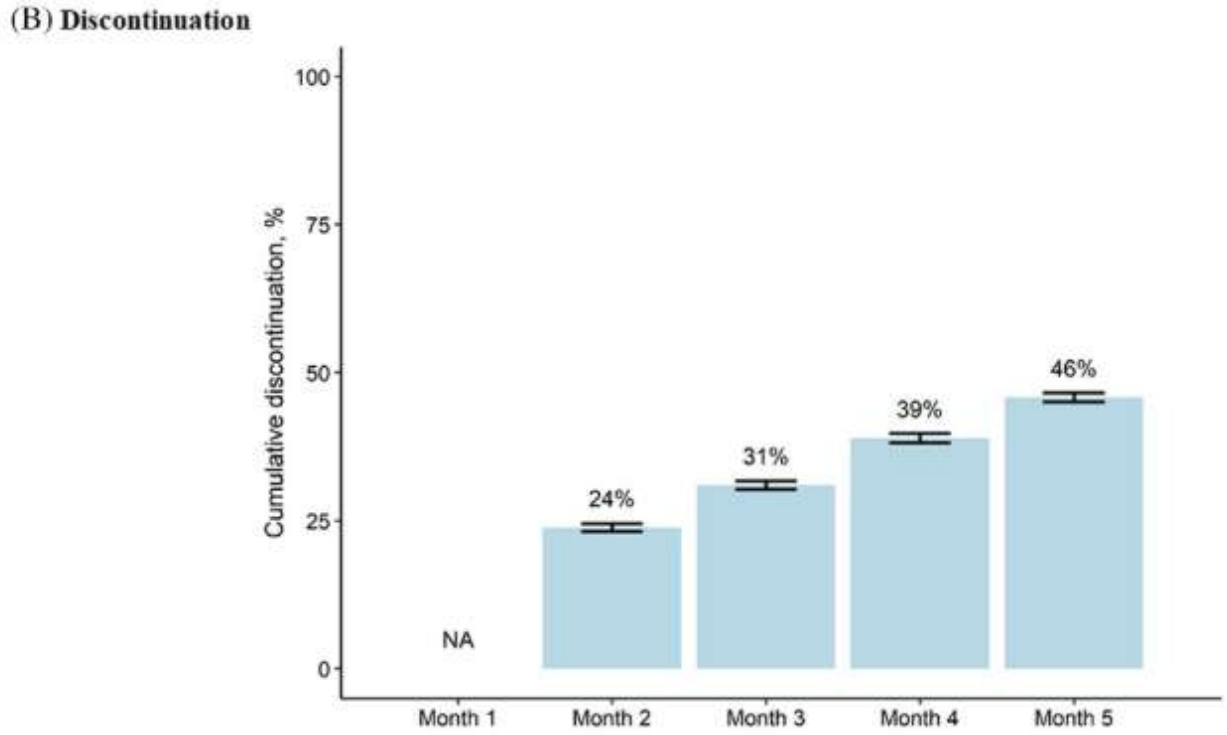
Tolerability

Consumers Cycle Doses and Frequently Discontinue Currently Approved GLP-1 Drugs

Xu Y, Carrero JJ, Chang AR, Inker LA, Zhang D, Mukhopadhyay A, Blecker SB, Horwitz LI, Grams ME, Shin JI. Titration and discontinuation of semaglutide for weight management in commercially insured US adults. Obesity (Silver Spring). 2025 Jul;33(7):1243-1248. doi: 10.1002/oby.24315. Epub 2025 Jun 4.



	Cohort	Month 1	Month 2	Month 3	Month 4
Discontinued at each month *	Denominator	15,811	15,811	12,044	10,911
	No. (%) of patients	0 (0%)	3,767 (24%)	1,133 (9%)	1,259 (12%)



Source: https://pubmed.ncbi.nlm.nih.gov/40464214/

Consumer / Private Pay Aspects of Obesity Management Have Become Quite Important

- The consumer has their hands on the weight loss drug steering wheel in the U.S. now.
- Only a quarter of the market is self-pay given where prices are now. But consumers with very good health plans are badgering their docs to find excuses to write prescriptions for the drugs.
- Consumer is surprisingly willing to pay for weight loss. They know what it means for health but are highly focused on what it means for appearance.
- Social / anthropological aspects of weight loss are very important. If your peer group drops weight the pressure on you to do it is high.
- Pressure is especially acute on women for whom the reality of an idealized "Barbie" like figure is often at variance with the reality of living in a society rich in nutritionally dense foods.
- Indeed, the consumer obesity market in the US is largely female and largely young.
- The consumer wants three things: (1) affordability, (2) optimization of aesthetics and (3) tolerability.

The Exploding Online Direct-to-Consumer Obesity Drug Market

The obesity market has been an area of high direct buying interest from consumers and digital entrepreneurs have been quick to enter the field.

The traditional obesity drug market (Lilly and Novo) in 2024 was $54 billion. It is expected to grow quickly from here.

In theory, a significant fraction of this market could be intermediated to consumers via the DTC market.

Evidation estimates that roughly half of obesity market scripts are getting done via the DTC route in Q2 2025 (private communication).

This market is going through major changes in 2025 because compounded versions of GLP-1's are impacted by cessation of shortages.

How the Online Obesity Market is Shaping Up

Based on disclosed data, the emerging ecosystem for online pharmaceuticals is now over $5 billion in size (maybe much larger). The ecosystem comprises three distinct types of players:

PharmaCo Portals

Pharma company selling portals like LillyDirect and Novocare Pharmacy are doing ever more business and cut out the middleman allowing the pharma company to sell product at a good price for the consumer but a high margin for the seller.

No official numbers are available, but we are hearing from reliable sources that, in combination, NovoCare and LillyDirect are on track to do well over $1 billion in sales in 2025.

Branded Marketers

There are numerous online marketers of pharmaceuticals, such as Ro and HIMS & HERS, who sell a wide range of prescription medications directly to consumers through telehealth platforms. Most of these companies originally built their business models around products like Viagra® for erectile dysfunction and hair loss treatments such as finasteride and minoxidil. Over time, they have diversified substantially, expanding their offerings to include treatments for mental health conditions, dermatologic issues, and chronic diseases. As the popularity of GLP-1 medications for weight management has exploded, several of these direct-to-consumer telehealth companies have moved quickly to capture demand by marketing Zepbound® and Wegovy® to interested patients seeking convenient online consultations and discreet home delivery. This approach appeals particularly to younger, tech-savvy consumers who prefer avoiding traditional in-person doctor visits and pharmacy pickups.

Compounded Drugs

Compounding pharmacies have played a crucial role in the obesity drug market by bridging gaps in access during the massive shortages of branded GLP-1 medications like semaglutide (Ozempic, Wegovy) and tirzepatide (Mounjaro, Zepbound).

These pharmacies often prepare alternative formulations, sometimes at lower cost, making treatment available to patients who either can't afford or can't tolerate the original products.

Compouded pharmacies and their marketing partners remain an important part of the market.

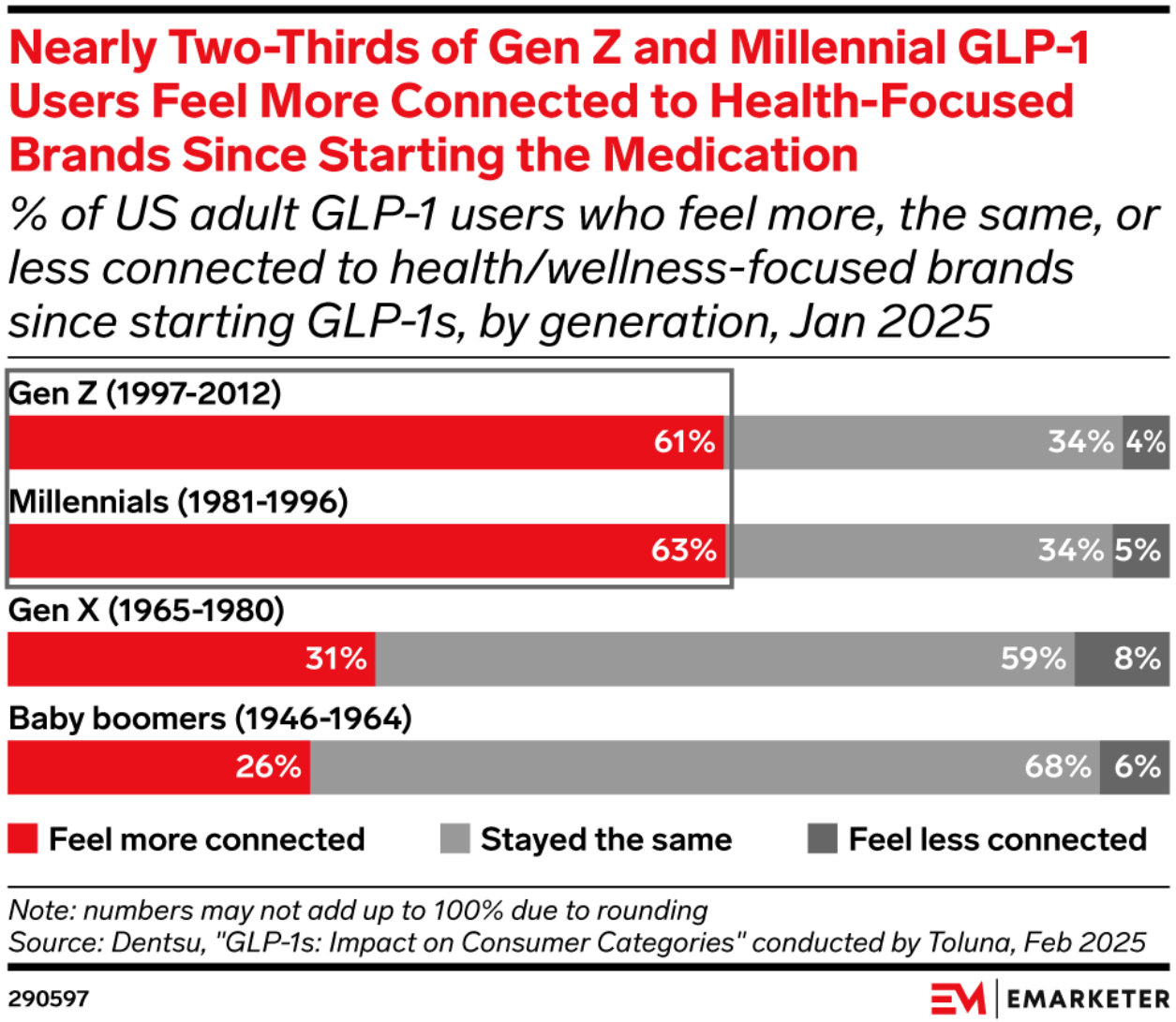
New Online Brands Like Ro are Capturing The Consumer

New data highlight a striking generational divide in how GLP-1 weight loss medications shape consumers' feelings toward health and wellness brands.

According to eMarketer, nearly two-thirds of Gen Z (61%) and Millennial (63%) users report feeling more connected to health-focused brands after starting GLP-1 medications (see chart at right).

In contrast, only about a third of Gen X (31%) and just over a quarter of Baby Boomers (26%) say the same. This suggests that younger consumers may view these drugs as part of a broader personal transformation narrative, where medication, fitness, and nutrition brands are intertwined in the pursuit of self-optimization.

The generational gap also underscores how perceptions of weight loss are evolving. Millennials and Gen Z consumers are often more immersed in wellness culture, social media inspiration, and influencer marketing that frames GLP-1 use as aspirational. For these groups, medication isn't only about improving health outcomes; it's tied to identity, belonging, and aesthetic goals.



Source: https://www.emarketer.com/content/impact-of-weight-loss-drugs-2025

The Consumer Interested in Weight Management Presents a Huge Opportunity in Health Care

- We find ourselves at an extraordinary moment in healthcare history.
- So many customers have moved away from primary care doctors and “Dr. Google” to LLM’s like Deepseek to self-diagnose.
- Without seeing it happen as a distinct event, the world has rapidly shifted to a virtual care approach mediated by surprisingly good health advice coming from AI engines.
- We believe that the millions of consumers that are buying weight loss drugs online are a perfect population with which to build out a much larger platform that will connect AI self-care to access to medications mediated by a caring physician.
- Authors such as Daisy Wolf and Julie Yoo of Andreessen Horowitz have thought deeply about this area and how healthcare could be better organized and delivered to the active consumer-patient of today using novel business models.

The Shifting Locus of Medicine

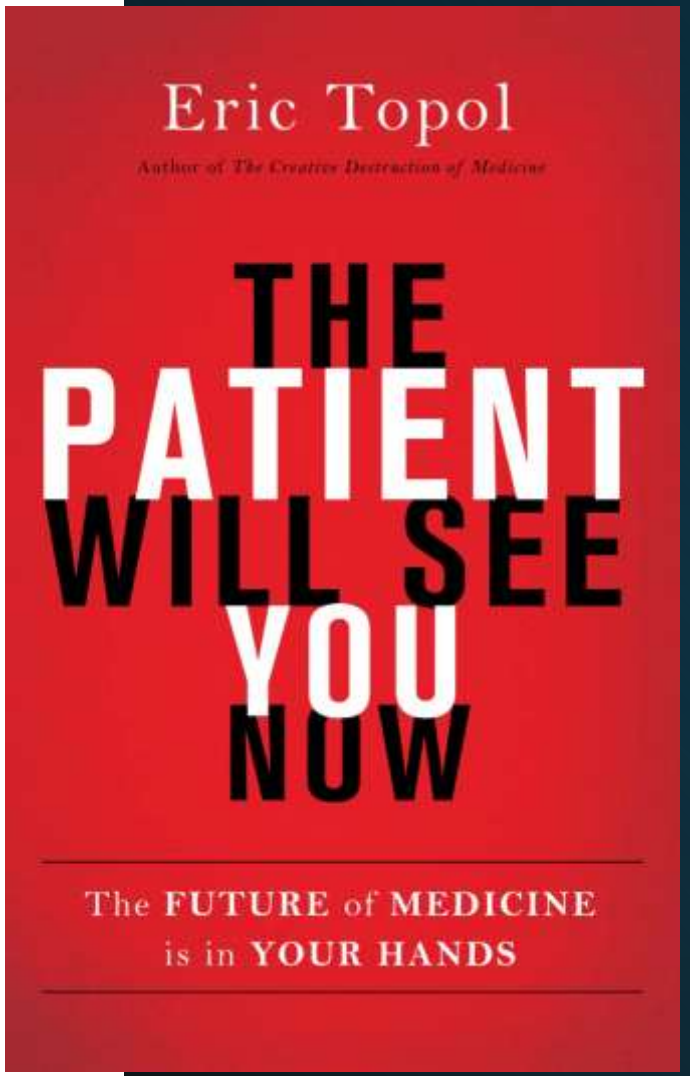
Richard Smith, editor of the *British Medical Journal* wrote: “The relationship between doctors and patients will surely be much more equal; indeed, health will primarily be the business of patients, with doctors as advisors, guides, and facilitators.”*

We have written elsewhere that the increasing involvement of consumers in their own healthcare is one of the most important developments in medicine in decades.

This shift was foreshadowed by Eric Topol in his highly readable 2014 book *The Patient Will See You Now*. He speaks extensively of a doctorless future where patients monitor their own health with smart watches and their phones. He talks of how well patients do when they take charge of their own healthcare.

The consumer’s movement to self-manage obesity drugs, triggered in part by shortages of these drugs through traditional channels, seems to have accelerated adoption of a self-care and self-Rx mentality. If the Pandemic got much of the population used to telehealth then GLP-1 shortages taught much of the population that they can and perhaps should access pharmaceuticals through self education where doctors participate peripherally in this activity.

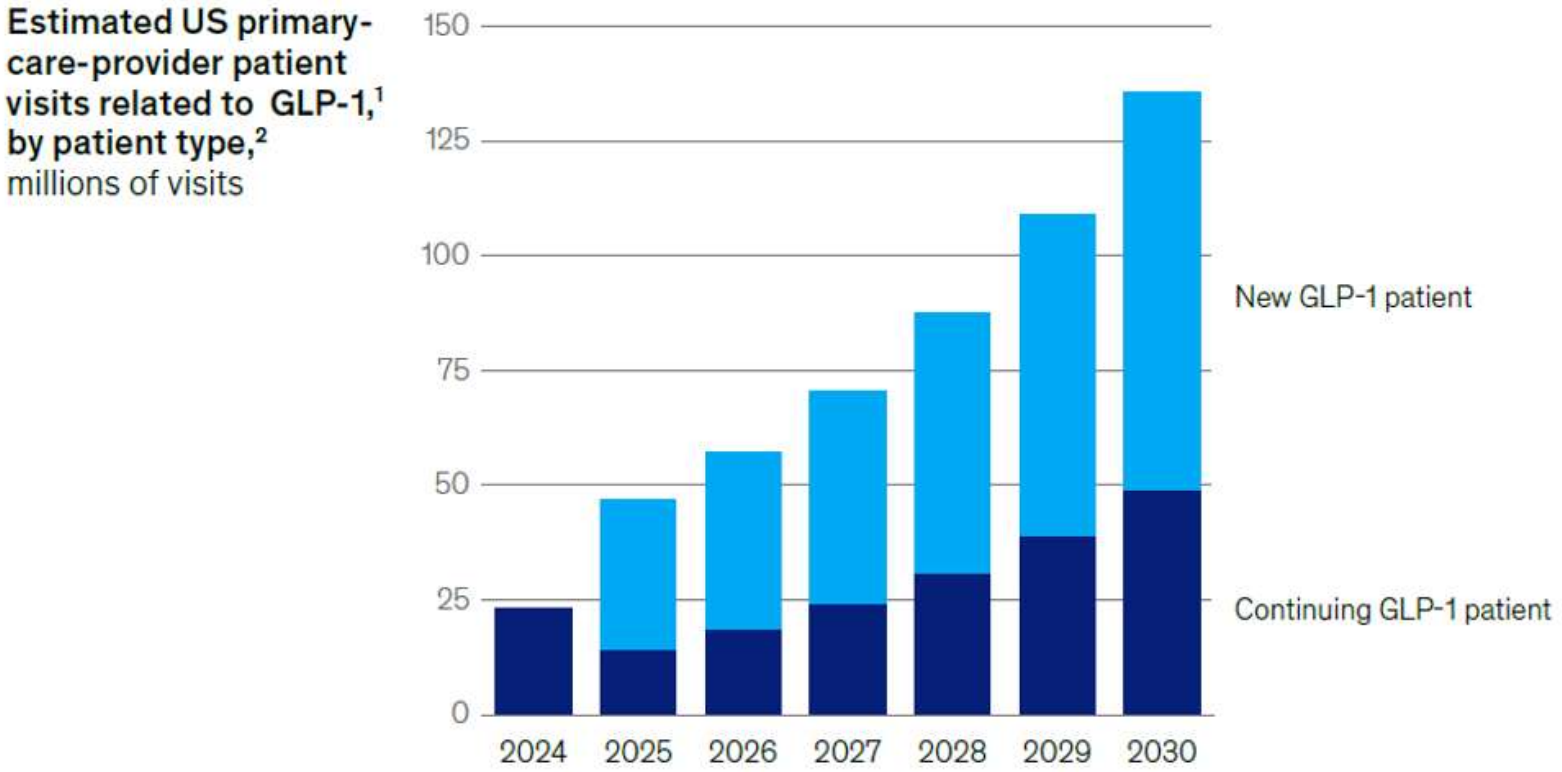
We believe that today’s Millennial is highly likely to be far more autonomous in their use of medicine than older generations. And we think that websites that offer access to obesity drugs (e.g., Ro.co) could very well be the type of platform that becomes a dominant consumer-centric alternative to today’s health system. We discussed a range of visions of how such a future platform might develop in a recent report on the future of healthcare.



See https://blogs.bmj.com/bmj/2014/02/14/richard-smith-teaching-medical-students-online-consultation-with-patients/

A Key Factor in Online Obesity Drug Access is Limits to Traditional Primary Care Capacity

McKinsey Health Institute, *The path toward a metabolic health revolution*, Report, May 20, 2025



Source: https://www.mckinsey.com/mhi/our-insights/the-path-toward-a-metabolic-health-revolution#/

In many parts of the U.S. it is not so easy to get access to primary care doctors. In fact, an ever-increasing portion of doctor time in the U.S. is being taken up by discussions surrounding GLP-1 prescriptions.

One can see how the online ability to access GLP-1's and interaction with physicians using more efficient portals has been attractive to the emerging healthcare consumer.

Controversy Regarding Role of Compounding Pharmacies in the U.S. Obesity Market

As of mid-2025, the U.S. Food and Drug Administration (FDA) has officially declared the shortages of semaglutide and tirzepatide—key ingredients in popular GLP-1 medications like Ozempic, Wegovy, Mounjaro, and Zepbound—to be resolved. This decision follows significant production expansions by manufacturers Novo Nordisk and Eli Lilly, which have successfully scaled up supply to meet the surging demand for these diabetes and weight-loss treatments. Consequently, compounded versions of these drugs, which were previously permitted under temporary FDA allowances during the shortage period, are now subject to stricter regulatory constraints.

During the shortage, compounding pharmacies and telehealth providers played a crucial role in filling the supply gap by offering more affordable, custom-mixed alternatives to the brand-name drugs. These compounded versions provided essential access for patients who either could not afford the high costs of the branded medications or faced insurance coverage limitations. However, with the FDA's determination that the shortages have ended, these entities are now required to cease the production and distribution of compounded semaglutide and tirzepatide, *unless specific patient needs justify their use under FDA guidelines*.

There has been increasing controversy in recent months regarding this market, particularly because it has been widely reported in the press that the FDA actions will cause all compounded GLP-1 product to come off the market. As it happens, this is not the case because compounders can continue to offer drug on a customized basis as long as a patient is not suited to an approved version or dosage of a drug. In general, customized sales of GLP-1's in the U.S. take place through 503a pharmacies. These pharmacies are highly regulated and subject to both FDA oversight and inspections carried out at the state level.

Hims and Hers Continues Offering Personalized Semaglutide

STRATEGY

15

The breadth of our weight loss offering continues to expand, addressing a variety of subscriber profiles

Wegovy® through NovoCare®

In long-term clinical trial
Avg >30lbs[1] weight lost or
15% of initial body weight

Launched April 2025

BMI of 30+ or 27+ with one or more comorbidities

Liraglutide

In long-term clinical trial
Avg 18lbs[1] weight lost or
8% of initial body weight

Launched March 2025

BMI of 30+ or 27+ with one or more comorbidities

Oral Weight Loss

After 8 weeks
Avg 8lbs[2] weight lost or
4% of initial body weight

Launched December 2023

Adaptable across BMI ranges

Personalized Semaglutide Dosage

Requires in depth documented clinical need

After 8 weeks
Avg 12lbs[2] weight lost or
5% of initial body weight

Launched July 2024

BMI of 30+ or 27+ with one or more comorbidities

(1) See page 40 for source. (2) All weight loss numbers based on Hims & Hers customer reported data for the applicable offering in the fourth quarter of 2024. Standard and personalized dosage weight loss numbers were not calculated or reported separately. Note: On February 21, 2025, the FDA resolved the semaglutide shortage, which has constrained and is expected to continue to constrain our ability to continue providing access to compounded semaglutide on our platform. The FDA does not limit compounding to drug shortages, and we believe there are paths to continue offering access to certain compounded GLP-1s after the period of FDA enforcement discretion has ended following resolution of the shortage, consistent with the statutory exemptions from the new drug approval requirements. As such, we intend to continue expanding our weight loss offerings and serving our Subscribers with a wide range of weight loss solutions.

hims & hers

From Hims and Hers, May 2025 Investor Presentation

GLP-1 Shortages Have Ended

Following the FDA's declaration in February 2025 that the semaglutide shortage had ended, Hims & Hers Health adjusted its approach to offering GLP-1 medications. The company acknowledged that, under FDA regulations, compounded versions of semaglutide are no longer permissible unless specific clinical needs justify their use.

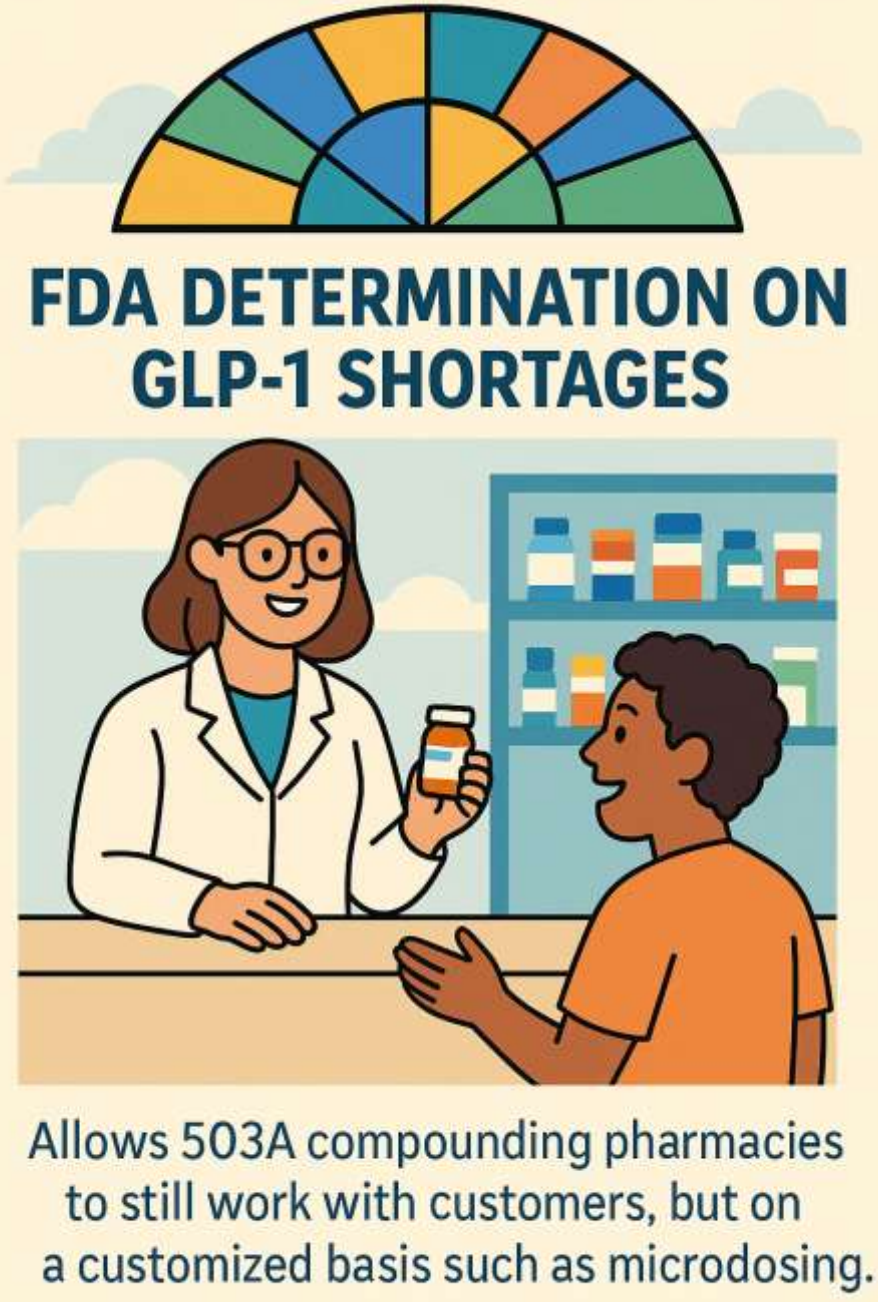
Consequently, Hims & Hers ceased offering standard compounded semaglutide formulations by the FDA's deadlines—April 22 for 503A pharmacies and May 22 for 503B outsourcing facilities. In its Q1 2025 10-Q Hims & Hers explained their position:

“Risk Factors - on February 21, 2025, the FDA resolved the semaglutide shortage, which has constrained and is expected to continue to constrain our ability to continue providing access to compounded semaglutide on our platform. The FDA does not limit compounding to drug shortages, and we believe there are paths to continue offering access to certain compounded GLP-1s after the period of FDA enforcement discretion has ended following resolution of the shortage, consistent with the statutory exemptions from the new drug approval requirements. As such, we intend to continue expanding our weight loss offerings and serving our Subscribers with a wide range of weight loss solutions.” (from HIMS disclosure)”

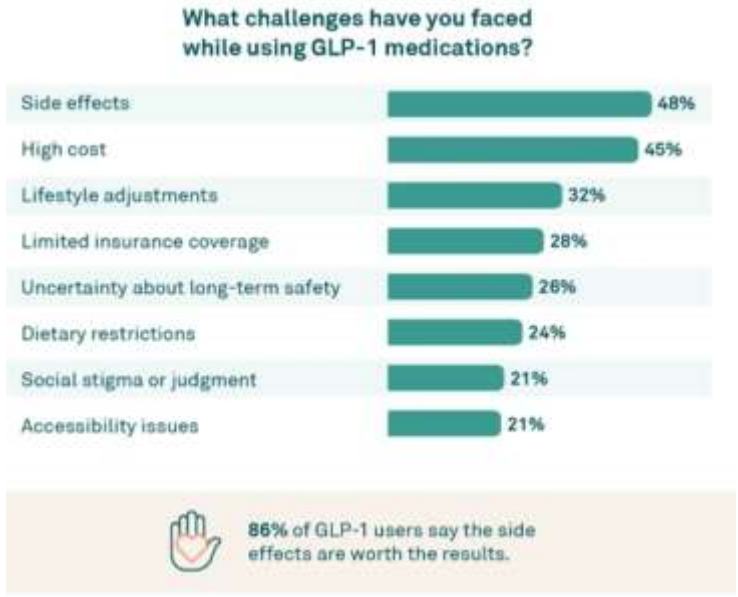
Compounded Drug Sector a Well-Established Route for Customizing Treatments – Especially Microdosing

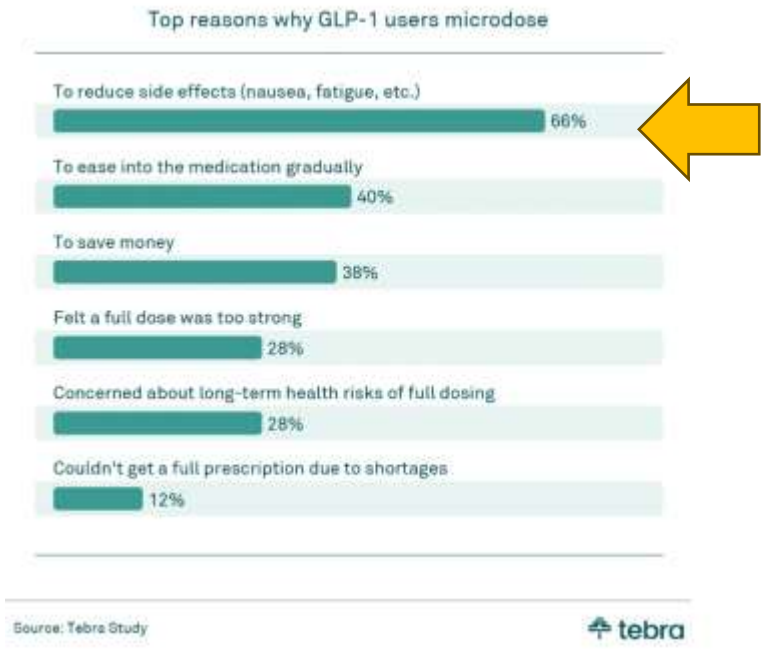
Importantly, many patients who take both semaglutide and tirzepatide experience side effects from using these drugs. This is the reason that online sales of compounded versions of both drugs have continued. In practice, many patients taking GLP-1's do not stay on the drugs for long. The reasons are many, but nausea is often cited as a reason for why patients come off the drugs. For example, one approach that has been popular in recent months has been microdosing of GLP-1's. This approach appears to reflect less nausea by consumers. There are many options that physicians can use.

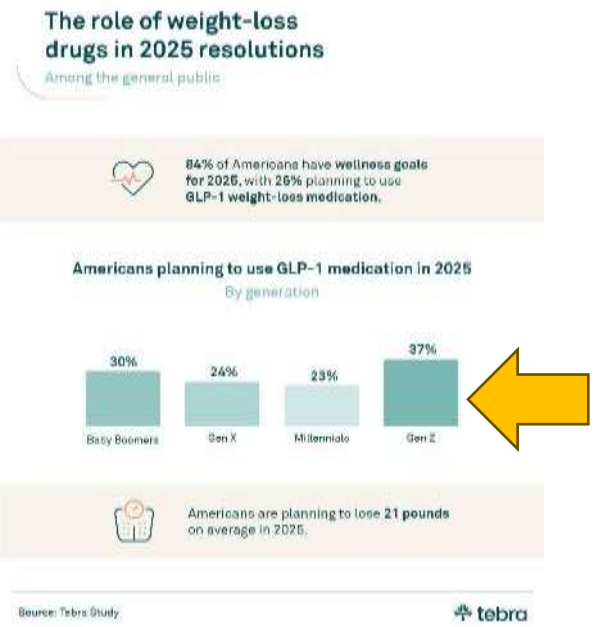
The right of 503A pharmacies to provide compounded drug product when specifically requested by a physician has been consistently upheld by the courts. This right is rooted in Section 503A of the Federal Food, Drug, and Cosmetic Act, as clarified by the Drug Quality and Security Act (DQSA) of 2013. Legal cases, such as *Medquest Pharmacy v. FDA*, have confirmed that the FDA cannot unduly interfere with 503A pharmacies operating within their legal bounds—namely, compounding based on valid prescriptions and complying with state pharmacy regulations.

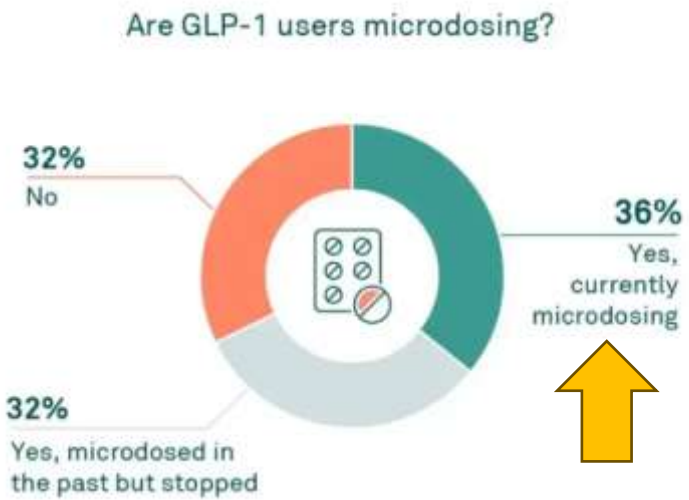


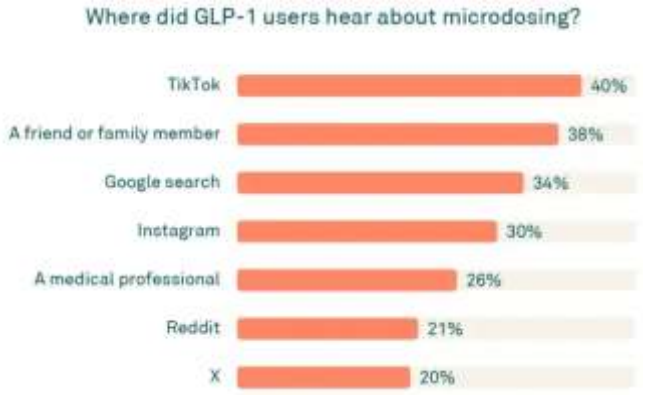
Tebra: Microdosing of GLP-1 Has Become a Tik Tok Phenomenon for Gen Z (people in 20's)





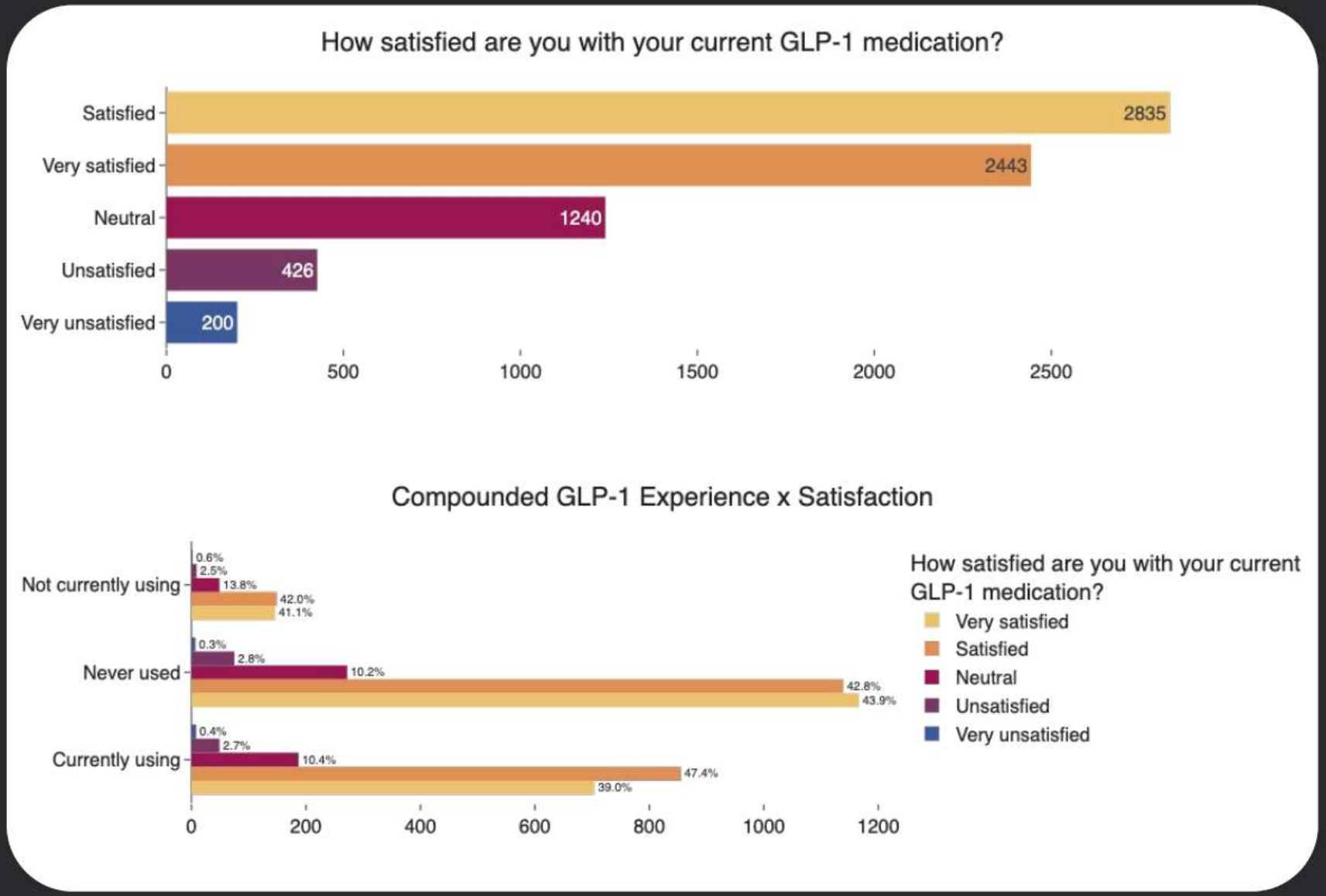






Sources: https://www.tebra.com/theintake/healthcare-reports/microdosing-glp-1

Patient Satisfaction May be Higher with Compounded GLP-1'S than Brands



Despite frequent warnings about compounded product from pharma companies the data do not suggest that consumers are having frequent "nightmare" experiences in this area.

This data from the research and data firm Evidation shows a higher satisfaction rate by consumers that use compounded GLP-1s than among those that are not currently using compounded product.

Source: https://evidation.com/resources/glp-1s-real-world-insights-from-10000-users

Trend #2: The Self-Pay Market is Going Global

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

The Obesity Self Pay Market Goes Well Beyond the United States

There is a gigantic market for GLP-1's for obesity outside the United States. There is no government system to pay for these drugs so the market is, essentially, all self pay.

Europe: Public payers are statutorily prohibited from covering weight-loss drugs, forcing patients into self-pay markets. For example, Denmark's largest private insurer halted Wegovy reimbursements in 2024 due to unsustainable demand

UK and France: Coverage requires strict criteria (e.g., BMI ≥35 with comorbidities), leaving many patients to seek private prescriptions

Southeast Asia: Recent introductions of tirzepatide in Asian countries has been met with wild enthusiasm. Inventory in Vietnam and Thailand sold out within a week of introduction in Q2 2025. This is all self pay. This is with a price of roughly $250 per month.

India: Tirzepatide was introduced in India in March 2025 and has been wildly popular at a price of $200 to $300 a month depending on the dosage used. Sales have gotten off to a good start and set to explode going forward.

It's interesting that Lilly is offering tirzepatide in lower dosage forms in Asia. This may reflect supply constraints or a desire to avoid transshipment into the U.S.

Eli Lilly Launches Weight-loss Drug Mounjaro® in India

Rishika Sadam, *Reuters*, March 21, 2025

Eli Lilly launched its blockbuster diabetes and weight-loss drug Mounjaro in India on Thursday, beating rival Novo Nordisk for a much-awaited entry into the world's most populous country grappling with increasing rates of obesity and diabetes.

Mounjaro, a once-weekly injection approved by India's drug regulator, is priced at 4,375 rupees ($50.67) for a 5 mg vial and 3,500 rupees ($40.54) for a 2.5 mg vial, its lowest doses, the company told Reuters exclusively. Its highest dose is 15 mg.

A patient in India may have to spend about $200 a month when taking a weekly dose of 5 mg, subject to doctor's prescription. Chemically known as tirzepatide, Mounjaro is currently sold in the UK and Europe under the same brand name for both diabetes and weight loss. It is sold as Zepbound for obesity in the U.S.

Mounjaro carries a list price of $1,086.37 for each monthly fill in the U.S., but the amount patients pay largely depends on their insurance plan. Lilly also offers 5 mg, 7.5 mg and 10 mg vials of Zepbound, with prices around $499 for a month's supply if customers pay directly in cash without any third-party entities.

Novo's India team has been pushing the global leadership to launch Wegovy as early as 2025 in the country as opposed to the company's target of a 2026 launch. The drugmaker told Reuters that Wegovy has already been approved in India, but said it did not have a confirmed date for the medicine's launch there. The active ingredient in Wegovy is semaglutide, which is likely to go off-patent in 2026 in India.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/eli-lilly-launches-weight-loss-drug-mounjaro-india-after-drug-regulator-approval-2025-03-20/

What the India Market Looks Like Today

Semaglutide offers real world 10% weight loss in a year at top dose. This is available in India now for $300 a month in the convenient pre-filled pen format from Novo Nordisk but is hard to access. Patients can get Lilly's tirzepatide for $257 a month but the 5mcg dose is also hard to find and in the real world delivers 8.4% weight loss in a year.

Patients can buy genuine Novo semaglutide (Wegovy®) Cost: $300 monthly for high dose and $200 for low dose

Dosage of up to 2.5mcg available (and, importantly, in pre-filled pen mode). This product is just entering the market now.

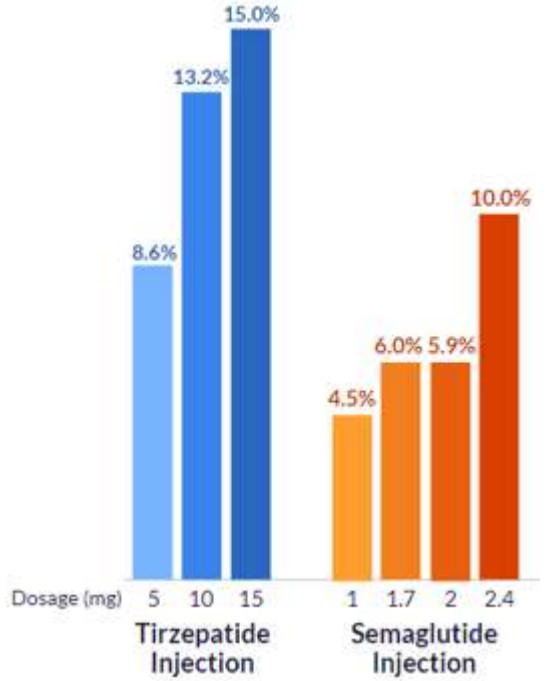
Patients can buy genuine Lilly tirzepatide (Mounjaro®) Cost: $257 monthly.

Dosage of up to 5mcg available (but in vials only and we can't find the 5mcg dose online – only 2.5mcg available due to high demand). Similar pricing and offering as LillyDirect in the US

Patients can buy a PFS version of generic tirzepatide Cost: $234 monthly.

Dosage of up to 7.5mcg available (very similar to the compounded online offering in the US)

Real World Weight Loss at One Year
(Epic data, N=413,557 patients)



Sources: Tirzepatide pricing and offerings: https://dir.indiamart.com/; Wegovy pricing and availability: https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/weight-loss-drug-wegovy-starts-at-17345-in-india/articleshow/122055009.cms; Real world weight loss statistics: https://www.epicresearch.org/articles/tirzepatide-and-injectable-semaglutide-correlated-with-greatest-weight-loss-among-glp-1-medications.

Zuellig Pharma Launches Lilly's Innovative Obesity and Diabetes Medicine in Thailand

***BioSpectrum Asia*, May 27, 2025**

Zuellig Pharma, a leading healthcare solutions company in Asia, has announced that Mounjaro (tirzepatide), the innovative obesity and diabetes medicine developed by Eli Lilly and Company, will be launched in Thailand at the end of May 2025. Zuellig Pharma holds the marketing authorisation for Mounjaro® (tirzepatide) in Thailand, having been granted the distribution and promotion rights for the medicine by Eli Lilly and Company this year.

Mounjaro® (tirzepatide) is a once-weekly prescription-only medicine indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise; as monotherapy when metformin is considered inappropriate due to intolerance or contraindications, in addition to other medicinal products for the treatment of diabetes; and as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance.

The availability of Mounjaro® (tirzepatide) is a significant advancement in the treatment of both obesity and type 2 diabetes, offering a single medication that can address both conditions through an easy-to-use prefilled pen. Mounjaro® KwikPen® (tirzepatide injection) is available in 2.5 mg, 5 mg, 7.5 mg and 10 mg, and gives healthcare providers the ability to personalise treatment plans better to meet individual patient needs.

Obesity is a critical public health concern in Thailand that affects 48% of the total population. The Ministry of Public Health classifies obesity as a Non-Communicable Disease (NCD) due to its strong link to rising rates for chronic illnesses, particularly type 2 diabetes. In 2024, the Department of Disease Control reported that 1 in 10 Thai individuals – a total of 6.5 million people – suffer from type 2 diabetes, impacting their physical, mental, and social well-being.

Source: https://www.biospectrumasia.com/news/25/26096/zuellig-pharma-launches-lillys-innovative-obesity-and-diabetes-medicine-in-thailand.html

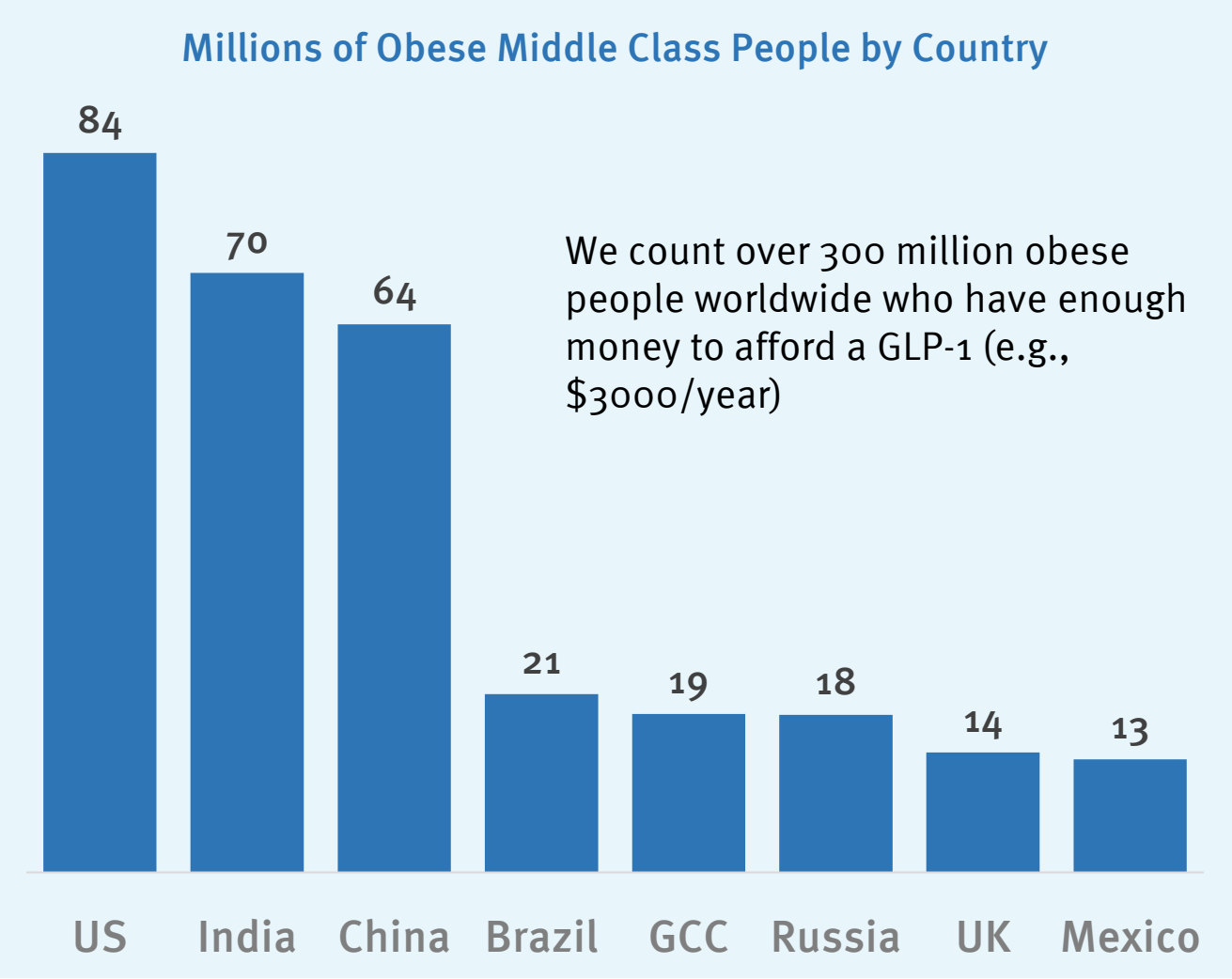
The Obesity Drug Craze in Brazil

Heather van Epps, *The Lancet Diabetes and Endocrinology*, June 2025, p. 467-468.

Rising demand for potent obesity drugs like semaglutide and tirzepatide is fuelling crime in Brazil. Armed robbers are targeting pharmacies, and smugglers are being apprehended at Brazilian airports with drug pens strapped to their bodies and concealed in their clothing. Around 8000 tirzepatide pens—not yet legally available in Brazil—have been seized since June, 2024, according to Brazil's Federal Revenue Service, and 39 pharmacies were robbed in 2024, compared with only one incident in 2022. Much of the illicit activity is centred in São Paulo, one of Brazil's wealthiest cities, where more pharmacies stock the expensive drugs and more people can afford them.

Source: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(25)00124-X/

Huge Global Market: The Motivated Monied Many



Source: UN, WHO, Stifel Calculations

Gigantic Ex-U.S. Self Pay Market

Based on our calculations there are 283 million obese persons with sufficient means to pay for a GLP-1 at $3k a year in India, Brazil, China, Russia, the UK, the Gulf countries (e.g., Bahrain) and Mexico. It would be reasonable to estimate that the actual ex-US market is more like 500 million persons.

500 mil
people willing to pay for an obesity drug outside the U.S.

x **$250 mo.**
$3000 a year price for the drug

x **10%**
penetration assumption

=

$150 billion market opportunity

for a $3000 a year obesity drug outside the United States. The TAM is $660 billion.

Trend #3: Eli Lilly Is Pulling Away from the Pack

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Business | Battle of the bulge

Eli Lilly looks set to steal Novo Nordisk's weight-loss crown

Despite a late start, the American firm is bearing down on its Danish rival

The Economist, May 4, 2025 (excerpt)

Being first to market with a drug can be crucial. Eli Lilly is proving that being second but better can also pay. Zepbound, the American firm's weight-loss jab, was approved in its home country in November 2023, more than two years after Wegovy, made by Novo Nordisk, a Danish rival. Over the following year it yielded $4.9bn in revenue, more than half Wegovy's $8.2bn. On May 7th Novo cut its sales forecast for 2025, citing "lower-than-planned" growth in weight-loss drugs. Its share price has fallen by a third since the start of 2024; Lilly's has risen by about as much (see chart 1). The momentum is now with Lilly. Visible Alpha, a data firm, expects its sales of obesity drugs to overtake Novo's by 2027… Even so, both firms can look forward to fat profits. More than 100 companies are developing weight-loss drugs, but for now it is a duopoly. Analysts expect that by 2030 Lilly will have 47% of a $90bn-plus market, to Novo's 40%. And Denmark's former star still has time to shape up.

Source: https://www.economist.com/business/2025/05/07/eli-lilly-looks-set-to-steal-novo-nordisks-weight-loss-crown

How Ozempic's Maker Lost Its Grip on the Obesity Market It Created

Novo Nordisk underestimated demand for its blockbuster weight-loss drug Wegovy, and shortages let rivals in the door

Peter Loftus, *Wall Street Journal*, June 28, 2025 (excerpt)

In 2023, Novo Nordisk was the most valuable company in Europe, surpassing LVMH on the back of soaring demand for Ozempic and Wegovy. Today, the Danish company has lost its grip on the anti-obesity market it carved out. The company has lost market share amid production missteps and a bungled rollout of Wegovy that led to shortages. Its U.S. rival Eli Lilly—initially in the rearview mirror—has been proven to have the more effective weight-loss drug and a more promising pipeline of next-generation treatments. Novo Nordisk's research-and-development machine has disappointed, and a key marketing strategy was slow to get off the ground.

Novo Nordisk's ability to stay atop a market that analysts see growing to $150 billion in annual sales is now in doubt. Its controlling shareholder this month forced a surprise ouster of the company's chief executive officer, Lars Fruergaard Jørgensen. And while it is still generating multibillion-dollar sales for Ozempic and Wegovy, shares have tumbled more than 50% over the past year. If Novo Nordisk doesn't turn things around, it could join a long list of companies that blew a first-mover advantage, from Sunshine Biscuits—whose Hydrox cookies were overtaken by now-iconic Oreos—to the MySpace social network.

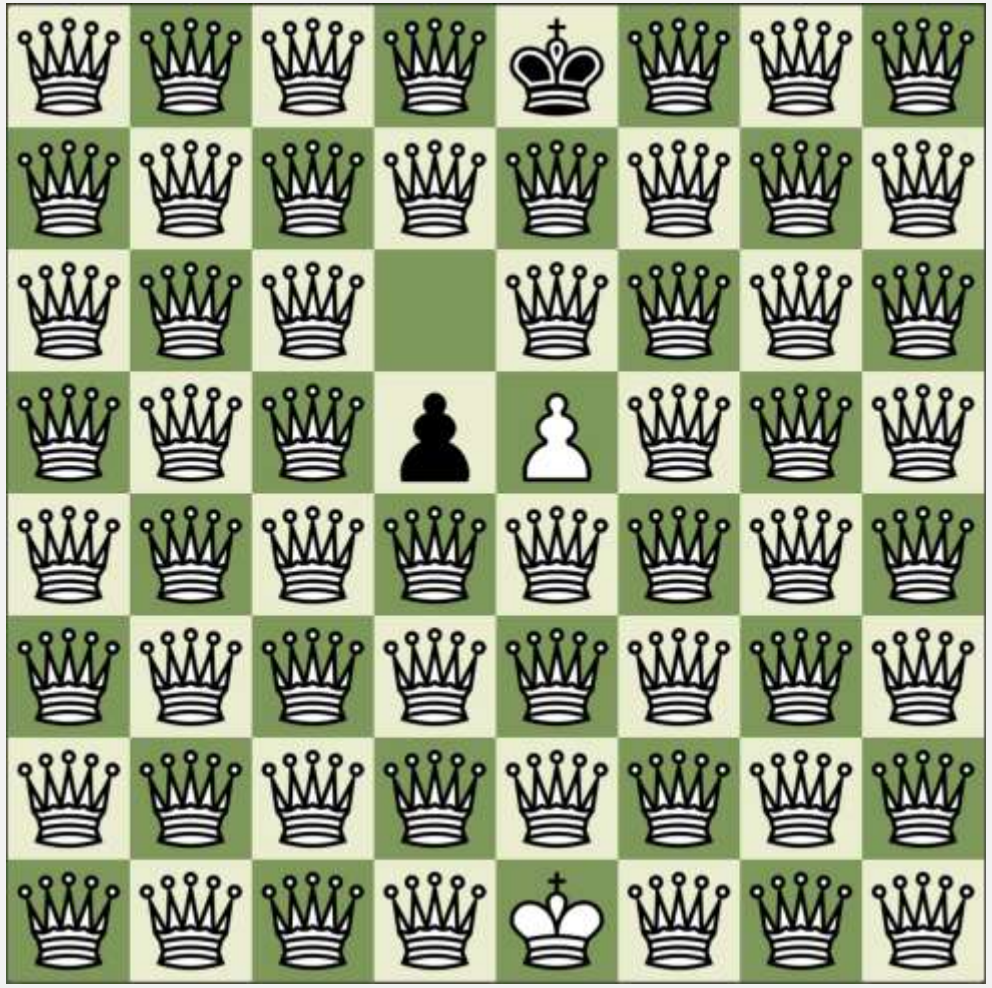
Some investors and industry watchers say Novo Nordisk's troubles stem from a cautious, reactive approach starting when the market first burst onto the scene, in contrast with a faster, more aggressive tack in production and marketing by Lilly.

Novo Nordisk thought Wegovy might run into the same market constraints as Saxenda, so the company planned modest production levels, using a combination of in-house and contract manufacturing capacity. It wasn't enough. It took only five weeks for the prescription rate of Wegovy to exceed the level that Saxenda had taken five years to reach. Jørgensen recalled later, in an interview in 2024, that he initially thought: " 'That's patients who've been lined up, there's pent-up demand, it will normalize.' It didn't. It just kept growing." The shortages gave rival Eli Lilly time to catch up. Lilly introduced Mounjaro for diabetes in 2022, followed by Zepbound, a weight-loss version of the same drug, in 2023. Zepbound has been shown in studies to induce greater weight loss than Wegovy, more than 20% of body weight.

Author Hanne Sindbæk, who has written two books about Novo Nordisk, says there has been an eternal tug of war inside the company between those who are guided by values—the idea that the company works for the common good rather than simply to make a profit—and those who run the business. If Novo Nordisk wants to stay in the game, it may have to lean toward the latter in choosing its next CEO.

Source: https://www.wsj.com/health/pharma/novo-nordisk-ozempic-anti-obesity-drug-market-5d5194a6

Lilly Portfolio Looking Really Good Now



Lilly strategy is to cover every important square on the obesity MOA chess board.

They have made this look easy. Tirzepatide is the best double incretin and has long-term patent protection.

Retatrutide isn't quite at the registration phase but looks to us likely to be the best triple incretin.

Orforglipron looks likely to be the best late-stage oral GLP-1 treatment for obesity.

Lilly picked up bimagrumab through M&A and just delivered data at ADA showing that this drug can preserve muscle when used with tirzepatide.

Lilly also has bet on eloralintide for an amylin agonist and has just delivered quite strong data at ADA. Lilly looks like it can win in amylin's, a development that we did not expect to see.

Lilly has other drugs in its early pipeline including an RNAi approach.

Putting aside Lilly's current strength, it is starting to look like it's going to be very difficult to compete against Eli Lilly in the future obesity drug market.

Lilly Positioning in Obesity Market Goes Beyond Portfolio

Willing to Enroll Patients

Based on its public disclosures, Lilly is planning to enroll 64,819 subjects in upcoming obesity clinical trials.*

Assuming $100k a subject, Lilly intends to spend north of $6bn on clinical trials.

Novo doesn't disclose its full plans for upcoming trials, particularly amycretin but it appears unlikely that they will be outenrolling Lilly.

Manufacturing

Lilly is using solid phase peptide synthesis rather than yeast expression like Novo Nordisk. This gives Lilly a huge manufacturing cost advantage. Lilly has been able to launch tirzapatide across the globe in 2025 while Novo has had to wait until it can catch up on manufacturing capacity.

DTC Platform

Lilly has also invested in a direct-to-consumer platform that is doing well. The DTC product offered by Lilly is the same as what is available in emerging Asia. It's less expensive but comes in vials at lower doses. This seems like a great strategy: limit cannibalization from compounders in the U.S. and generics in Asia with a genuine Lilly product that has substantially lower COGS than the higher dose U.S. pen product.

* Sum of patient counts in upcoming obesity trials outlined in its Q1 2025 earnings presentation.

Lilly's 3-Step Strategy to Dominate the $95 Billion Obesity Market

Hillary Bruek, *Business Insider*, July 7, 2025 (excerpt)

Investors are increasingly buzzing about the world's most valuable healthcare company, the one that they say has left its rivals in the dust. Danish drugmaker Novo Nordisk, the company that developed Ozempic, initially seemed unbeatable in the new market for injectable diabetes and weight loss medications. But ever since 2022, when Eli Lilly's tirzepatide was first approved for use in the US, Lilly's been steadily gaining ground.

Now, the company is developing a menu of other obesity drugs that could cater to anyone. There's a pill for weight loss instead of an injection. There are drugs that tap into new appetite-regulating hormones; an antibody injection to protect muscles while burning up excess fat.

So, we caught up with Eli Lilly Executive Vice President Ken Custer, the man overseeing it all. Custer is the new president of Lilly's cardiometabolic health division, and in a recent one-on-one with BI, he shared the strategy behind the company's success so far and how they plan to maintain their big lead in the long run.

Eli Lilly is set to dominate the market by 2030.

1. Speed: 'This ratchet mindset' drives Lilly to develop drugs faster and faster

Eli Lilly CEO Dave Ricks shared some of the secrets behind the big speed up that's shifted the company from an 11-year average time to market (when he first became CEO in 2017) to a six-year average now.

"We really track things very carefully on speed," Ricks said in an interview last October on the "All-In" podcast. "The big idea is like this ratchet mindset that every time we beat a timeline, that becomes the new norm. We just re-benchmark internally."

Case in point: It took about two decades to get Trulicity, Eli Lilly's first GLP-1 drug, on the market. Tirzepatide? About eight years — "blistering speed," Custer said.

2. Convenience: a cheap(er) pill to rival Ozempic

Eli Lilly is in the late stages of developing the first Ozempic-like pill, designed to be just as strong as Novo's injectable drug. The drug, orforglipron, could be available as early as 2026.

There are only about 8 million people currently on Mounjaro, Ozempic, Wegovy, and Zepbound in the US, which speaks to both the high cost of the injectable drugs and the supply bottlenecks.

"The injectable GLP-1s are wonderful medicines, but manufacturing those medicines is hard," Custer said. "The factories that you have to use to do the sterile filling of the vials, the syringes, the devices, the cartridges are extraordinarily hard to build and operate."

3. Creating a laundry list of new options to get ahead

The north star of Eli Lilly's strategy now is variety — developing a broader range of options for consumers than any of their competitors. "If you have a billion people around the world or more living with overweight or obesity, they're not all going to be helped by one medicine," Custer said. "We see this segmenting it into several logical categories."

Source: https://www.businessinsider.com/eli-lilly-3-step-strategy-dominate-95-billion-obesity-market-2025-7

Lilly Versus Novo Nordisk

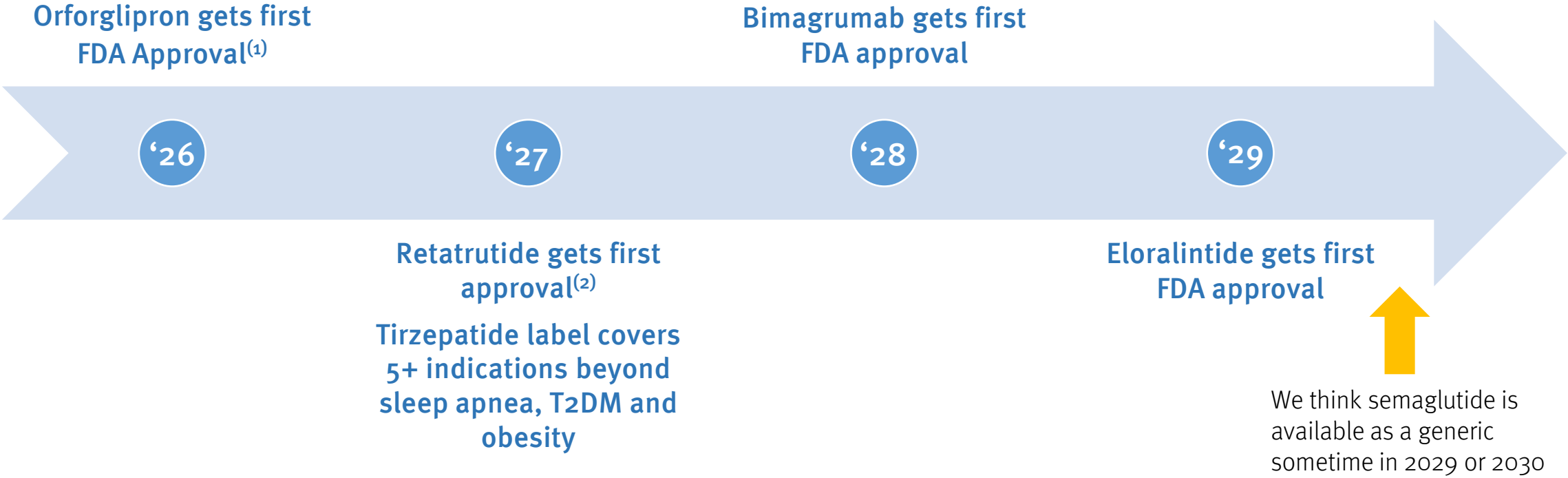
Lilly has been highly focused on delivering on its obesity franchise and appears to have outgunned Novo Nordisk. Its shares have returned 137% in the last three years while Novo has returned 26%. Both companies know the obesity and diabetes field really well and Novo continues to build up its early pipeline. However, Novo's core bet on CagriSema turned out to be the wrong one. We think the explanation is simple enough based on the data shown in this deck on amylin analogues: cagrilintide is not that good of an amylin analogue – at least based on the data we can see. In other words, the idea of a GLP-1/amylin double was good, but the implementation did not quite hit the mark. At this point, it looks like it will be difficult for Novo to catch drugs like orforglipron and retatrutide with its Cagrisema franchise. To make matters more challenging, Novo has entered into a settlement with generic companies for U.S. entry into the semaglutide market. The entry date for generics is not disclosed but we would guess it is near end of decade. Given this reality, it appears likely to us that Novo needs to focus on its next generation of products. It is possible that amycretin could still work out for them. Amycretin is Novo's best hope for competing against Lilly in the next five years. However, this drug has yet to go through a large multi-center study so it is hard to handicap how it will compete against Lilly's upcoming pipeline. Novo also has a number of early pipeline bets that look quite interesting, so it is still too early to count them out for the post-2030 period.

Eli Lilly and Novo Nordisk Share Price Evolution, July 1, 2023 to July 1, 2025

Source: CapitalIQ

Lilly's Near-Term Timeline and the Competition

Eli Lilly's strategy in obesity is to have a broad portfolio of best-in-class assets that gets to market well ahead of competitors. Our sense based on the timeline outlined below is that other players in the field are going to have a tough time getting established in the marketplace given Lilly's positioning. Lilly is betting big (spend over $10 billion on trials, development and CMC) making it very tough for others to enter and take share. By the time semaglutide goes generic (less than five years from now) Lilly appears likely to have a great triple incretin in the market, an excellent oral option, a muscle enhancing drug and a very competitive amylin analogue. The conversation will quickly turn to commercial elements. Competitors, including a number of the players with highly competitive Chinese sourced molecules may still be able to thrive via alternative commercial models or clinical differentiation. If we had to pick a few competitors out of the pack to take on retatrutide it would likely be either Kailera's HRS9531 (GIP/GLP-1 agonist) which has posted 36-week weight loss and tolerability data that is surprisingly similar to retatrutide in a large clinical or Viking's VK2735 which has posted some of the best 12-week weight loss we have seen to date. The various biased incretin agonists from companies like Metsera and Roche also look interesting, but we have yet to see longer-term clinical data on these molecules.



(1): https://www.reuters.com/business/healthcare-pharmaceuticals/lilly-expects-orforglipron-obesity-results-third-quarter-2025-06-21
(2): https://www.primetherapeutics.com/glp-1-pipeline-update-may-2025

Parallels to Development of the Oncology Market

In recent years, the key to thriving in oncology has been capturing rights to the backbone therapy, capturing front-line patients and then building out the space of combinations with the backbone to maximize market share. A very similar dynamic is now playing out in obesity.

There are several interesting parallels between the current development of the obesity drug market and that in the past for oncology drugs. Of course, the underlying disease states are different, the players are different, and the evolution has not been the same. But consider these similarities:

1. One player that emerged dominant in early days lost out to the #2 player. In oncology, BMS was the first to develop the PD-1 inhibitor and then Merck came along with Keytruda® and outspent BMS on clinical trials. The consequences have been clear. Last year, Keytruda generated $30 billion in revenue while OPDIVO generated $10 billion. Merck has effectively defined Keytruda as the **backbone therapy** in most solid tumor cancers.
2. Similarly, Novo Nordisk emerged with semaglutide and saw itself as a dominant player with sema as the **backbone** obesity therapy. Two years ago, when we looked at the obesity market closely, we saw Novo as the most likely long-term dominant player, positioned to run against Lilly step for step with its emerging CagriSema franchise. We believed that Amgen was likely going to become the #2 or #3 player. Instead, Lilly has outspent Novo on pipeline and clinical studies to support its pipeline. Lilly's obesity pipeline today, anchored by retatrutide, orforglipron and eloralintide looks to us likely to tower over Novo's pipeline for years to come.
3. Then, in oncology, the strategy started to shift about 30 months ago. We saw Merck go out and start to scoop up ADCs like the Kelun TROP2 – after Gilead had done its Immunomedics deal. Merck, indeed, focused on building out the space of all key combinations that would allow it go front line with a giant deal with Daiichi-Sankyo. The idea was that Merck would combine its PD1 antibody with the various ADCs to create front line combo products that would block competition. BMS started to follow the same strategy but, in retrospect, was too spread out following the Celgene acquisition. BMS seemed to be chasing everything in virology, immunology and oncology all at once and while it brought in some good products that would complement OPDIVO® like the Systimmune HER3 x EGFR bispecific, it didn't follow such a comprehensive strategy as Merck in oncology which seemed to be following the Lilly playbook of making a "bet on every square of the chess board".
4. Then out of the blue, Summit Therapeutics picked up a PD1 x VEGF bispecific from Akeso Pharma and quickly moved into Phase 3 position with this molecule. Summit has shown that this class outperforms PD1 antibodies alone in the most important indication in oncology – NSCLC. In recent months we have seen all major players in oncology pick up a similar bispecific. These include BMS, Merck and Pfizer. We read in the news that AZ is likely to be next. If you will, Summit redefined the backbone therapy for the bulk of solid tumor oncology drug players.
5. Today, Lilly has redefined the backbone therapy with retatrutide which looks very likely to surpass semaglutide and tirzepatide as the all-time market leader. This happened after tirzepatide set the standard as the most effective obesity therapy sometime around 2023. Lilly today looks a lot like Summit did a few years ago. It stands alone with a really good backbone therapy. But it also looks like Merck does today in oncology. It has made all the right bets on combo therapies (an activin drug, an amylin drug etc.).
6. Lilly has emerging competitors for sure. Metsera and Roche have bet on biased agonists of GLP-1. AstraZeneca, Merck and Roche have bet on going the oral route but have to be able to catch orforglipron etc.

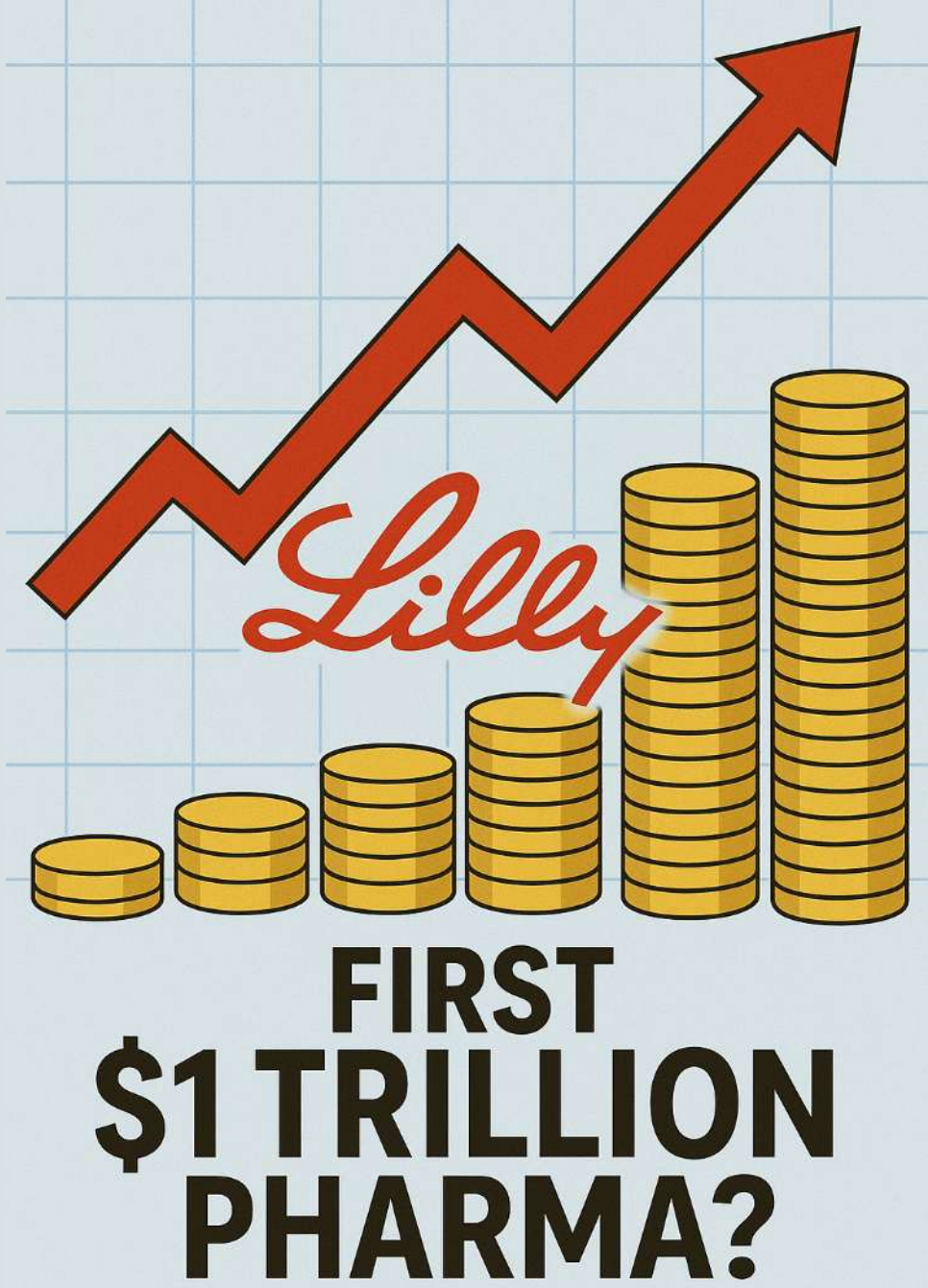
Does Lilly Become a Trillion Dollar Pharma?

As we write this in July 2025 Eli Lilly's market cap is $740 billion. We have been surprised that its market cap has not gone up more after it delivered so much great data at the ADA conference. Perhaps investors didn't notice. Or, more likely, investors have been so distracted by what is happening at the political level with our industry that they simply haven't paused to absorb the financial implications of Lilly's obesity portfolio. In this report, we are arguing that:

1. The end market revenue opportunity in the United States for obesity drugs is at least $200 billion and, very likely, much more.
2. The end market revenue opportunity *outside* the U.S. is also quite large – easily over $100 billion and, more likely, over $150 billion.
3. Eli Lilly has an exceptionally strong portfolio that competes well on every square of the strategic chess board in the obesity field. Lilly is well positioned to take the lion's share of the market.

Let's be a little bit extreme and suppose that generic semaglutide enters the market in 2029 and costs less than $100 monthly (a pessimistic assumption). Further, lets suppose that major governments around the world remain hesitant to reimburse obesity drugs at anything like today's prevailing prices despite stunning upcoming outcomes data. Even in this downside case, we think it is quite likely if not inevitable that Lilliy's market cap goes over a trillion dollars. Putting patients on retatrutide plus an optional amylin agonist or muscle drug, we think, would be a highly compelling market opportunity that should garner well over $100bn in revenue given the market size. This should be enough to propel Lilly's market cap over $1 trillion.

The interesting part is that there is room for the valuation to go well above $1 trillion if Lilly can continue to innovate well, execute well and have a little luck along the way.



The Elephant in the Room: Entering the Obesity Drug Market is Going to be Challenging

A company that is in Phase 2 today could reasonably expect to enter the obesity market by 2029 or 2030. That competitor is going to have compete against a full panoply of Lilly drugs and generic semaglutide. They may also have to face off against a great combo oral (if Novo can replicate the early results seen with amycretin in upcoming Phase 3 studies).

The importance of this year's ADA conference is that with Lilly's bima and elora data, the music just stopped in the competition game called obesity musical chairs. And there might not be that many chairs left for competitors to sit in. This perspective is quite different than that expressed as recently as a year ago when the prevailing view was that the obesity market was in "early innings."(1)

Generic semaglutide can reasonably be expected to be available for about $60 a month.(2) Sema is quite a good product that consumers love. At 48 weeks in clinical trials of semaglutide, patients lose well over 10% of body weight versus placebo. We have also heard talk of generic Rybelsus® entrants which will make the orals field a tough place to enter as well. Semaglutide is the product that broke open the obesity market. So, any new entrant to the market must have a product that will be sufficiently better than semaglutide to justify a premium price to 10%+ weight loss that costs less than $800 a year.

We believe that, at this point, one needs to be very sober when entering this gigantic market. Our view is that it is going to be difficult (albeit possible) to succeed in a world where Lilly offers great premium products, has a DTC platform and generic semaglutide is available by end of decade. A further consideration is that consumers are increasingly comfortable with injectable products given how unobtrusive today's pens have become. Our sense is that the patient's desire for orals while still present isn't nearly as strong as surveys suggested a few years ago. Further, the manufacturing cost advantage of orals will become less relevant given how inexpensive generic semaglutide is going to be.

It strikes us that the notion that being the second to fifth entrant with an oral or a triple G type product will be enough to make money against a drug like orfo or retatrutide is challenging because the window of time before semaglutide goes generic is so short and Lilly has such an opportunity to build the market and associated contracting strategies ahead of the competition.(3) We hear the many stories about the benefits of long-acting drugs or various incretin variations or orals.

The prevailing view has been that the market will leave room for many types of competitors. We ourselves have advocated this perspective in our 2023 and 2024 reviews of the obesity market. As we assess the commercial picture in mid-2025 we are less optimistic about much of today's pipeline. It's our belief that new entrants are going to need to adopt strategies that are far more disruptive and radical than much of the incremental innovation found in today's obesity pipeline.

(1) See, for example, https://www.statnews.com/2023/09/07/weight-loss-drugs-biotech-novo-lilly/.
(2) See a story about the Canada price for generic sema: https://dailyhive.com/canada/cheaper-ozempic-variations-canada. This is before competition heats up so the price could drop more.
(3) It is true that, historically, being best-in-class has been better than being first-in-class but in this case the first-in-class drugs appear to be quite good.

Key Competitor Bets on the Table

Company	Strategy	Key Drugs	Current Phase	Delivery Approach	Phase 3 Readouts (Stifel estimate)	Approval Date (Stifel estimate)	Key Features / Notes
AMGEN	Market a monthly antibody that works well	MariTide	Phase 3	SC	2027	2028	Emerging trade-off between efficacy and tolerability looks challenging. Will try a longer run-in for Phase 3 studies and could still pull it out. Emerging undisclosed oral portfolio adds potential to obesity strategy.
AstraZeneca	Market a competitive daily oral GLP-1 and LA amylin	AZD5004 / AZD6234	Phase 2b	Oral	2028	2029	AZ is betting big on its oral GLP-1 licensed from Eccogene. It's long-acting amylin also has promise but could be interesting in an increasingly competitive marketplace. On track for an approval with the GLP-1 in 2029.
kailera	Beat retatrutide on efficacy	KAI-9531	Phase 3	SC	2027	2029	Data look good and agent is advanced. Oral program on track to hit in 2030. Looks like the best positioned competitor vs. Lilly and avoids baggage of a third MOA in the triplet. Key for them is capital and speed of enrollment. Hengrui a huge plus.
MERCK	Market a competitive daily oral GLP-1 in combination with other approaches	HS-10535	Phase 1	Oral	Unclear	End of decade	Merck has not enunciated its strategy, but our best guess is that they intend to combine the Hansoh oral GLP-1 with other oral agents such as its PCSK9 drug or other undisclosed targeted drugs.
Metsera	Biased GLP-1 and amylins with monthly dosing	MET-097i / MET-233i	Phase 2b	SC	2028	2029	Differentiated offering that could carve out market share for combo of biased LA GLP-1 and amylins in a Lilly centric world. Somewhat similar to Roche strategy. The combo, however, is in Phase 1 now so has a very long way to go.
novo nordisk	Market a competitive SC combo GLP-1/ amylin drug. Also has oral.	Amycretin	Phase 2	SC / oral	2028	2030	Like Kailera the data for SC amycretin look really good. The question is how well this drug does in larger multi-center Phase 3s. Novo still could pull it out here and has a deep portfolio of early obesity drugs.
Pfizer	Oral GIP inhibitor	PF-07976016	Phase 2	Oral	2028	Early 2030s	Pfizer is developing a host of oral bets for obesity but has yet to declare its full strategy. Pfizer apparently has a meaningful portfolio of undisclosed obesity drugs in early development.
REGENERON	Dual incretin plus muscle drugs / GPR75 drugs	Garetosmab / Trevogrumab / GLP-1 / GIP	Phase 2	SC / IV	2028 to 2029	2030	Regeneron has not yet clarified its strategy but recently brought in a triple incretin which could obviously be developed with its muscle enhancing drug portfolio. Hasn't said much on rest of portfolio - which could be interesting.
Roche	CT-388 / Petrelintide	CT-388 / Petrelintide	Phase 2	SC	2028	2029	Roche has a very good bet with a biased GLP-1/GIP that could outperform retatrutide in Phase 3 studies. Roche intends to combine this drug with Zealand's amylin agonist going for deep weight loss.
VIKING THERAPEUTICS	GLP-1 / GIP dual agonist	VK2735	Phase 1	SC and oral	2028	2029	Viking has a highly promising drug in VK7395 and is now starting its Phase 3 program. It is now on track for an approval at end of decade. Upcoming clinical data will define its potential to compete against Lilly.

Source: Stifel research of various company's disclosures.

Imagine it is 2030: Scenario of a Lilly-Centric World

Lilly will have tremendous contracting leverage and global reach if it can deliver its visible pipeline. We imagine that the market will segment into "good, better and best" submarkets that given consumers a tradeoff between spend and drug features.*

Semaglutide is Generic

This molecule is incredibly cheap (like $600 a year) and, miracle of miracles, with the lower cost, the U.S. government starts to cover this drug as it's a big money saver. Self-pay use goes through the roof augmented by a gigantic DTC market. USPTC finally determined that everyone overweight should get these and so private insurance coverage is also much better. Today's obesity drug craze looks small time as routinized use of GLP-1's takes the U.S. by storm and starts to really make a dent in chronic disease for the first time.

Good Treatment Available for All

Tirzepatide is Lilly's "second SC molecule"

Lilly fights generic share by offering tirzepatide in vials at doses of up to 7.5mg and ramps up its LillyDirect platform in a big way. This is a better product giving more weight loss (approx. 16% WL a year) but at a higher price than generic. The idea is that the younger weight-minded consumer can reach in the pocket a little to get the better drug at a price of somewhere around $3000 a year. Likewise, budget minded employers can offer their employees a better drug than semaglutide. Lilly makes tens of billions in this market. Patients get to enjoy the lower nausea rates of tirzepatide over semaglutide.

Better Treatment at a Reasonable Price

Retatrutide is Lilly's "first SC molecule"

Retatrutide enters the market around 2028 and is offered at a premium price only (e.g., around $8000 a year for the top dose). This drug delivers 20%+ WL in a year. The employer who really cares covers this. The discerning consumer who can afford the drug pays this price. Importantly, Lilly runs combo trials of retatrutide with bimagrumab and offers reta with bima at a single premium price. Similarly, Lilly offers reta in a fixed dose with elora plus bima at a single premium price. Wealthier consumers who care about body composition and keeping weight off opt for this combo approach.

Best Treatment at a Premium Price

Orforglipron offered at a premium price

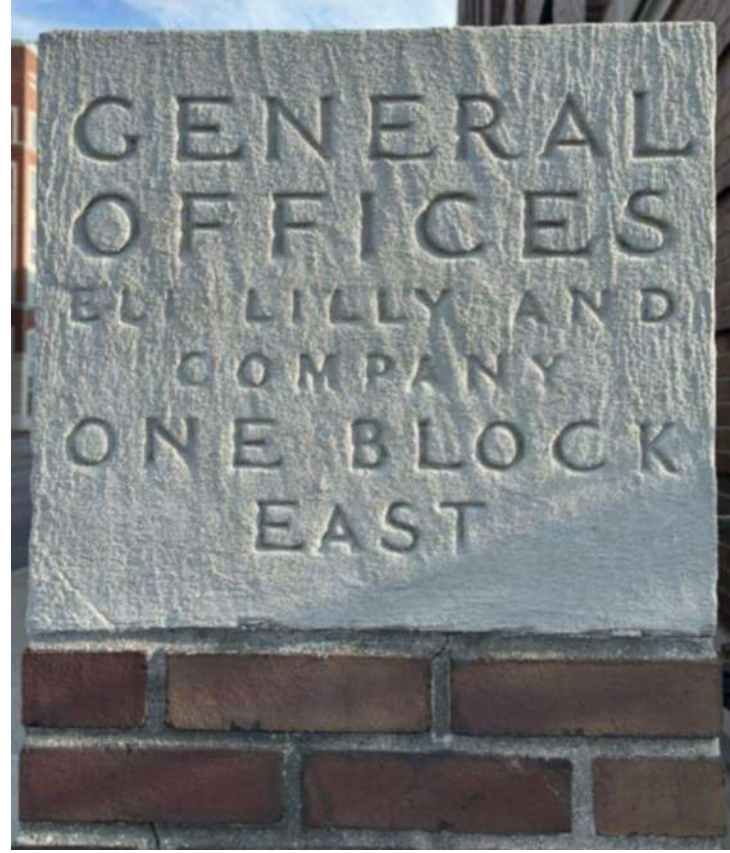
Something like 30% to 50% of consumers prefer an oral with slightly less weight loss potential to the injectables like tirzapatide and retatrutide. These consumers prefer orfo and are willing to pay the $8000 a year that this product costs to make. A dogfight starts to brew as companies with true small molecule GLP-1's like AZ, Metsera and Roche start to enter the market and offer to bring prices down with drugs that do a good job of balancing efficacy and tolerability. This puts downward pressure on pricing for orals and it looks like orals start to gain share from injectables.

Oral Option Starts at a Premium Price

Market Entry Strategies

We see a dozen or so possible strategies to compete going forward:

1. Product that does not cause nausea (all of Lilly's main obesity products are associated with some nausea). A subset of consumers care about this.
2. Create a product that has less post-treatment rebound (insurance companies will love this because today they are committing to long-term cost when they cover incretin drugs).
3. Create a product that beats retatrutide straight on based on substantially better efficacy and side effects (the quad incretin from Pep 2 Tango or triple oral from Protagonist look like possibilities). The issue, obviously, is that 22% weight loss in a year with reta is already so good.
4. Do a better job in the self-pay market (as layed out in the previous section).
5. Create a product that has benefits that go beyond just weight loss (e.g., an oral GLP-1 with an oral PCSK9). One can imagine various types of oral combo pills as an effective competitive approach.
6. Create a product that has higher adherence through less frequent dosing (e.g., a biannual RNA approach like inclirisan). This remains an interesting area, and we might still expect better long-term results with Roche's CT-388 which is a biased agonist or MariTide, which is a once monthly approach.
7. Go very low cost with a drug that can compete against generic semaglutide on features and price. Perhaps a population health type contracting approach (e.g., inclirisan in the UK). Metsera seems like a company that could thrive via population health contracting strategies.
8. Create a product that does not require a prescription (some type of OTC, digital product or nutritional). Our sense is that many consumers would prefer a good OTC approach to weight loss.
9. Create a better muscle drug (while good, bimagrumab, is not quite as good as Lilly's other drugs).
10. Create a product that would be a good add-on to a triple-G like retatrutide that is not an amylin analogue. The add-on would need to add enough value to justify its price and the inconvenience of taking a second drug.
11. Adopt a harm reduction strategy that beats the harm reduction from either tizepatide or retatrutide (going to be hard to do). See our extensive discussion from a year ago on this topic.
12. Adopt a strategy that resets the body's overeating behavior –so called "fatty brain". There appear to be a number of good strategies here but these are, as yet, largely undeveloped.



Lilly is a great competitor but perhaps not an impossible one to beat. The next section of this presentation focuses on strategies that might be able to disrupt the emerging Lilly-centric status quo in the obesity drug market.

Trend #4: Opportunities for Disruptive Innovation Growing

Alexandria Center for Life Sciences, South San Francisco, CA. Source: Stifel

Next Generation Drug Pipeline is Rich and Diverse

There are three ways to impact weight of a human: (1) cause the human to eat less (appetite suppression), (2) fail to store energy in food as fat or (3) cause the stored energy to be used less efficiently. A final approach to obesity involves no change in weight but instead looks to preserve muscle mass. We count 66 separate drug mechanisms that fall into one of these categories.

Appetite Suppressants (138 Agents)

Cannabinoid Agonist
DAT Antagonist
Duodenum Masker
GDF15 analogue
Ghrelin Inverse Agonist
GLP-1 Receptor Agonist
GLP-2 Receptor Agonist
Glucagon Receptor Agonist
Incretin: Amylin Analogue
5-HT2A receptor agonist
GPR40 receptor antagonist
Gut Blocker
IGF-1 Agonist
INSR Agonist
IRS2 modulator
Leptin sensitizer
Leptin analogue
MAS/Angiotensin System
Melanocortin 4 Agonist
Mucin Enhancer
NPYR2 Agonist
Nutrient receptor agonists
PTP1B inhibitor
Psychedelic
PYY Agonist
Serotonin 6 Antagonist
Serotonin-2c Agonist
Spirolina modulators
Taste Receptor: TASR2

Energy Storage Blockers (24 agents)

Acarbose
Delta-5-Desaturase
GIP inhibitor
HDAC11 inhibitor
INHBE Modulator
Lipase Inhibitors
LPL Activator
MGAT2
Microbiome modulators
mir-515-5p modulator
Mots-c Modulator
RASP Modulator
SLC13A5 protein inhibitors
SPTBN1
VEGF Inhibitor

Energy Usage Efficiency (40 agents)

Adenosine A3 Agonist
Adipocyte Biology: IL-22
Adipogenesis: GPR75
AMPK activator
Apelin Receptor Agonist
FGF21 agonist
Glucagon RA
Inflammation: NLRP3
IP6K Modulator
Lipolysis Agonists
MAP/ERK modulator
mir-22-3p modulator
Mitochondrial Uncoupler
Nuclear Rec: ERR Agonist
SCD-1 Inhibitor
SHIP1 agonist
Sirt1 Activator
THRB Agonist

Muscle Preservants (16 agents)

Activin receptor II inhibitor
AUF1
IGF-2 Fusion Protein
Myostatin inhibitor
SARM
Testosterone Replacement

Selected Next Generation Approaches to Obesity in Development

These are just a few of the promising novel approaches in development to improve upoon obesity pharmacology by 2034.

= our view on this category has improved in the last year

= our view has stayed the same

= our view has gone down

Amylin Agonists

Amylin affects glucose by slowing gastric emptying through reduced glucagon secretion after eating, and by appetite suppression. Recent positive data from Novo Nordisk on its oral amycretin and CagriSema and Zealand Pharma's Petrelintide clearly show that amylin agonists can be additive to GLP-1 agonists. Amylin agonism is here to stay in the long-run.

Apelin Receptor Agonists

Apelin agonists, like BioAge's azelaprag, can control obesity by improving metabolism when combined with incretin drugs. Azelaprag is an oral small molecule that mimics apelin, a peptide hormone that's released during exercise. In preclinical trials, azelaprag has shown the potential to increase weight loss and restore muscle.

Biased GLP-1 Agonists

A major issue with GLP-1 agonists is that weight loss tails off over time. Many users report that the drugs initially work for them but become less effective in time. This is likely due to receptor internalization. Biased agonists from Roche, Metsera, Verdiva, Structure and others may beat internalization. Early results with CT-388 look highly promising.

CB1 Blockers

CB1 receptor inhibition lowers appetite and increases energy expenditure. Sanofi's rimonabant, an approved CB1, was pulled due to impact on CNS. More recently, Novo acquired Inversago which has a peripheral only CB1 blocker. This drug and a competing mAb from Skye are in Phase 2 studies. Corbus has Phase 1b data coming up in Q3 2025.

GIP Inhibitors

GIP antagonists hold promise by reducing insulin secretion, enhancing fat breakdown, improving insulin sensitivity, regulating appetite, and increasing energy expenditure. Amgen's MariTide contains a GIP inhibitor which shows powerful weight loss. Other companies developing drugs in this class include Antag, GMAX and Orion.

Glucagon Agonism

Glucagon agonism can help with weight loss through stimulation of lipolysis and increasing energy expenditure. Glucagon is a hormone produced by the pancreas that primarily works to increase blood glucose levels in the liver. Strong weight loss seen with pemvidutide, survodutide and mazdutide illustrates the potential of glucagon drugs.

GPR75 Antagonism

Genetic studies show that individuals with loss-of-function mutations in GPR75 have a reduced risk of obesity. GPR75 and its ligand 20-Hete are involved in appetite regulation, thermogenesis and improvement of glucose use. The pipeline of drugs in this area from Confometrx, Orion and Regeneron is early but highly promising.

Programmable Algae

Lumen Bio is delivering obesity drugs via spirulina, a form of photosynthetic algae. Lumen will shortly be reporting out on a clinical trial that should show high weight loss with an orally available, incredibly inexpensive to make drug that agonizes a key gut receptor. We see this product as one of the most significant threats to incumbent players in the market.

Muscle Preservers

Myostatin is a growth factor that negatively regulates muscle growth. It signals through the Activin receptor type II (ActRIIB). Blockers of myostatin or ActRIIB can increase muscle mass, an important need in obesity management. A related approach, SARMS, promote muscle protein synthesis. Data to date in this area from Versanis (Lilly), Veru and others is promising.

Nuclear Receptor Modulators

Nuclear receptor modulators such as ER, GR, LXR, FXR and PPAR control obesity by targeting receptors involved in the regulation of metabolism, energy expenditure, and adipogenesis. Compounds in development by companies such as Pelagos improve insulin sensitivity, reduce lipid accumulation, enhance fatty acid oxidation, and regulate appetite. Early and exciting area.

Source: Stifel analysis of internal obesity program database.

Key Background Conversations on Strategy and Pipeline

Orals: How Big Will They Be?

The role of orals for obesity was a big topic at the ADA conference this year. Not only are consumers becoming more comfortable with injectables given how small needles are but there is such a great diversity of upcoming injectable products to make one increasingly nervous about the idea that orals might take over the market.

Endocrinologists at ADA are very comfortable with the market as it is emerging now – a pen / needle centric world and argue that orals will only become preferred if their efficacy and tolerability matches injectables (a tall order indeed). In contrast, others see PCP participation in obesity drugs as key to maximizing value for the obese consumer and there is a view that primary care physicians will prefer to prescribe oral medications even if they aren't quite as good as the SubQ's. Indeed, there is a push underway to make GLP-1's frontline instead of diet and exercise. We think orals do become important but are unlikely to dominate the market anytime soon because of lower efficacy than available with the SC drugs. By analogy, we are seeing oral autoimmune drugs take market share from injectables but don't take over the market because they are less effective.

Do Longer Acting Drugs Really Matter?

Amgen, Metsera and the various RNA companies have been arguing that longer acting drugs will make a big difference for obese patients. Indeed, in the immunology market we have seen a long-acting IL-23 drug (Skyrizi®) do well. Skyrizi is excelling in a world where Humira® is available at a much lower cost. But the story is more one of efficacy. Trials comparing Skyrizi to Humira have favored Skyrizi. For example, in one study, 72% of patients on Skyrizi achieved 90% clearer skin compared to 47% on Humira. In our opinion, Amgen and Metsera will need to show superior long-term compliance and efficacy to take substantial share from Eli Lilly. We are quite optimistic about RNAi drugs in development for obesity (more on this later). These drugs seem to avoid the nausea issue. We have not seen human data yet but, if good, this could be a huge market for RNAi. A key question will come down to cost given how inexpensive obesity drugs are going to become. Inclirisan for cholesterol sells for around $6500 a year in the U.S. and has not done that well given how inexpensive statins are. Low volume RNAi drugs can cost more than $1000 a year to make but at higher volumes costs can come down. This will be critical for this drug class assuming efficacy is in the same league as incretins.

Outcomes Studies: Do They Matter?

A key aspect of Lilly and Novo's strategy has been the generation of datasets that show how effective semaglutide and tirzepatide are in reducing the consequences of obesity. These studies are crucial to obtaining government and private insurance reimbursement for these drugs.

These studies also motivate physicians to write prescriptions for their obese patients. Both Lilly and Novo have major studies reading out in the next 18 months that are likely to show further benefits from managing down obesity. This is particularly important where putting a patient on a drug can knock out a more costly therapy. For example, requiring a patient with sleep apnea to start on tirzepatide before getting a Resmed machine seems like a no-brainer and Medicare is starting to do just this. However, we are skeptical of the value of outcomes studies in the long run for two reasons: (1) semaglutide is going to go generic with massive documented benefit from outcomes studies – meaning that incremental approvals aren't going to help that much and (2) the DTC market is driven largely by aesthetic factors rather than documented outcomes. We see this segment ultimately becoming the largest part of the market.

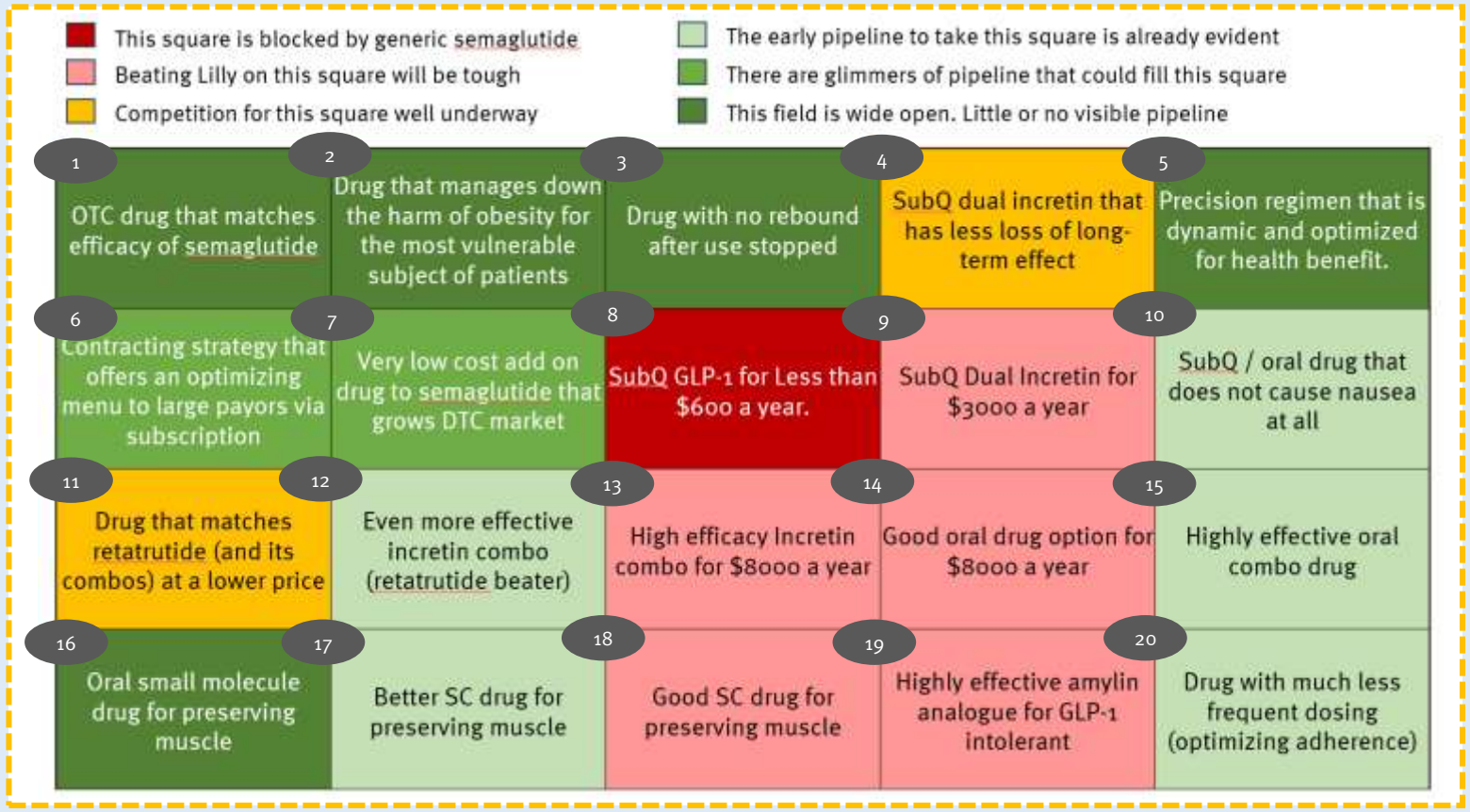
Open Spots on the 2030 Obesity Drug Strategic Chessboard

- This square is blocked by generic semaglutide
- Beating Lilly on this square will be tough
- Competition for this square well underway
- The early pipeline to take this square is already evident
- There are glimmers of pipeline that could fill this square
- This field is wide open. Little or no visible pipeline

OTC drug that matches efficacy of semaglutide	Drug that manages down the harm of obesity for the most vulnerable subject of patients	Drug with no rebound after use stopped	SubQ dual incretin that has less loss of long-term effect	Precision regimen that is dynamic and optimized for health benefit.
Contracting strategy that offers an optimizing menu to large payors via subscription	Very low cost add on drug to semaglutide that grows DTC market	SubQ GLP-1 for less than $600 a year.	SubQ Dual Incretin for $3000 a year	SubQ / oral drug that does not cause nausea at all
Drug that matches retatrutide (and its combos) at a better price	Even more effective incretin combo (retatrutide beater)	High efficacy Incretin combo for $8000 a year	Good oral drug option for $8000 a year	Highly effective oral combo drug
Oral small molecule drug for preserving muscle	Better SC drug for preserving muscle	Good SC drug for preserving muscle	Highly effective amylin analogue for GLP-1 intolerant	Drug with much less frequent dosing (optimizing adherence)

Matching Today's Pipeline to Key Future Market Opportunities

The good news is that there is plenty of spots left to compete in and there is pipeline out there that can be successful in the market, making room for more dealmaking and financings. However, if one analogizes this to the game of basketball, many of the dealmaking opportunities remaining are for "three pointers" – that is shots from higher risk spots on the court where the risk of the bet is high. Buyers need to be prepared to go into "heavy traffic" (e.g., crowded areas like amylin analogues) and fight it out or shoot from "far away" where the probabilized rewards may be higher but the odds of scoring are lower.



1 Better OTC

BrightSeed
Empros
Lumen

2 Harm Reduction

See our 2024 issue

3 No Rebound

Fractyl gene therapy
See our 2024 issue

4 Better Long-Term

Biased GLP-1s
GIP antagonism (possibly MariTide)
Possibly amylins
Metsera, Verdiva

5 Precision Approach

See pp. 61 to 63 of our May 30, 2025 issue.

6 Better Long-Term

Contracting strategies that optimize menu for government and employers (possibly Metsera)

7 Low-cost drug that goes with Gx semaglutide

Lumen, oral GIP's antagonists, oral amylins, GPR75's

10 No nausea drug

Lumen, AbbVie, oral GIP's antagonists, oral amylins, GPR75's, RNA therapies, various new MOAs

11 Retatrutide beater on price

Possibly Kailera or amycretin. Also Metsera, Brightgene, Regeneron

12 Retatrutide beater on features

Pep2Tango, Kailera or amycretin. Also Metsera, Brightgene, Regeneron are contenders. Phase 3 data key.

20 Less frequent dosing

RNA players like Arrowhead, Wave. Monthly players like Amgen and Metsera

17 Better SubQ drug for muscle

Biohaven, iBIO, Progen, Regeneron. Regerna Therapeutics

16 Oral muscle building drug

Veru, Lipocine, Orals that preserve muscle: Rivus, OrsoBio

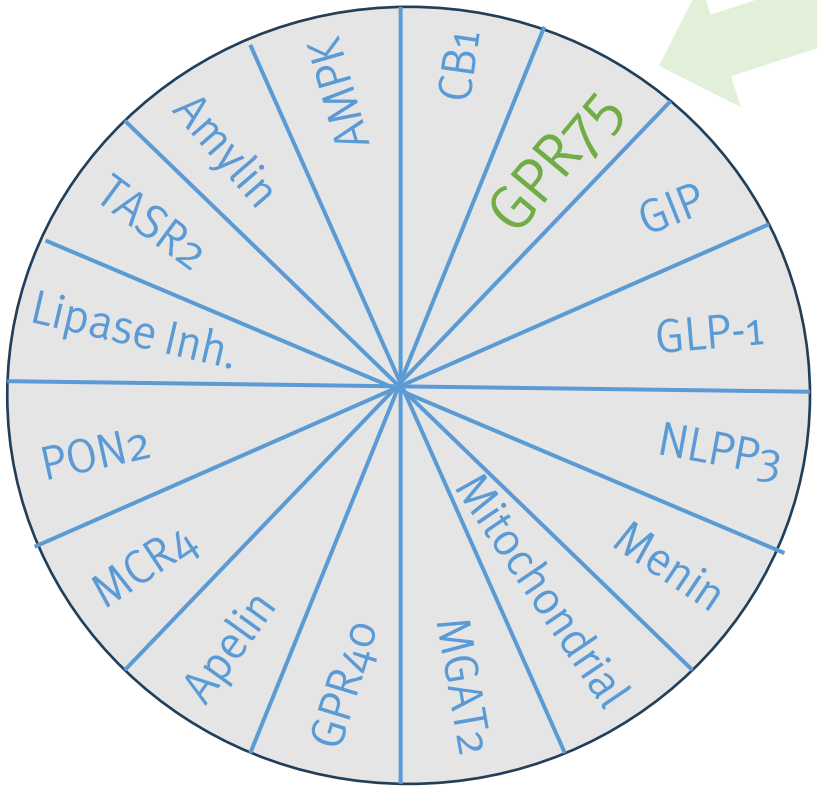
15 Oral combo drug

Lumen, Orion, AZ, Pfizer, Protagonist, Regeneron, Structure, oral GIP's antagonists such as oral amylins, RNA therapies, CB1s, various new MOAs

GPR75 Antagonists

The Promise of GPR75 Antagonists

The pipeline is full of oral obesity drug candidates in development.



GPR75

An exceptional target opportunity:

Heterozygous GPR75 knockouts in humans are substantially less likely to be obese.

Mutations that cause a disease do not necessarily identify the sole cause of a disease as there may be multiple causes of that disease. In contrast, mutations that protect against a disease, generally identify a *necessary* condition for the disease to occur. Discoveries of such mutations (like PCSK9) are rare.

The underlying way in which GPR75 functions substantially derisks pharmacologic strategies for this target.

GPR75: A Natural Target for Obesity

TARGET BACKGROUND

G-Protein Receptor 75 is an orphan GPCR

A 2021 genomic study of 640,000+ humans sponsored by Regeneron found that individuals with at least 1 inactive copy of the GPR75 gene have ***lower BMI*** and, on average, tend to ***weigh about 12 pounds less*** and face a ***55% lower risk of obesity*** than those without the mutation.[1]

Individuals with *GPR75* GENE MUTATION

Novel mechanism of action which selectively targets fat mass and not lean mass.

We are aware of at last three companies developing GPR75 antagonists (Regeneron, Orion and Confo). We believe that Orion is particularly well positioned to be the first with human data.

We believe that multiple pharmas and VC's are developing GPR75 antagonists as well. In general, the pipeline of undeclared oral drugs seems quite high presently.

1. https://www.science.org/doi/10.1126/science.abf8683

Protective Mutations are Unique

Not all known protective mutations have led to efforts to replicate the effect of a mutation with pharmacology.

However, all pharmacology that has been taken into the clinic to replicate the effect of a protective mutation has been successful thus far.[1]

Regeneron has described drugs that replicate “loss of function” protective mutations as having “superpowers” – pointing to ways that a drug is highly likely to be effective.[2]

We like to describe protective mutations to pointing to a highway interchange. If you can take out the interchange, you can shut down the entire highway system by removing redundancies (see picture). In contrast, gain of function mutations may point to a pharmacologic approach but when replicated with drugs often do not work. Similarly, knocking out one part of a freeway doesn’t shut down the system.

Examples of successful drugs targets first identified as protective mutations: PCSK9 (Repatha®), CCR5 (gene edit), T119M (acoramidis).

[1] See Musunuru K, Kathiresan S. Genetics of Common, Complex Coronary Artery Disease. Cell. 2019 Mar 21;177(1):132-145 and MacArthur DG et. Al., A systematic survey of loss-of-function variants in human protein-coding genes. Science. 2012 Feb 17;335(6070):823-8.
2. See https://www.regeneron.com/stories/protective-genetics.

GPR75 Pathway / MOA Elucidated in Late 2024

Jiang et.al., "Adopting GPR75 in treating obesity: unraveling the knowns and unknowns of this orphan GPCR," *Trends in Cell Biology*, Jan 9, 2025.

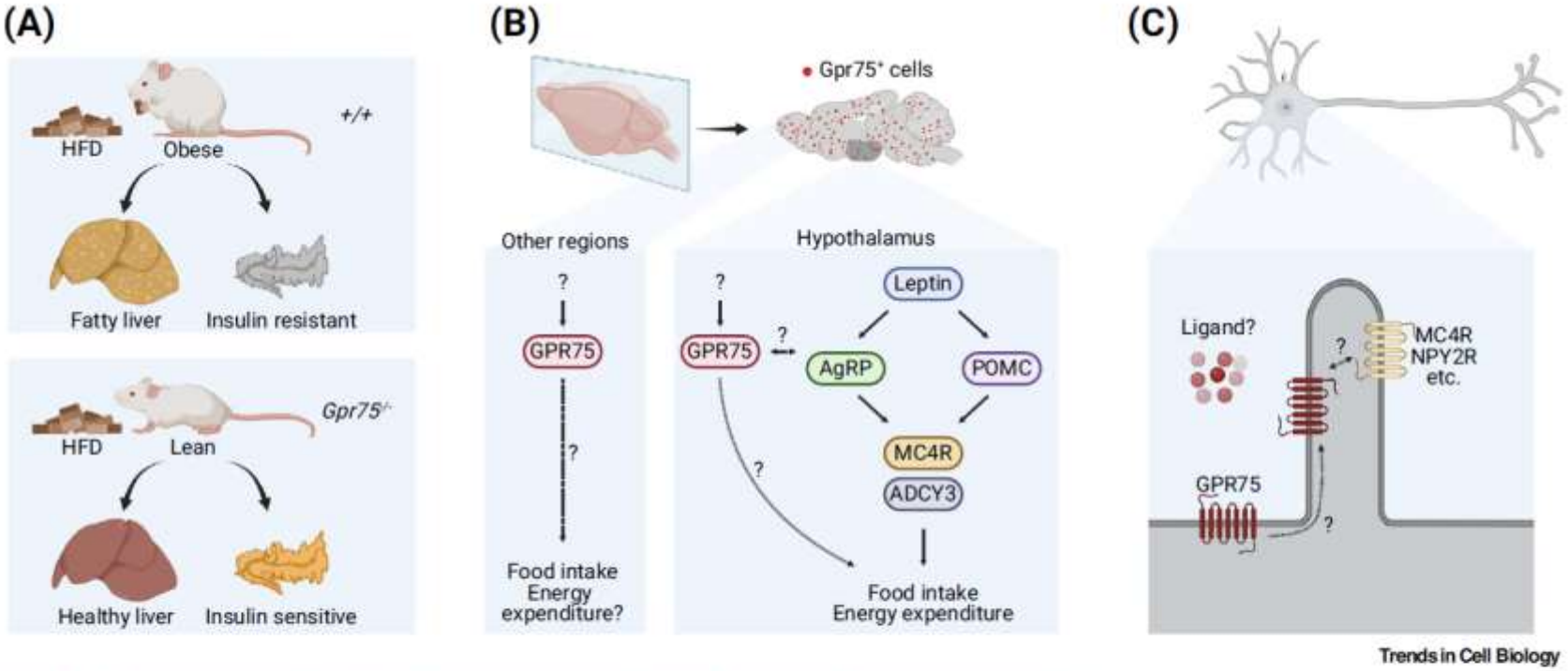


Figure 1. The emerging role of G protein-coupled receptor 75 (GPR75) in regulating energy homeostasis. (A) Wild-type (+/+) mice on a high-fat diet (HFD) gain excess weight, leading to obesity, fatty liver disease, and insulin resistance. By contrast, *Gpr75* knockout ($Gpr75^{-/-}$) mice consume less HFD, reducing fat accumulation and fatty liver and improving insulin sensitivity. (B) *Gpr75* is highly expressed in the brain, particularly across various neurons, including the hypothalamus. The leptin–melanocortin pathway is a well-established central regulator of food intake and energy expenditure. Leptin activates its receptor on pro-opiomelanocortin (POMC) and agouti-related protein (AgRP) neurons, which release α-melanocyte stimulating hormone (α-MSH) and AgRP, respectively. These signaling molecules act on melanocortin 4 receptors (MC4Rs) in second-order neurons, influencing adenylate cyclase 3 (ADCY3) activity to regulate energy homeostasis. Since $Gpr75^{-/-}$ mice do not resist obesity in leptin-deficient (*ob/ob*) or *Adcy3* mutant mice, GPR75 likely operates in a pathway parallel to leptin–melanocortin signaling.

Cilia in the brain are tiny, hair-like projections from cells that play critical roles in signal transduction.

It has been understood for several years that neuronal cilia heavily influence eating behavior and certain ciliopathies lead to morbid obesity. Interestingly, the paper at left by Jiang et.al. reports that GPR75 plays a similar role in the brain and the hypothalamus, promoting eating.

Further, the path by which GPR75 KO might see suppression of appetite works through cilia.

Source: https://www.cell.com/trends/cell-biology/abstract/S0962-8924(24)00259-9

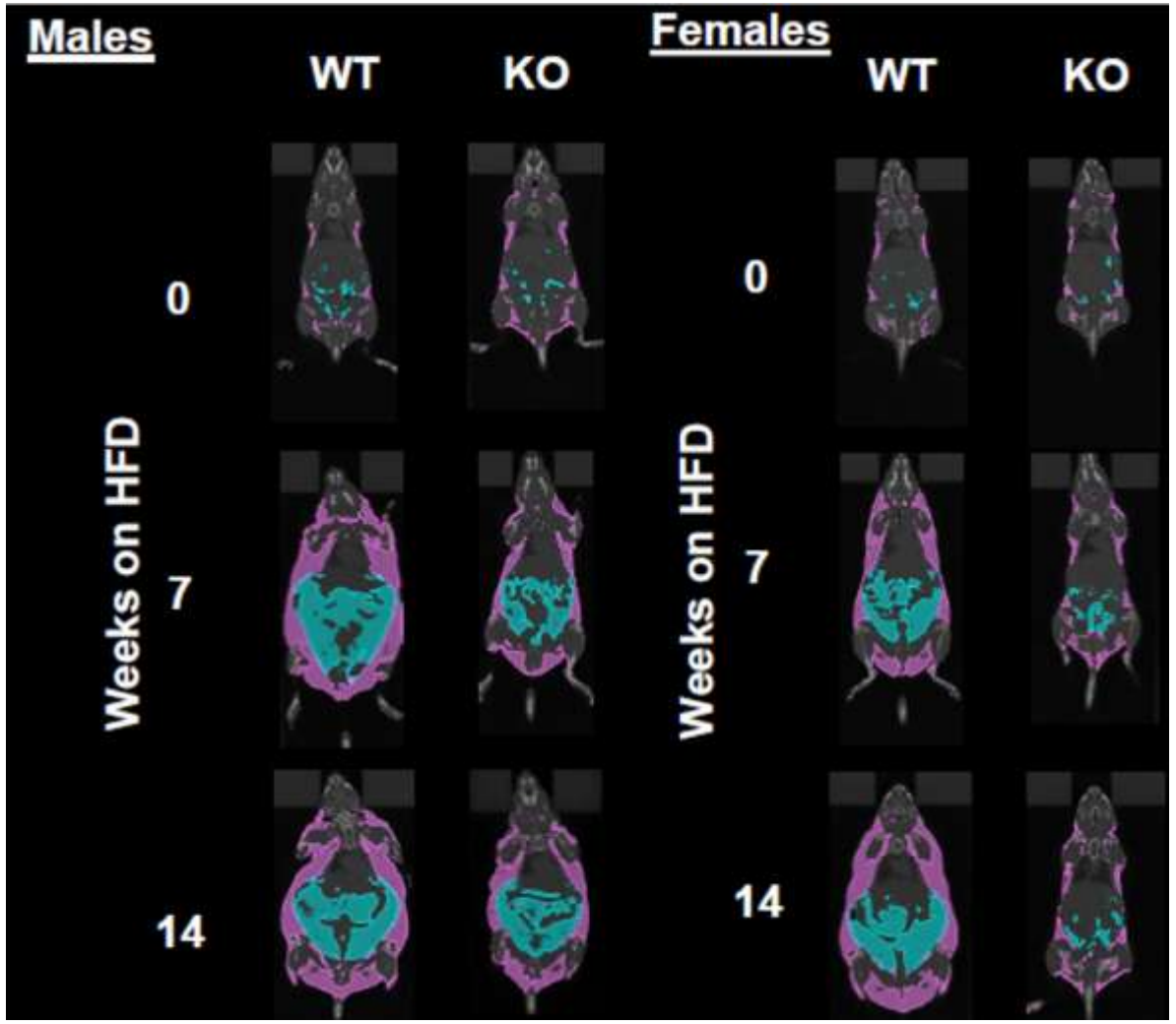
GPR75-Deficient Mice are Protected from High-Fat Diet Induced Obesity

Assessment of adipose tissue volume by microCT showed striking differences between WT & KO GPR75 genotypes.

In both male and female WT, the volume of visceral (VAT) and subcutaneous (SAT) adipose tissues increased in response to HFD feeding, whereas the KO in both sexes was largely attenuated.

Assessment of fat-free volume indicated no differences between WT and KO

WT= wild type KO= knock out

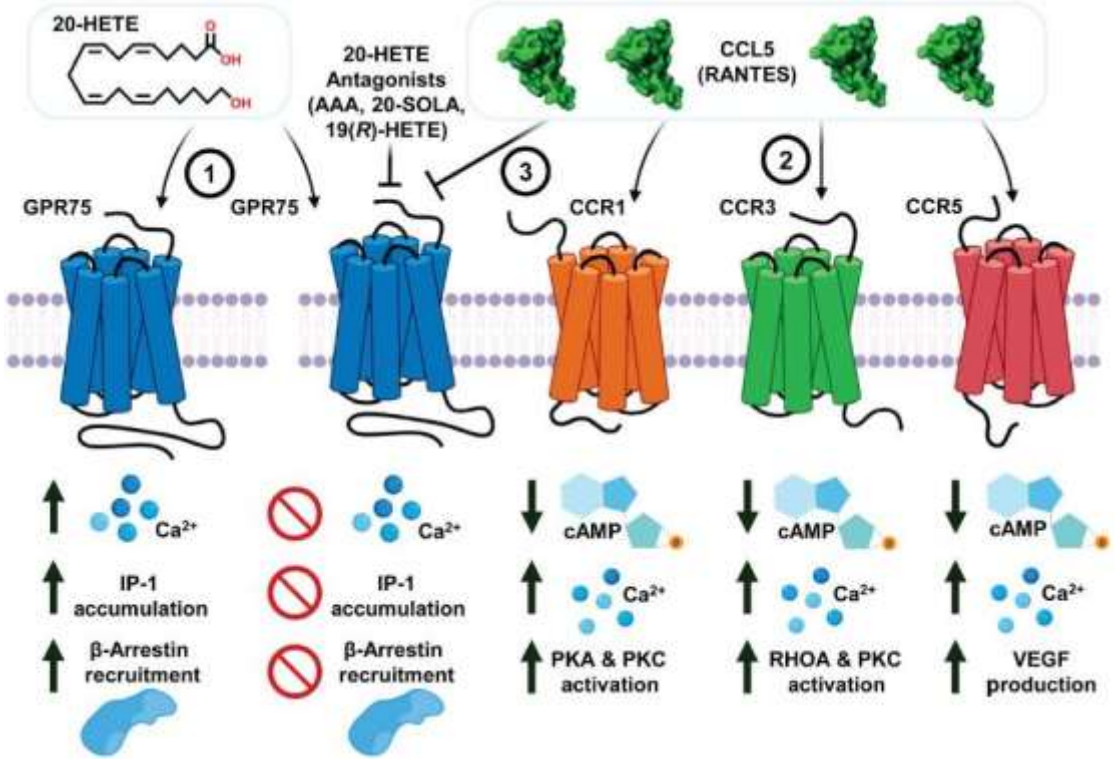


Source: Schwartzman et al. Obesity 2023

20-HETE is the Principal Ligand of GPR75

Pascale JV, Park EJ, Adebesin AM, Falck JR, Schwartzman ML, Garcia V. Uncovering the signalling, structure and function of the 20-HETE-GPR75 pairing: Identifying the chemokine CCL5 as a negative regulator of GPR75. *Br J Pharmacol.* Sep 2021, pp. 3813-3828.

The G-protein-coupled receptor GPR75 (Gq) and its ligand, the cytochrome P450-derived vasoactive eicosanoid 20-hydroxyeicosatetraenoic acid (20-HETE), are involved in the activation of pro-inflammatory and hypertensive signalling cascades contributing to diabetes, obesity, vascular dysfunction/remodelling, hypertension and cardiovascular disease. Little is known as to how, where and with what affinity 20-HETE interacts with GPR75. PR confirmed 20-HETE binding to GPR75 with an estimated KD of 1.56 × 10-10 M. In GPR75-transfected HTLA cells, 20-HETE stimulated intracellular Ca2+ levels, IP-1 accumulation and β-arrestin recruitment, all of which were negated by known 20-HETE functional antagonists. Computational modelling of the putative ligand-binding pocket and mutation of Thr212 within the putative 20-HETE binding site abolished 20-HETE's ability to stimulate GPR75 activation. The chemokine CCL5, a suggested GPR75 ligand, binds to GPR75 (KD of 5.85 × 10-10 M) yet fails to activate GPR75; however, it inhibited 20-HETE's ability to activate GPR75 signalling. We have identified 20-HETE as a high-affinity ligand for GPR75 and CCL5 as a low-affinity negative regulator of GPR75, providing additional evidence for the deorphanization of GPR75 as a 20-HETE receptor.



Source: https://pubmed.ncbi.nlm.nih.gov/33974269/

GPR75 Drug Pipeline is Filling Out

Hit-to-Lead Stage

ConfometRx

Melio Bio

Lead to IND Stage

ORION biotechnology

REGENERON science to medicine

SHUIMU BIOSCIENCES

Phase 1

TAISHO PHARMACEUTICAL

(20-Hete inhibitor, abandoned)

Both Regeneron and Shuimu are generating highly promising GPR75 antagonist small molecules. Orion's pre-clinical animal data with their GPR75 peptide antagonist are highly impressive and suggest that drugs in this area are likely to work well for obesity.

There are also quite a few stealth GPR75 antagonist programs at present. It's striking to us how quiet competitors have been in this space, presumably to avoid creating any further competition.

Regeneron is pursuing three modalities to target GPR75:

- *siRNA collaboration with Alnylam*
- *Small molecule collaboration with AstraZeneca*
- *Antibody approach*

Orion Data Show Impact of GPR75 Inhibition in Mice

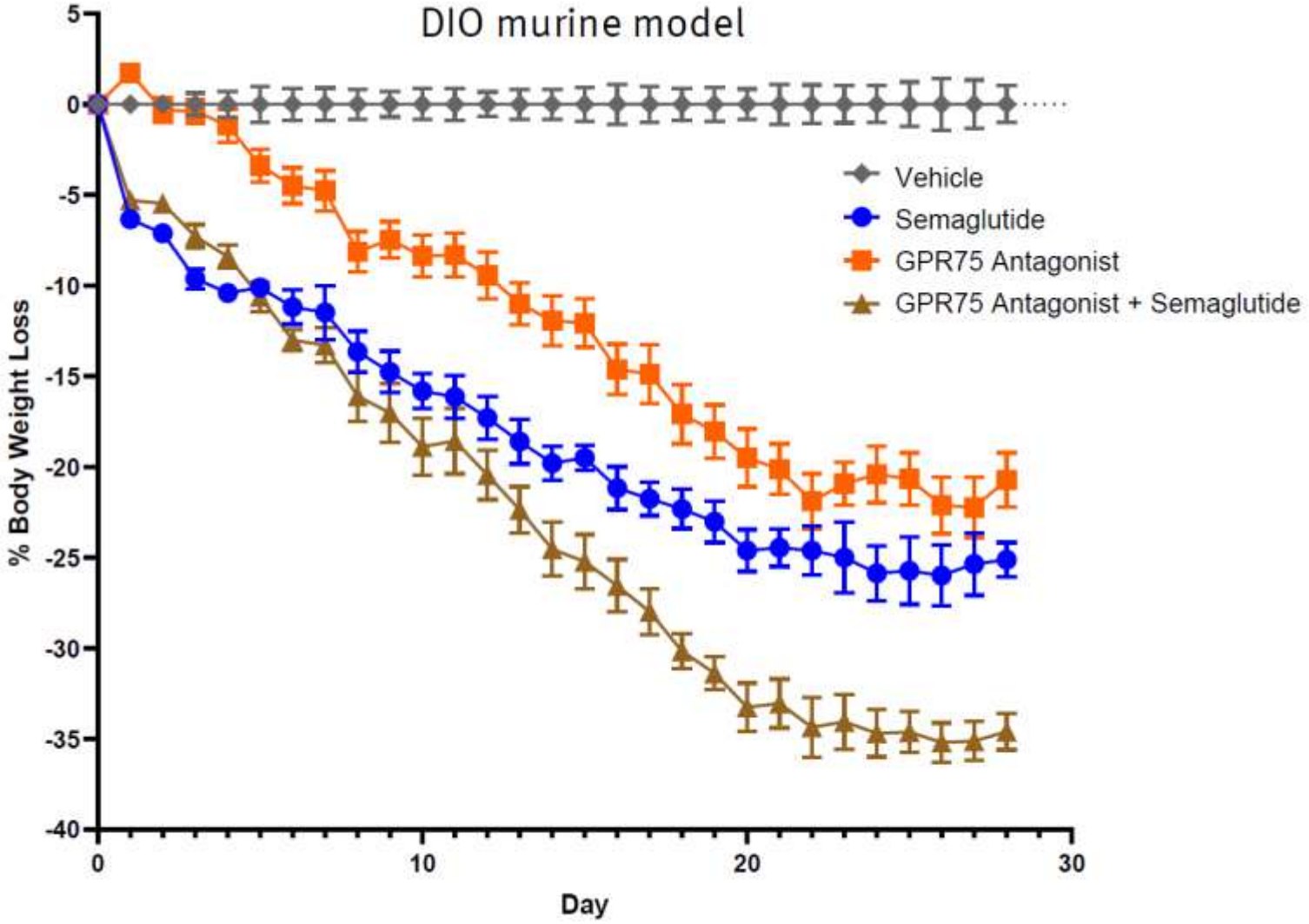
Orion's GPR75 antagonist can deliver quality weight loss via GPR75 inhibition through either oral or subQ formulations.

GPR75 antagonist monotherapy: weight loss equivalent to GLP-1 while preserving muscle mass and reducing fat mass.

Differentiated mechanism of action, with food intake suppression not observed to level of GLP-1.

GPR75 antagonist & GLP-1 additivity: GPR75 antagonist added to daily GLP-1 drives an additive effect on weight loss.

Orion is planning to be in Phase 1 testing with this drug in 2026.



≥20% body weight reduction monotherapy
≥30% body weight reduction in combination

Source: Orion Biotechnology

Programmable Algae

Lumen Bio Programmable Cyanobacterium Platform

We know this one is unusual so please bear with us as we try to explain why a biotech in Seattle that you have never heard of might be one of the best remaining approaches to upset the current direction of the obesity pharmaceutical market.

Lumen is in a Phase 2 study with a drug called LMN-801 that is encoded within ingestible blue-green algae known as spirulina (already approved as a food).

Spirulina is a cyanobacterium, which is commonly referred to as “blue-green algae.” It grows naturally in freshwater and alkaline lakes and is harvested and dried to produce a high-protein dietary supplement. The same harvest material can include ingestible proteins that are programmed in such as incretins/hormones targeted for gut receptors.

Lumen has not publicly disclosed which specific protein their drug releases into the gut but, interestingly, it not an incretin that is under current development by any of the larger pharmas in the obesity field.

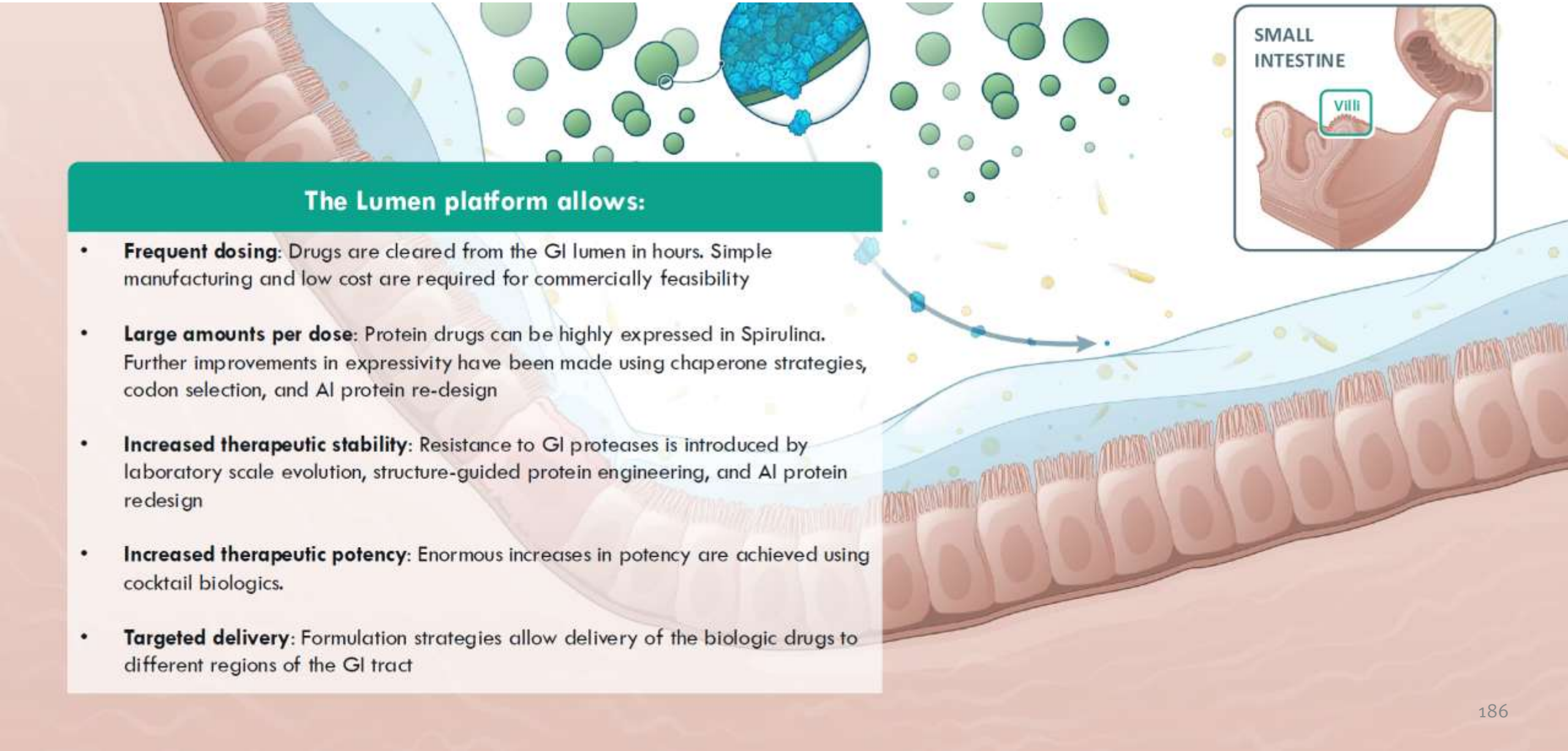
The product has incredibly low COGS and may have a short path to market.

We have strong reason to believe that this company will have positive POC data for a new approach to treating obesity later in 2025. Early efficacy data looks quite good.

Our sense is that such an approach could radically grow the DTC type market for obesity drugs.

There is obviously substantial risk remaining in this type of technology but having spent time with Lumen, our view is that they are onto something very big in obesity treatment.

Lumen Platform Delivers Protein to Gut Targets via Ingestible Algae



The Lumen platform allows:

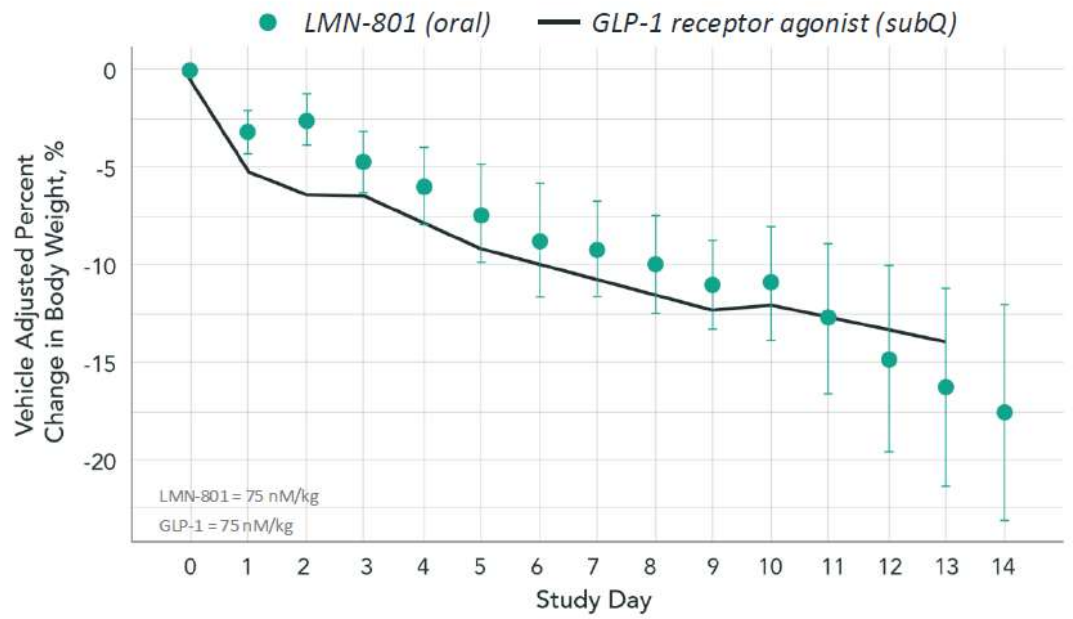
- **Frequent dosing**: Drugs are cleared from the GI lumen in hours. Simple manufacturing and low cost are required for commercially feasibility
- **Large amounts per dose**: Protein drugs can be highly expressed in Spirulina. Further improvements in expressivity have been made using chaperone strategies, codon selection, and AI protein re-design
- **Increased therapeutic stability**: Resistance to GI proteases is introduced by laboratory scale evolution, structure-guided protein engineering, and AI protein redesign
- **Increased therapeutic potency**: Enormous increases in potency are achieved using cocktail biologics.
- **Targeted delivery**: Formulation strategies allow delivery of the biologic drugs to different regions of the GI tract

Lumen Bio: Illustrative Animal Data for a Spirulina Weight Loss Product versus GLP-1's

LMN-801

- Oral delivery; no nausea or lean muscle loss
- Ultra-low COGS
- Massively scalable GMP

Chronic oral delivery in the DIO mouse model



GLP-1 receptor agonist data from Killion 2018 Figure 3C (doi.org/10.1126/scritanslmed.aat3392)

Lumen Can Make Obesity Drug at Less than $1 / Dose

Lower Drug Cost

- Simple, stable cell-line establishment
- Robust cultivation
- Inexpensive growth medium:
  - Light is the energy source
  - CO_2 is the carbon source
- High productivity
- Minimal downstream drug processing
- No cold chain for storage or distribution

Superior Scalability

- Simple food grade production space
- True continuous manufacturing
- Inexpensive steel frame bioreactors
- Low tech growth and harvesting

Lower regulatory complexity

- Intrinsic safety of manufacturing platform
- Low toxicity of topical delivery
- Easy assembly of cocktail therapeutics

De-risking

Lumen GMP plant already built
No fighting Novo/Lilly for CDMO space

Clinical safety
LMN-801 is oral, but leverages decades of prior clinical research in the riskier parenteral context

Proven regulatory path/team
To date, Lumen team/platform has received clearance for human trials with 13 NMEs

Proven in vivo model
DIO mouse model is highly predictive; Lumen results replicated at two big pharmas

LUMEN BIOSCIENCE

Lumen patented the only methods for bioengineering spirulina

(12) **United States Patent**
Takeuchi et al.

(10) **Patent No.:** **US 10, 131, 870 B2**
(45) **Date of Patent:** **Nov. 20, 2018**

(54) **TARGETED MUTAGENESIS IN SPIRULINA**

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(72). Investors: **Ryo Takeuchi**, Seattle, WA (US)
James Roberts, Seattle, WA (US)

(73) Assignee: **LUMEN BIODCIENCE, INC.**, Seattle, WA (US)

WO.	WO-2009/098089 A2.	8/2009
WO.	WO-2010/048568	4/2010
WO.	WO-2010/075440	7/2010
WO.	WO-2012/087963	6/2012
WO.	WO-2012/087982	6/2012
WO.	WO-2013/116517	8/2013
WO.	WO-2014/164232	10/2014
WO.	WO-2014/164566	10/2014

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-022-01249-7

OPEN

Development of spirulina for the manufacture and Oral delivery of protein therapeutics

- **Advent of new genetic engineering methods is** the thread that connects the origins of all biomanufacturing platforms
- **Lumen was the first** (and only) team to discover genetic engineering methods for spirulina

Nucleic Acid and Gene Therapy Approaches

Rich Pipeline of RNAi Drugs for Obesity in Development

Sponsor	Target Gene	Agent	Modality	Dosing Frequency (times per year)	Stage of Development	Key Features / Notes
Alnylam	ACVR1c	ALN-2232	siRNA	Not Disclosed	Preclinical	Alnylam is in animal testing with an ACVR1c knockdown siRNA drug aimed at adipose tissue. Starting Phase 1 studies later in 2025.
Alnylam	INHBE	Undisclosed candidate	siRNA	Not Disclosed	Preclinical	Alnylam is in animal testing with an INHBE knockdown siRNA drug. Has not disclosed clinical plans
Argo Biopharma	INHBE	Undisclosed candidate	siRNA	Not Disclosed	Preclinical	Argo is developing an INHBE RNA knockdown drug but has not disclosed details.
arrowhead pharmaceuticals	INHBE	ARO-INHBE	siRNA	Four	Phase 1b	Subcutaneous GalNAc-conjugated siRNA; potent knockdown of Activin E in NHP models; intended for obesity and metabolic disease.
arrowhead pharmaceuticals	ALK7	ARO-ALK7	siRNA	Not Disclosed	Phase 1	Has just started human testing with this program.
Canary Cure	CB1r / zfp423	CCT-217	siRNA	One or Two	Preclinical	Canary Cure's CCT-217 therapy targets the CB1r gene, which is part of the endocannabinoid system (ECS)
novo nordisk	INHBE	Undisclosed candidate	siRNA	Not Disclosed	Discovery	Dicerna filed patents covering INHBE-targeting RNAi molecules before its acquisition; Novo Nordisk likely evaluating metabolic applications.
WAVE LIFE SCIENCES	INHBE	WVE-007	siRNA	One or Two	Phase 1b	Wave's GALNAC program to knock down INHBE is in Phase 1 testing. Doubles semaglutide weight loss in animal models when added to sema.

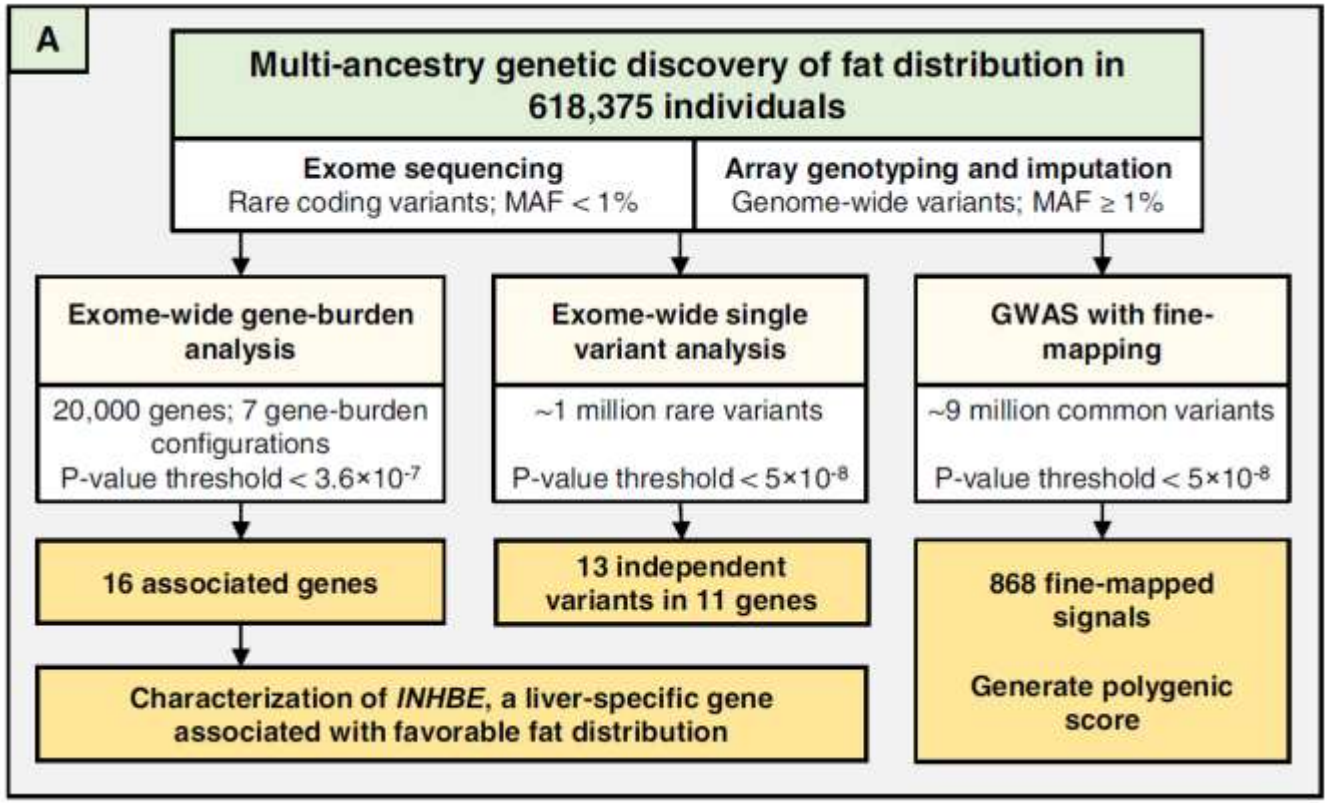
Note: There are quite a few undisclosed programs in the RNAi field and obesity. Lilly, for example, has collaborated with Olix of South Korea to develop several RNAi programs with undisclosed gene targets for obesity.

Source: Stifel research of various company's disclosures.

INHBE Influences Belly Fat

Multiancestry exome sequencing reveals *INHBE* mutations associated with favorable fat distribution and protection from diabetes

Akbari et. al., *Nature Communications*, Aug 23, 2022



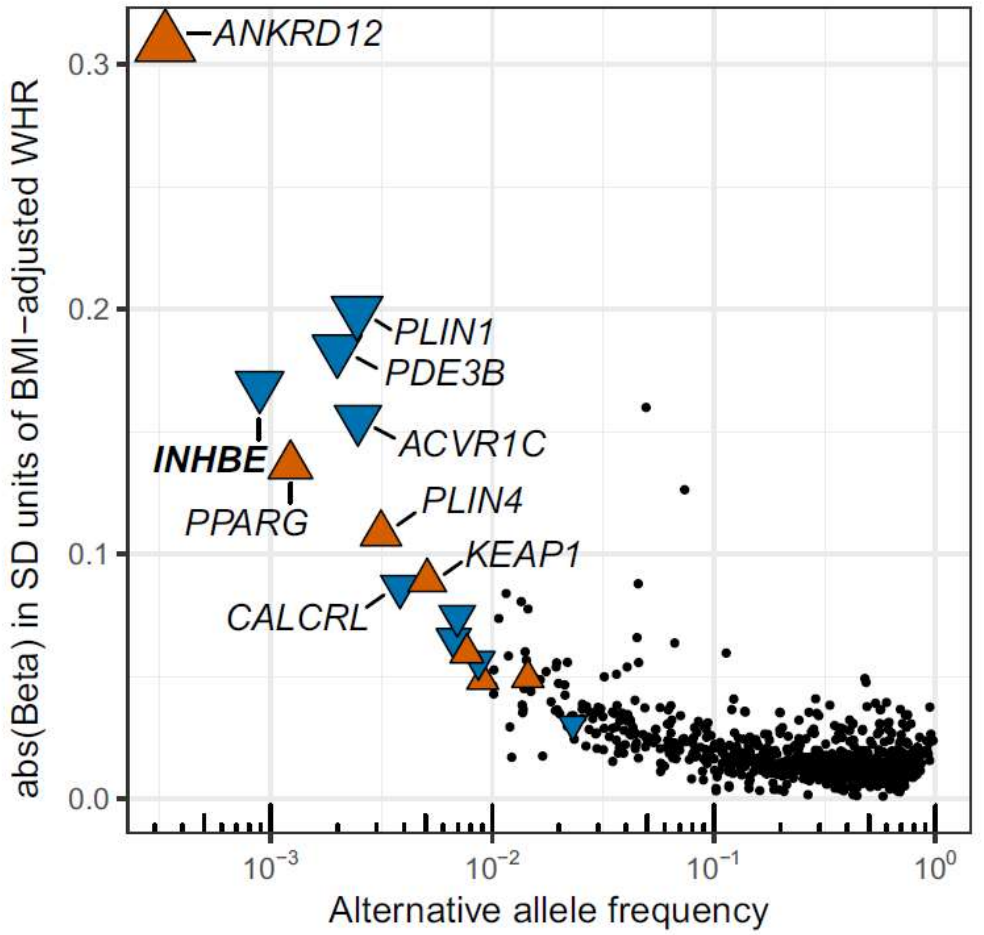


Fig. 2 | Associations with BMI-adjusted WHR for common and rare alleles in the multi-ancestry analysis. The 16 genes with exome-wide significant gene-burden associations are shown as colored triangles, with the triangles pointing upwards (orange) or downwards (blue) indicating associations with higher and lower BMI-adjusted WHR, respectively. The 868 fine-mapped common variants are indicated as black dots. The alternative allele frequency for each variant or gene-burden genotype is indicated on the *x*-axis. SD standard deviation, WHR waist to hip ratio, BMI body mass index.

Source: https://www.nature.com/articles/s41467-022-32398-7

Wave RNAi Program Targets INHBE for Healthy Weight Loss

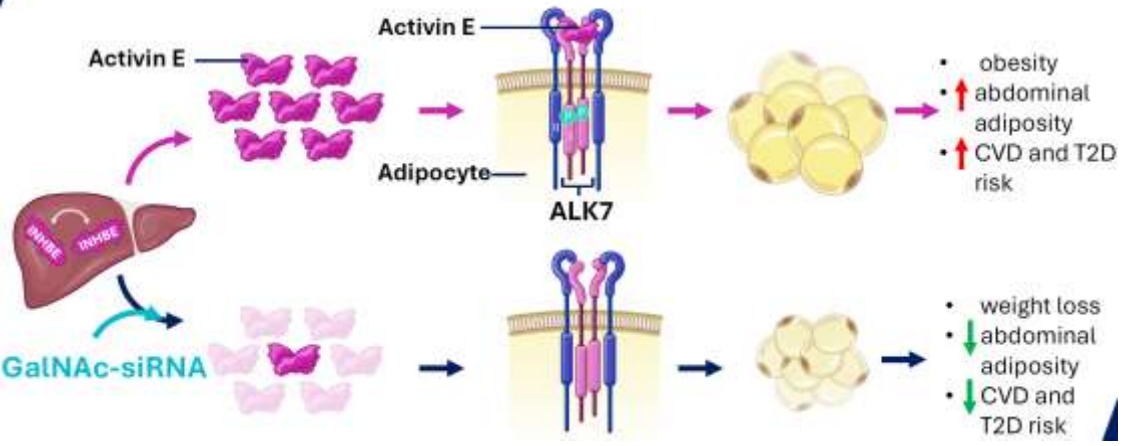
WAVE LIFE SCIENCES

siRNA-INHBE Silencing in Mice Recapitulates Human Genetic Data and Demonstrates Improved Healthy Weight Loss Profile

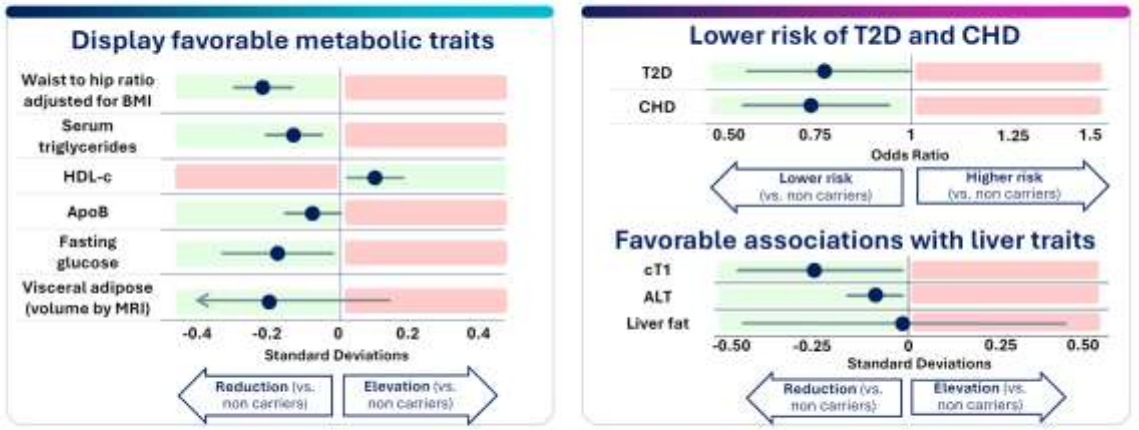
Hsiu-Chiung (Ginnie) Yang, PhD
SVP, Translational Medicine

June 20, 2025

Human genetics-inspired approach to address obesity-associated metabolic disease



Human *INHBE* loss of function (LoF) variant carriers have a healthy metabolic profile



Silencing *INHBE* mRNA in hepatocytes by ≥50% is expected to recapitulate the healthy metabolic profile of heterozygous *INHBE* LoF carriers

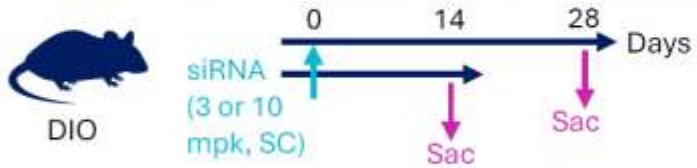
WAVE LIFE SCIENCES

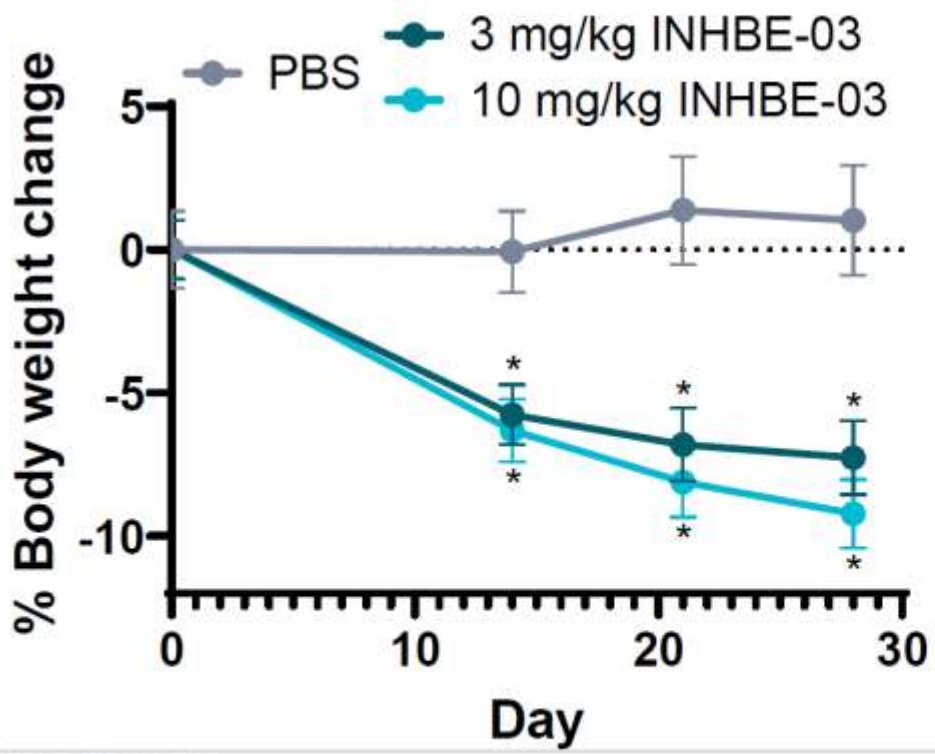
- Preclinical data show that in DIO mice, *Inhbe* GalNAc-siRNAs:
  - Lower *Inhbe* mRNA and induce weight loss mainly through reduction of fat mass
  - Reduce pro-inflammatory macrophage recruitment in adipose tissue
  - Double weight loss, when added on to semaglutide
  - Curtail weight regain upon cessation of semaglutide
- Preclinical data suggest that *Inhbe* GalNAc-siRNAs and GLP1-RAs induce weight loss in mice primarily through independent mechanisms
- Wave is advancing investigational WVE-007, an *INHBE* targeting GalNAc-siRNA, as a novel, long-acting, muscle-sparing approach for treatment of obesity
  - Data from the ongoing INLIGHT phase 1 study expected in second half 2025

Source: https://ir.wavelifesciences.com/static-files/18068be0-5164-425c-b7c4-3270ba38c78e

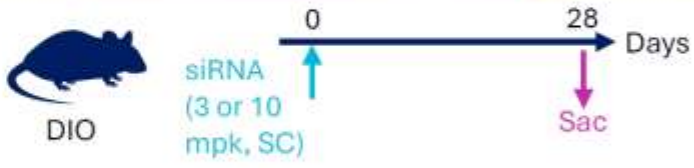
Weight loss by a single dose of *Inhbe* GalNAc-siRNA is driven by fat loss with preservation of muscle

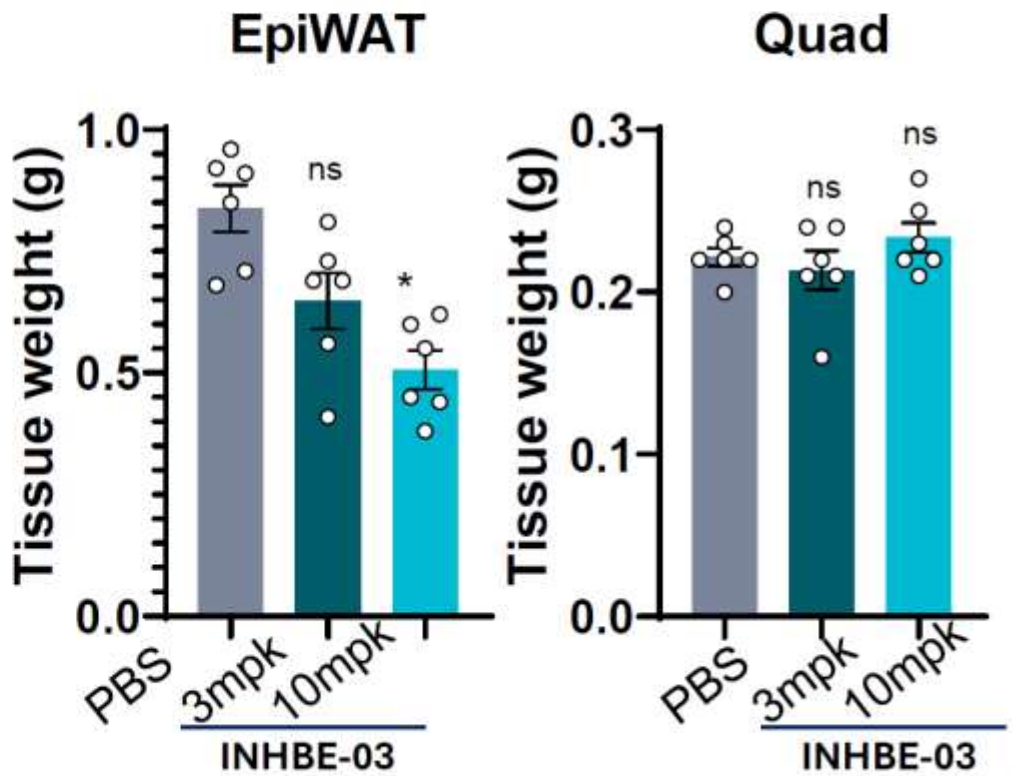
Body Weight





Tissue Weight





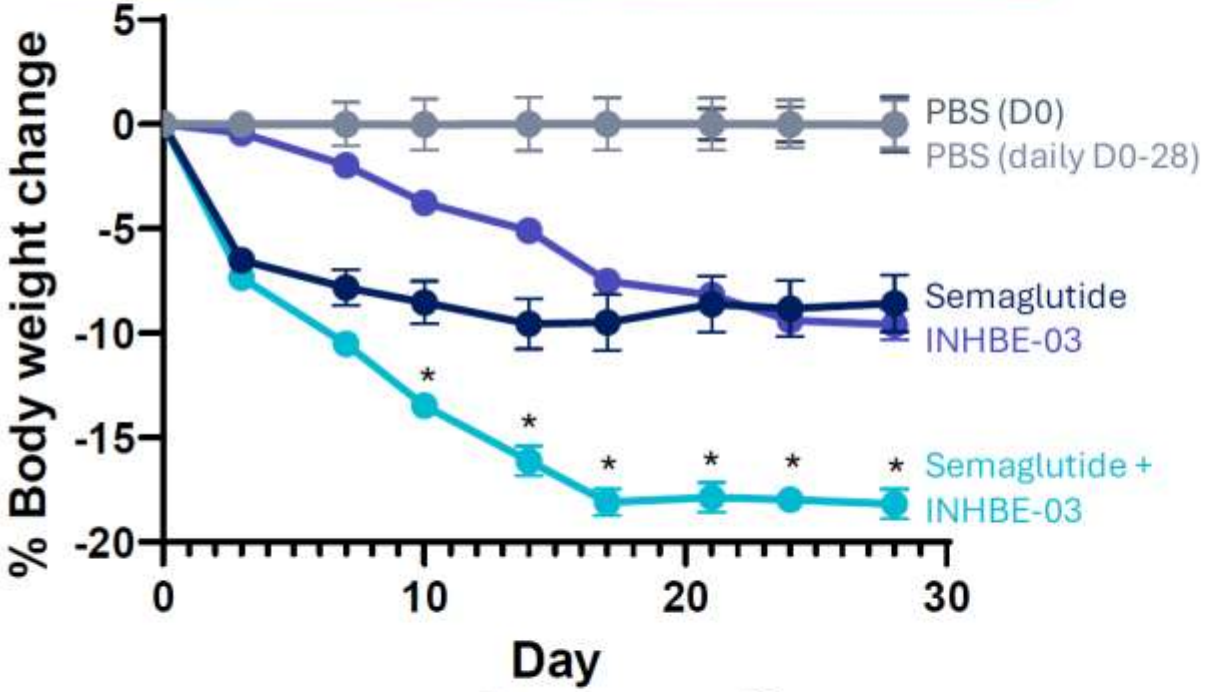
WAVE LIFE SCIENCES

At ~25 weeks old (Day 0, D0), C57Bl6 diet induced obesity (DIO) mice received a single SC injection of 3 or 10 mg/kg (mpk) INHBE-03 or PBS (control). Left, Mean body weight change (%) from D0 ±SEM (n=12-18); Stats: marginal treatment effects versus PBS per timepoint; * $p < 0.05$. Right, a single epididymal white adipose tisse (epiWAT) fat pad and quadriceps muscle (Quad) were collected and weighed on D28. Stats: Mean weight (g) ±SEM, post hoc comparisons of marginal treatment effects versus PBS per tissue type; * $p < 0.05$; ns, nonsignificant.

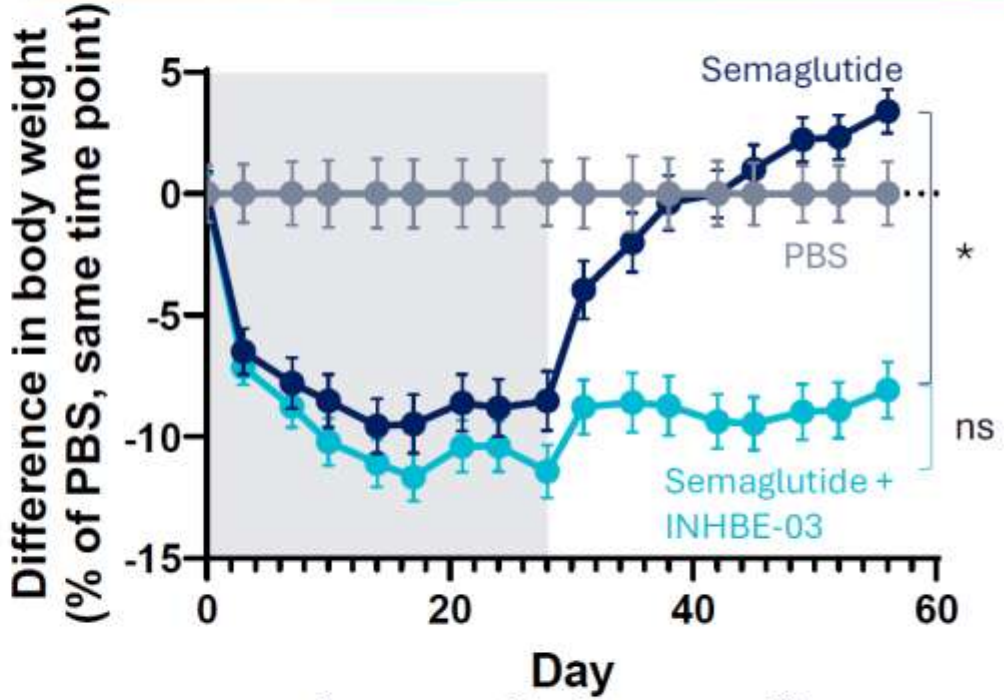
Source: https://ir.wavelifesciences.com/static-files/18068be0-5164-425c-b7c4-3270ba38c78e

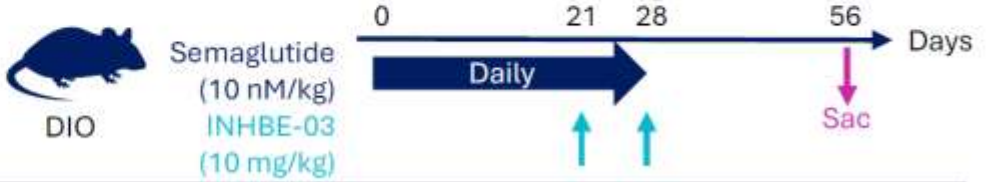
Treatment with *Inhbe* GalNAc-siRNA augments semaglutide-induced weight loss in DIO mice

~2x greater overall weight loss when added to GLP-1RA



Curtails weight regain after the cessation of GLP1-RA





WAVE LIFE SCIENCES

Stats: Mean weight difference as a % of PBS control on the same day (±SEM, n=10). Left, Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects for semaglutide versus semaglutide and INHBE-03 per time point; * $p < 0.05$ compared to semaglutide group. Right, Linear Mixed Effects ANOVA with post hoc comparisons of marginal time point effects between D28 and D56 per treatment group; * $p < 0.05$; ns, nonsignificant. GLP1-RA: GLP-1 receptor agonist

Source: https://ir.wavelifesciences.com/static-files/18068be0-5164-425c-b7c4-3270ba38c78e

INHBE Program from Arrowhead

Strong effect of INHBE KO on obesity. Potential for longer run obesity control with RNAi

Liver-specific silencing of INHBE with ARO-INHBE, an siRNA therapeutic, for metabolic diseases

Arrowhead ADA Poster, June 2024

Michelle Ngai, Feng Liu, Puhui Li, Xiaokai Li, Cole Christy, Holly Hamilton, Maria Afrazi, Pierce Sullivan, Tao Pei, James Hamilton, Zhi-Ming Ding
Arrowhead Pharmaceuticals Inc., Madison, WI, USA

INTRODUCTION

- Incretin-based therapies are powerful and effective for obesity and metabolic outcomes, but significant loss of lean mass and adverse GI events at high dose levels has prompted the identification of a novel mechanism of action
- Large-scale human genetic studies support an association between pLOF INHBE variants and 1) reduced WHRadjBMI, 2) improved metabolic profile including lower TG, higher HDL, and reduced fasting glucose levels
- Activin E signaling regulates adipose lipid storage and mobilization
- Activin E levels are elevated in individuals with obesity, insulin resistance, and NAFLD
- siRNA targeting hepatic INHBE has potential to be a novel therapeutic for metabolic diseases

AIM

- Evaluate the potential therapeutic benefits of INHBE silencing in obese and diabetic mouse models with a mouse surrogate of ARO-INHBE
- Evaluate the pharmacodynamic effects of ARO-INHBE in cynomolgus monkeys

METHODS

Rodent studies

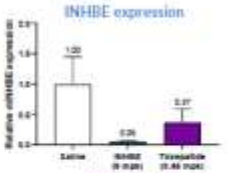
- Diet-induced obese (DIO) and db/db mouse models
- Dosing regimen: weekly 9 mpk subcutaneous (SC) dosing of mouse surrogate ARO-INHBE; daily 0.48 mpk tirzepatide as benchmark; co-treatment of weekly INHBE (9 mpk) and daily tirzepatide (0.48 mpk)
- Body weight, body composition (lean versus fat mass) via Dual X-ray Absorptiometry (DEXA) scans, glucose homeostasis (fasting glucose, insulin, HOMA-IR, oGTT), lipid metabolism (non-esterified fatty acids, beta-hydroxybutyrate) assessed at various points over the course of the studies

Non-human primate study

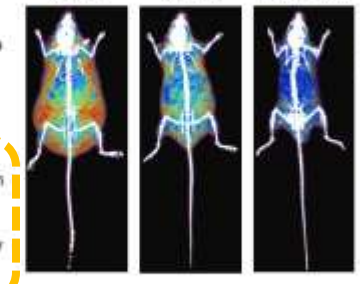
- Cynomolgus monkeys (n=3) received 2 SC doses (D1 and D29) of ARO-INHBE at 3 mpk
- Liver biopsies were collected for INHBE mRNA expression via qRT-PCR

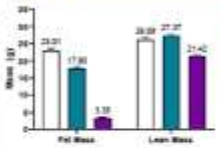
PHARMACOLOGICAL STUDIES OF INHBE siRNA IN RODENT MODELS

Knockdown of hepatic INHBE mRNA expression with surrogate RNAi-trigger results in an improved body composition with 1) BW suppression, 2) fat mass loss, 3) lean mass retention



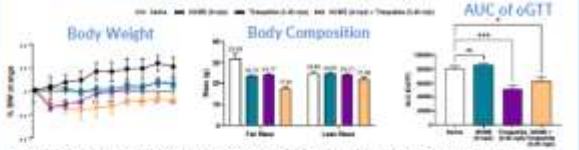
- DIO mice were administered with saline (weekly), mouse surrogate ARO-INHBE (9 mpk, weekly), or tirzepatide (0.48 mpk, daily)
- n=10 for each treatment group
- INHBE mRNA expression reduced by ~95%
- INHBE silencing led to a 19% suppression of body weight compared to saline controls





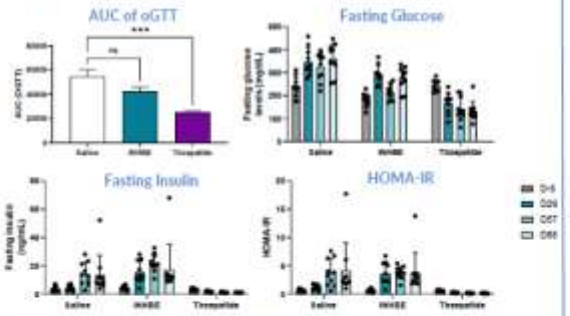
- Body composition analysis through DEXA imaging indicates a 26% loss of fat mass and preservation of lean mass with INHBE silencing

INHBE silencing in the db/db mouse model results in an improvement in body composition



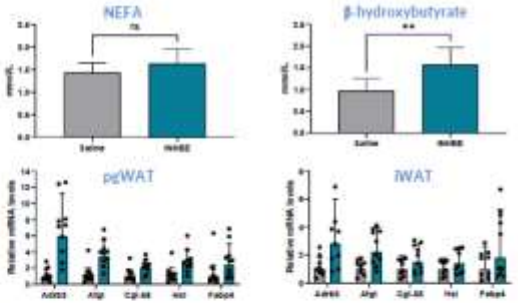
- Weekly SC dosing of mouse surrogate ARO-INHBE in db/db mice (n=10 per treatment group) resulted in: 1) 15% suppression in BW compared to the saline group, 2) 26% loss of fat mass, 3) lean mass retention, 4) lack of improvement in oGTT

Impact on glycemic control is mild based on oGTT, fasting glucose, fasting insulin, and HOMA-IR indicators



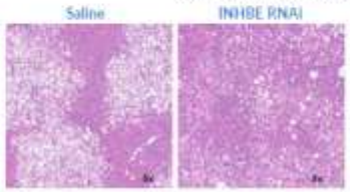
- Animals were fasted for 6 hours prior to glucose homeostasis analysis

INHBE KD improves catecholamine sensitivity, increasing lipid mobilization and oxidation



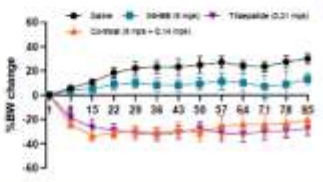
- INHBE KD animals treated with CL316,243 (1 mpk, IP) had increased circulating ketone levels and expression of lipolytic genes relative to control group

Increased lipid mobilization with INHBE silencing does not lead to liver steatosis



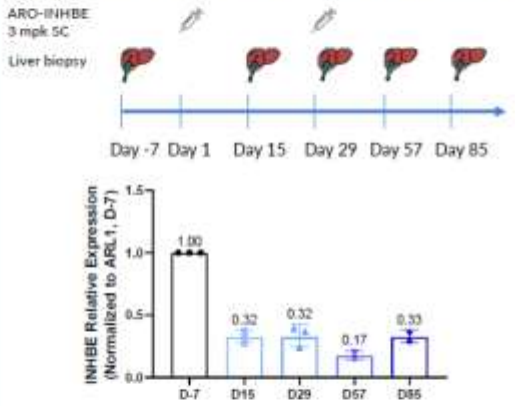
- H&E staining of the liver indicate there is less fat accumulation in DIO mice treated with INHBE RNAi

Co-treatment of tirzepatide with INHBE siRNA allows use of lower tirzepatide dose for similar therapeutic effect in DIO mice



- Co-treated DIO mice (n=10 per treatment group) were administered 9 mpk mouse surrogate ARO-INHBE weekly and 0.14 mpk tirzepatide daily
- Co-treated mice showed similar levels of %BW change as mice treated with a higher dose level of tirzepatide

PHARMACODYNAMIC STUDY OF ARO-INHBE IN CYNOMOLGUS MONKEYS

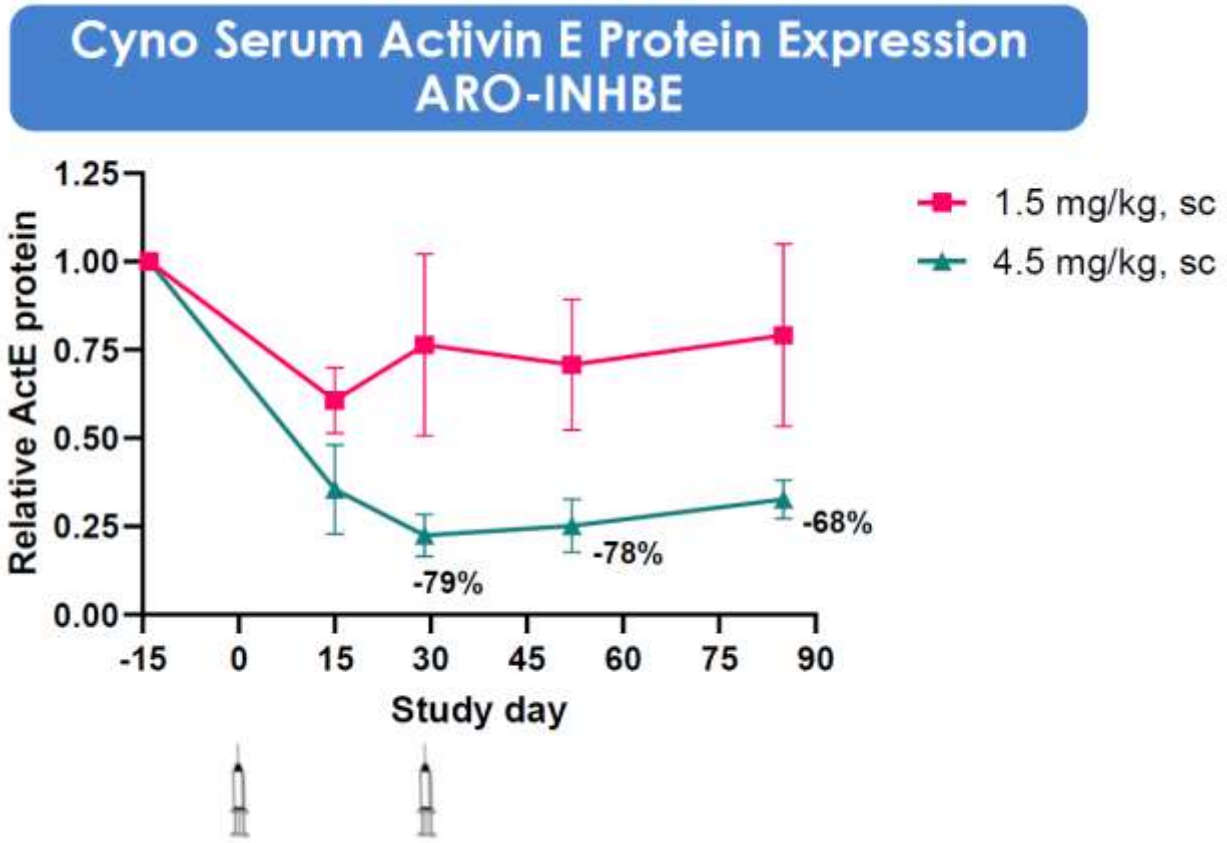


- After a single 3 mpk SC dose, hepatic INHBE mRNA expression was reduced by ~70% (n=3; n=2 on D57 and D85)
- Knockdown was maintained through D85 with a second dose on D29

CONCLUSIONS

- ARO-INHBE is a potent RNAi therapeutic capable of silencing hepatic INHBE mRNA expression
- Pre-clinical studies with a mouse surrogate of ARO-INHBE in DIO and db/db models indicate that INHBE KD potentially leads to a suppression in body weight gain, loss of fat mass, and preservation of lean mass likely due to the increased lipolysis
- Co-treatment of tirzepatide with INHBE RNAi has the potential to allow for the use of a lower tirzepatide dose without compromising the therapeutic effect

Arrowhead Showing Impressive Monkey Data



Source: Arrowhead Corporate Presentation, May 2025

This preclinical data from Arrowhead's ARO-INHBE program in cynomolgus monkeys show that subcutaneous administration of the RNAi therapeutic led to potent, dose-dependent, and sustained reductions in serum Activin E protein. This is highly suggestive of human response. At the higher 4.5 mg/kg dose, protein levels dropped by approximately 79% at Day 30 and remained suppressed by about 68% at Day 90, demonstrating durable target engagement consistent with long-acting RNA interference mechanisms. In contrast, the lower 1.5 mg/kg dose produced a more modest and variable reduction, underscoring a clear dose-response relationship and supporting the feasibility of infrequent dosing regimens in humans.

Activin E, a hepatokine encoded by *INHBE*, belongs to the TGF-β superfamily and plays emerging roles in metabolic regulation and potentially muscle health. While much remains to be learned, evidence suggests that Activin E contributes to lipid storage, insulin resistance, and negative regulation of lean mass, sharing some functional similarities with better-known family members like myostatin and Activin A. Lowering circulating Activin E may therefore improve metabolic health by reducing fat accumulation and possibly fostering a more anabolic environment in muscle

Arrowhead Phase 1/2a Data Coming Up

Arrowhead Pharmaceuticals Initiates Phase 1/2a Study of ARO-INHBE for the Treatment of Obesity

PASADENA, Calif.--(BUSINESS WIRE)--Dec. 23, 2024-- Arrowhead Pharmaceuticals, Inc. (NASDAQ: ARWR) today announced that it has dosed the first subjects in a Phase 1/2a clinical trial of ARO-INHBE, the company's investigational RNA interference (RNAi) therapeutic being developed as a potential treatment for obesity. Arrowhead also filed recently a request for regulatory clearance to initiate a clinical trial for its second obesity candidate, ARO-ALK7. Both ARO-INHBE and ARO-ALK7 are designed to intervene in a known pathway that signals the body to store fat in adipose tissue.

"ARO-INHBE is an important program for Arrowhead that complements our strategic focus on developing and commercializing important RNAi-based therapies for cardiometabolic diseases. Further, our preclinical studies have yielded promising results for this novel mechanism to reduce body weight and potentially preserve lean muscle mass resulting in improved body composition," said James Hamilton, M.D., Chief of Discovery and Translational Medicine at Arrowhead. "The Phase 1/2 study will evaluate ARO-INHBE as a monotherapy in part 1 and as a combination therapy with tirzepatide in part 2, with both parts enrolling patients with obesity."

About ARO-INHBE

ARO-INHBE is designed to reduce the hepatic expression of the INHBE gene and its secreted gene product, Activin E. INHBE is a promising genetically validated target in which loss-of-function INHBE variants in humans are associated with improved fat distribution and lower risk of metabolic diseases, such as type 2 diabetes. Activin E acts as a ligand in a pathway that regulates energy homeostasis in adipose tissue. Inhibiting this pathway with investigational ARO-INHBE treatment has the potential to increase lipolysis, and reduce adipose hypertrophy and dysfunction, visceral adiposity, and insulin resistance.

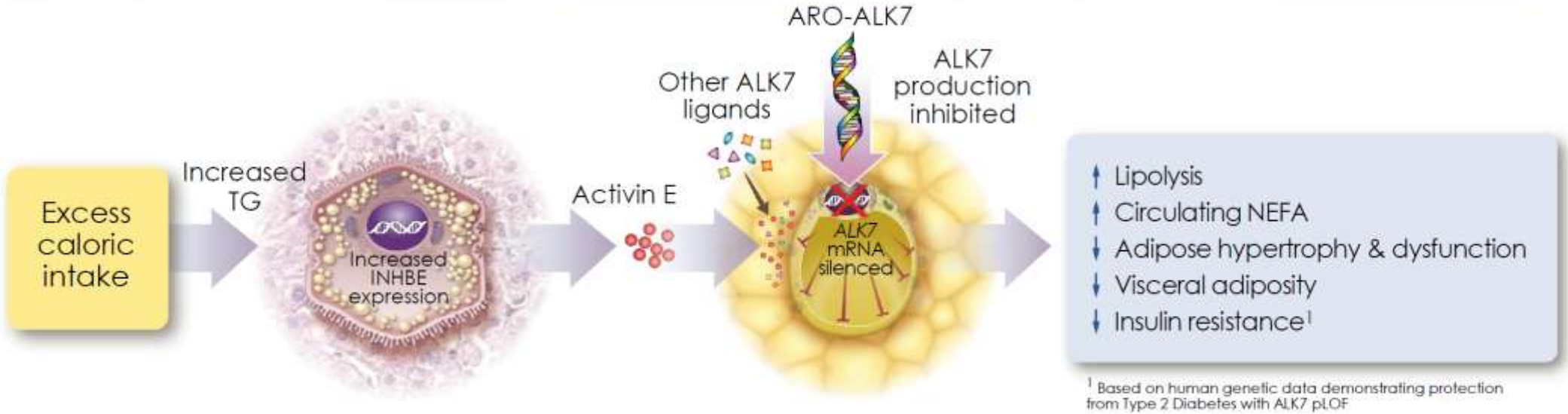
About the AROINHBE-1001 Phase 1/2 Study

AROINHBE-1001 (NCT06700538) is a Phase 1/2a dose-escalating study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ARO-INHBE in up to 78 adult volunteers with obesity. Part 1 of the study is designed to assess single and multiple doses of ARO-INHBE monotherapy, and Part 2 of the study is designed to assess ARO-INHBE in combination with tirzepatide, a subcutaneously administered GLP-1/GIP receptor co-agonist that has been approved in the United States and the European Union for management of type 2 diabetes mellitus since 2022 and weight management since 2023/2024 respectively.

Source: https://ir.arrowheadpharma.com/news-releases/news-release-details/arrowhead-pharmaceuticals-initiates-phase-12a-study-aro-inhbe

Arrowhead Also Developing a Silencer of ALK7 mRNA

Activin Receptor-like Kinase 7 (ALK7, *ACVR1C*) is a Genetically Validated Adipose Target



[1] Based on human genetic data demonstrating protection from Type 2 Diabetes with ALK7 pLOF

- ALK7 is a TGF-β receptor superfamily member preferentially expressed on adipocytes
- Ligands may include: GDF3, GDF11, ActB, ActE, ActAB, ActC, Nodal
- ALK7 signaling suppresses lipolysis, increasing adipocyte size and lipid content

Emdin et al, *Diabetes* 2019; 68(1):226-234. DOI: 10.2337/DB18-0857

pLOF *ALK7* Variants Are Associated with Lower Risks of Obesity and Type 2 Diabetes

Table 2—Association of variants in *ACVR1C* with WHRadjBMI and with type 2 diabetes

		WHRadjBMI		Type 2 diabetes	
Variant	Minor allele frequency (%)	β (95% CI)	*P* value	OR (95% CI)	*P* value
Asn150His	1.1	−0.089 (−0.11, −0.067)	3.4×10^{-17}	0.88 (0.83, 0.94)	8.7×10^{-5}
Ile195Thr	0.2	−0.15 (−0.09, 0.19)	1.0×10^{-9}	0.79 (0.67, 0.93)	0.005
Ile482Val	7.2	−0.019 (−0.01, −0.027)	1.6×10^{-5}	0.95 (0.93, 0.97)	4.8×10^{-6}
rs72927479	5.1	−0.035 (−0.045, −0.025)	2.6×10^{-12}	0.93 (0.89, 0.97)	6.0×10^{-4}

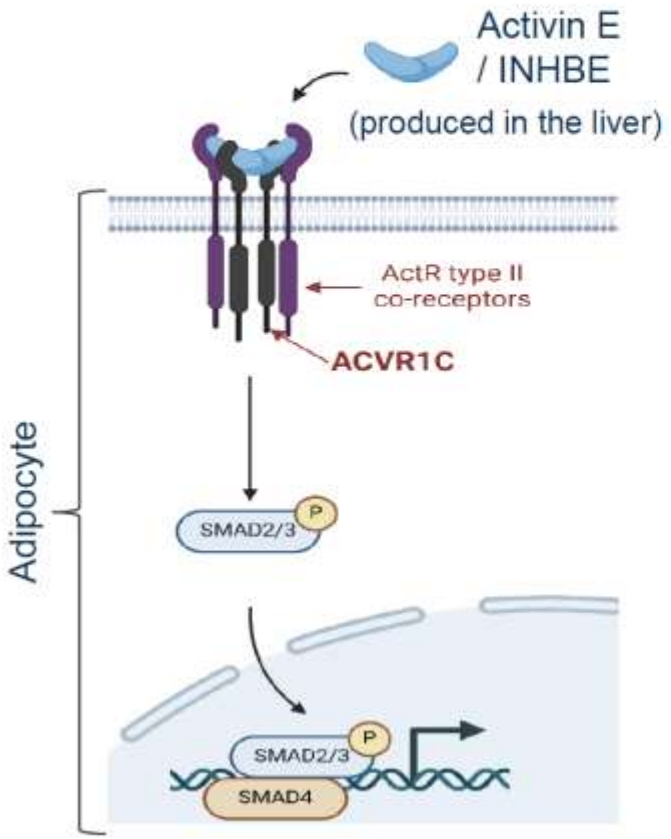
Estimates for WHRadjBMI were derived through linear regression analysis in UK Biobank. Estimates for type 2 diabetes were derived through meta-analysis of UK Biobank and the DIAGRAM ExTexT2D Consortium.

Source: Arrowhead Corporate Presentation, May 2025

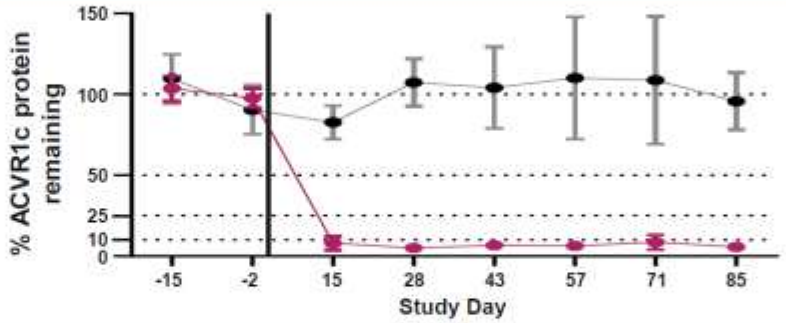
Alnylam Targeting ACVR1c and INHBE with SiRNA

Long-acting siRNA with the Aim to Achieve Safe and Sustained Weight Loss

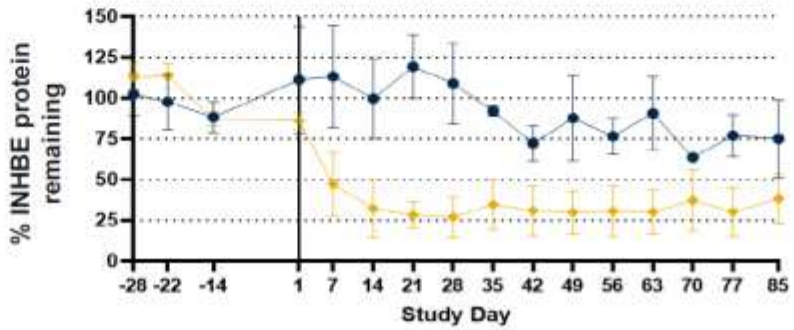
Ligand/Receptor Inhibin/Activin Pathway: INHBE (in liver) and ACVR1c (in adipose)



95% ACVR1c Knockdown in NHP Adipose



INHBE Knockdown in NHP Liver



- Deep and durable knockdown with single dose
- Highly potent with exquisite tissue specificity
- Infrequent, sub-cutaneous dosing
- Fat loss, lean mass preservation & weight regain attenuation

Alnylam

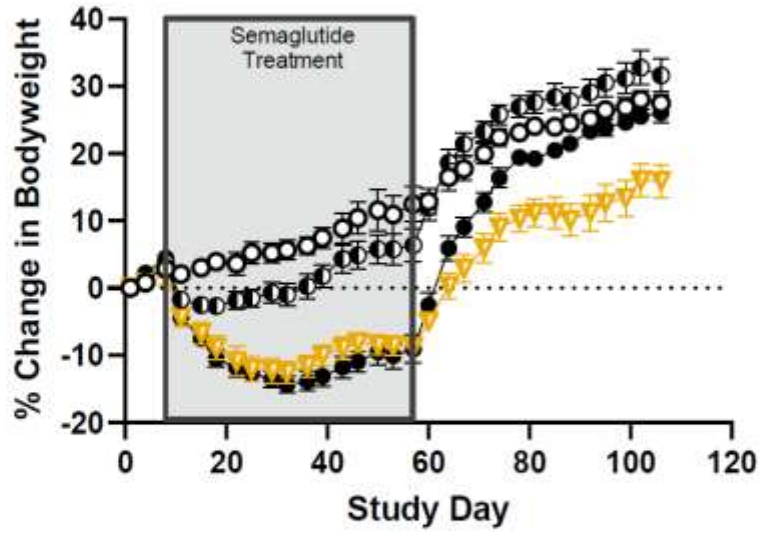
Source: https://capella.alnylam.com/2025/02/25/alnylam-rd-day-2025

Alnylam Going into Clinic with Multigene Approach

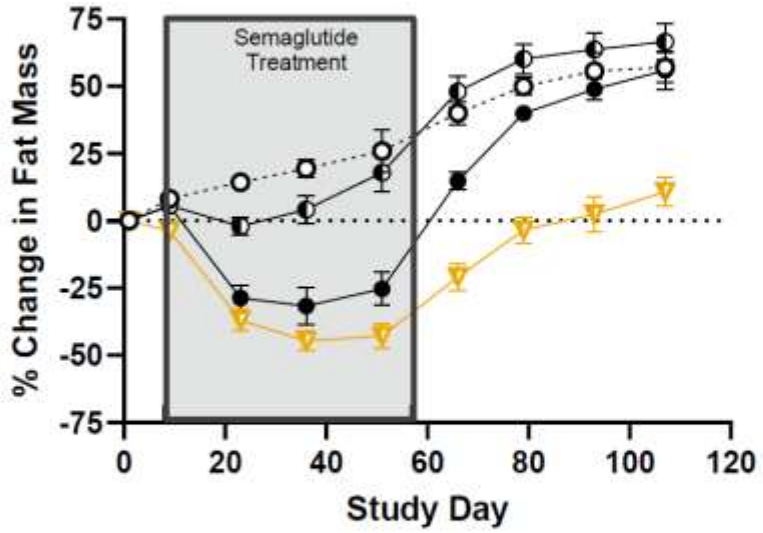
Novel siRNA Combinations Enhances Fat Loss with Sustained Weight Loss

Rodent models

Weight Loss



Fat Loss



PBS + vehicle

PBS + low dose semaglutide

PBS + high dose semaglutide

ACVR1C siRNA + "Gene X" siRNA + low dose semaglutide

Emerging Potential Profile	Enhanced fat loss (~45%)	Sustained weight loss	Increased lean mass	Prevention of weight regain

Plan to progress ALN-2232 (ACVR1c), the first Alnylam adipose tissue program, into the clinic in 2025

Source: https://capella.alnylam.com/2025/02/25/alnylam-rd-day-2025

Emerging Interest in microRNA Therapies for Obesity

Molecular Therapy: Nucleic Acids Vol. 26 December 2021

miR-21 mimic blocks obesity in mice: A novel therapeutic option

Said Lhamyani,[1,13] Adriana-Mariel Gentile,[1,13] Rosa M. Giráldez-Pérez,[2] Mónica Feijóo-Cuaresma,[3] Silvana Yanina Romero-Zerbo,[1,4] Mercedes Clemente-Postigo,[5] Hatem Zayed,[6] Wilfredo Oliva-Olivera,[7] Francisco Javier Bermúdez-Silva,[1,4] Julián Salas,[8] Carlos López Gómez,[9] Abdelkrim Hmadcha,[4,10] Nabil Hajji,[11] Gabriel Olveira,[1,4] Francisco J. Tinahones,[7] and Rajaa El Bekay[1,12]

Interestingly, in vivo treatment with the miR-21 mimic blocked weight gain induced by a high-fat diet in obese mice, without modifying food intake or physical activity. This was associated with metabolic enhancement, WAT browning, and brown adipose tissue (AT) thermogenic programming through vascular endothelial growth factor A (VEGF-A), p53, and transforming growth factor β1 (TGF-β1) signaling pathways. Our findings suggest that miR-21 mimic-based therapy may provide a new opportunity to therapeutically manage obesity and consequently, its associated alterations.

Companies Working on microRNA's Targets for Obesity

APTAMIR

Pesalis THERAPEUTICS

The clinical potential of circulating microRNAs in obesity

Chenbo Ji[1]* *and Xirong Guo*[1,2]*

Abstract | Obesity is a complex condition that is characterized by excessive fat accumulation, which can lead to the development of metabolic disorders, such as type 2 diabetes mellitus, nonalcoholic fatty liver disease and cardiovascular diseases. Evidence is accumulating that circulating microRNAs (miRNAs) act as a new class of endocrine factor. These miRNAs are released by many types of tissue, including adipose tissues. miRNAs might serve as endocrine and paracrine messengers that facilitate communication between donor cells and tissues with receptor cells or target tissues, thereby potentially having important roles in metabolic organ crosstalk. Moreover, many miRNAs are closely associated with the differentiation of adipocytes and are dysregulated in obesity. As such, circulating miRNAs are attractive potential biomarkers and hold promise for the development of miRNA-based therapeutics (such as miRNA mimetics, anti-miRNA oligonucleotides and exosomes loaded with miRNA) for obesity and related disorders. Here we review the latest research progress on the roles of circulating miRNAs in metabolic organ crosstalk. In addition, we discuss the clinical potential of circulating miRNAs as feasible biomarkers for the assessment of future risk of metabolic disorders and as therapeutic targets in obesity and related diseases.

Exosomes
Homogenous extracellular vesicles (40–100 nm) that originate from the endocytic recycling pathway, with specific markers such as CD9, CD63, ALIX, flotillin 1 and TSG101.

Microvesicles
Heterogeneous extracellular vesicles (50–1,000 nm) that are produced directly through the outward budding and fission of membrane vesicles from the plasma membrane with no definite markers.

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https://doi.org/10.1038/s41574-019-0260-0

Obesity is a major global health issue that contributes to the occurrence of metabolic disorders, such as type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD)[1,2]. The mechanisms that connect obesity with metabolic disorders are complicated, however, the dysregulation of adipose tissue-derived molecules is probably an important factor[3–5]. Many studies have focused on the role of hormones (such as leptin and adiponectin) and circulating lipids (such as free fatty acids) with well-defined target tissues and signalling pathways in the development of obesity-associated disorders[3].

Evidence is accumulating that microRNAs (miRNAs) act as a new class of endocrine factor[6,7]. Defined as single-stranded non-coding RNAs containing 19–22 nucleotides, miRNAs are found in all eukaryotic cells and some viruses, and act to negatively regulate gene expression on a post-transcriptional level via binding complementarily to the target mRNA[8–11]. Mature miRNAs are formed inside the cell and exert their function in the cytoplasm as well as being released into the circulation and various body fluids in animals (for example, urine, saliva and lymphatic fluid)[11,12] (BOX 1). Of note, miRNAs can be packaged within structures called extracellular vesicles[13,14]. These vesicles, which include exosomes and microvesicles, are cell-derived membranous structures which contain numerous miRNAs and transfer between cells, thereby establishing intercellular communication as well as travelling between distant organs to foster interorgan crosstalk[13,15]. In addition, miRNAs are protected from RNase degradation within extracellular vesicles by forming complexes with RNA- binding proteins and by the lipid bilayer that surrounds the vesicle. Extracellular vesicles facilitate miRNA trafficking to distal organs and/or cells via receptor-mediated endocytosis, phagocytosis or direct fusion with the plasma membrane of target cells[13].

Importantly, distinct circulating miRNA profiles are reported between patients with metabolic disorders (for example, obesity and T2DM) and healthy individuals[16–19]. As such, circulating miRNAs have potential as biomarkers for obesity and related metabolic disorders. The specific circulating miRNAs that are associated with metabolic effects and their tissue and cellular sources have attracted considerable attention among researchers. In addition, miRNAs are carried within extracellular vesicles, which can effect various functions of neighbouring and distal cells[20,21] (FIG. 1). The potential roles of miRNAs in metabolic organ crosstalk provide a new angle for us to understand the mechanisms of obesity-related complications in various organs and lead to new and improved treatments.

In this Review, we summarize findings on the roles of obesity-related and adipose tissue-derived or adipose tissue-enriched circulating miRNAs in metabolic

Source: https://www.nature.com/articles/s41574-019-0260-0

Resalis Has Started a Phase 1 Trial for its Innovative LNCRNA Therapy for Obesity

Resalis Therapeutics Announces Initiation of Phase 1 Clinical Trial for RES-010 in Obesity

Torino, Italy, December 03, 2024 – Resalis Therapeutics today announced the initiation of its first-in-human, Phase 1 study for RES-010, a non-coding RNA-based compound designed to provide a disease-modifying approach to obesity treatment. Preclinical studies have demonstrated that RES-010 reduces fat mass, preserves lean body mass, and enhances energy expenditure. By targeting fat reduction across various regions of the body, including visceral and hepatic stores, RES-010 has the potential to complement existing therapies such as GLP-1 receptor agonists, and support sustainable, long-term weight management. The Phase 1 trial (EUCT No: 2024-514871-17-00) will explore the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of RES-010 in healthy, overweight, and moderately obese volunteers.

"The initiation of our Phase 1 trial with RES-010 marks a significant milestone in our commitment to address obesity's complex biological roots. By targeting the miR-22 pathway, a key metabolic regulator, RES-010 is designed to selectively reduce fat while preserving muscle mass. This unique mechanism of action can potentially improve and extend the effectiveness of current obesity treatments," said **Almut Nitsche, Chief Medical and Development Officer of Resalis Therapeutics**. "The trial is an essential step toward translating our preclinical insights into clinical advancements, paving the way toward a new generation of long-term obesity management treatments."

The Phase 1 trial is a randomized, double-blind, placebo-controlled study conducted in the Netherlands. It consists of two parts: a single ascending dose (SAD) phase and a multiple ascending dose (MAD) phase. In the SAD phase, up to 48 healthy male and female participants will receive incremental single doses of RES-010 to evaluate safety and pharmacokinetics. The subsequent MAD phase will involve 24 overweight and 8 moderately obese participants who will receive multiple doses to further assess RES-010's safety and tolerability. The trial's primary objective is to assess the safety and tolerability of RES-010, while also evaluating its pharmacokinetics profile. Additionally, exploratory endpoints include assessing the effect of RES-010 on specific metabolic markers, change in lipid metabolism, body weight, appetite, and glucose tolerance. Data from the combined SAD/MAD study, which involves multiple phases of dose escalation and extensive safety evaluation, are expected by mid-2026.

Source: https://www.resalistherapeutics.com/news-events/

Fractyl's Gene Therapy Approach Continues to Look Interesting

Single-Dose GLP-1-Based Pancreatic Gene Therapy Prevents Obesity and Diabetes in High-Fat Fed Mice

Timothy J. Kieffer,[1] Chelsea Hutch,[2] Stace Kernodle,[2] Alice L. Fitzpatrick,[1] Emily Cozzi,[1] Shimyn Slomovic,[1] Jay Caplan,[1] Harith Rajagopalan,[1] Randy J. Seeley[2]

[1]Fractyl Health, Inc., Burlington, Massachusetts, USA, [2]University of Michigan Medical School, Michigan Medical, Ann Arbor, Michigan, USA.

Introduction and Study Design

- Glucagon-like peptide 1 (GLP-1) is an incretin that signals satiety and regulates diet hormone secretion. GLP-1 drugs manage diabetes and promote weight loss, but most patients discontinue, leading to weight regain and metabolic decline.
- We have developed a novel, single-dose, pancreatic gene therapy (PGTx) for sustained, meal-regulated GLP-1 production from pancreatic beta cells (Figure 1.).
- In murine models, we have previously shown that GLP-1 PGTx can improve glucose control, induce weight loss, and durably maintain weight loss after semaglutide withdrawal.

Here, we assessed the potential for GLP-1 PGTx to prevent metabolic disease progression in diet-induced obesity (DIO) and lean mice (Figure 2.).

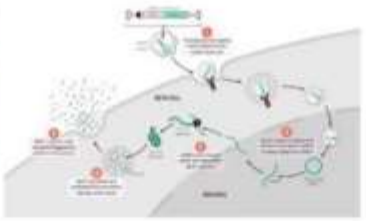


Figure 1. GLP-1 PGTx Therapeutic Mechanism of Action. 1) The GLP-1 transgene construct, consisting of insulin promoter and GLP-1 sequences, is packaged into adeno-associated virus (AAV) 9 vectors which are taken up by the beta cell. 2) Vectors enter the nucleus and release the transgene, which is transcribed into GLP-1 mRNA. 3) GLP-1 mRNA exits the nucleus and is translated into protein. 4) GLP-1 proteins are packaged into secretory vesicles with insulin. 5) GLP-1 with insulin release is triggered by nutrient stimulation.

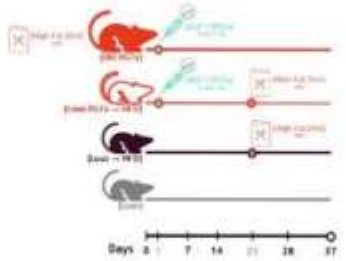


Figure 2. Study Design and Methods. We generated an adeno-associated virus (AAV) 9 vector encoding a GLP-1 receptor agonist transgene under an insulin promoter for beta-cell-specific pancreatic gene therapy (GLP-1 PGTx). Four murine groups were studied for 37 days (n=8 per group): 1) started on 60% high-fat diet (HFD) for >20 weeks, treated with a single intraperitoneal dose of GLP-1 PGTx (8.3e11 vector genomes [VG]), and maintained on HFD (DIO PGTx) 2) started on chow diet, given GLP-1 PGTx, and switched to HFD at day 21 (Lean PGTx→HFD) 3) started on chow diet and switched to HFD at day 21 (Lean→HFD) 4) started and maintained on chow diet (Lean). Body weight, food intake and blood glucose were evaluated throughout the study time course.

Results

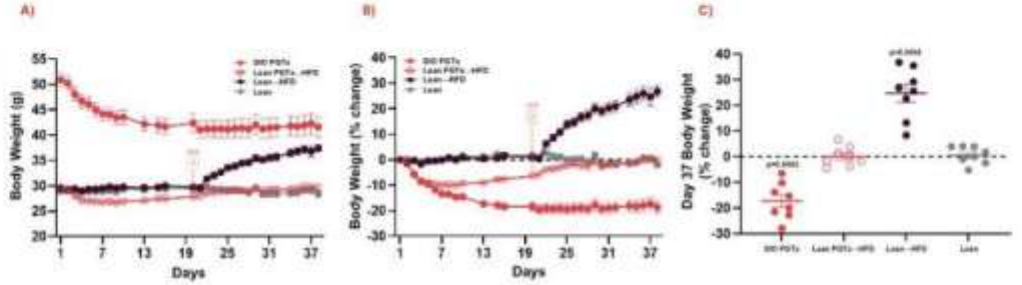


Figure 3. Single-Dose GLP-1 PGTx Reduced Body Weight in Diet-Induced Obesity Mice and Prevented Weight Gain in Lean Mice Challenged with High-Fat Diet. GLP-1 PGTx was well-tolerated in diet-induced obesity (DIO) and lean mice. In the DIO PGTx cohort, GLP-1 PGTx reduced body weight (BW) by 20% at day 21 (B) and maintained weight loss through day 37 on high-fat diet (HFD) (-17%) (A, B and C; p<0.0002). BW at day 37 increased by 25% in the Lean→HFD cohort when switched to HFD (A, B and C; p<0.0002). However, in the Lean PGTx→HFD group, BW was reduced by 6% at day 21 (B), and did not rise above baseline after the HFD switch (A, B and C). Data are reported as mean absolute and percent change from baseline ± standard error of the mean, n=8 per group. HFD=high-fat diet.

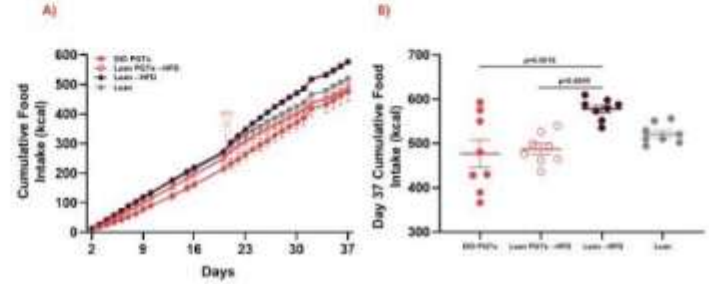


Figure 4. Body Weight Changes are Reflected by Alterations in Food Intake. GLP-1 PGTx reduced cumulative food intake in diet-induced obesity (DIO) mice at day 37 when compared to lean mice challenged with high-fat diet (HFD) (A and B; p=0.0018). Likewise, lean mice treated with GLP-1 PGTx had reduced food intake compared to untreated mice at day 37 after HFD challenge (A and B; p=0.0055). Data are reported as mean ± standard error of the mean, n=8 per group. HFD=high-fat diet.

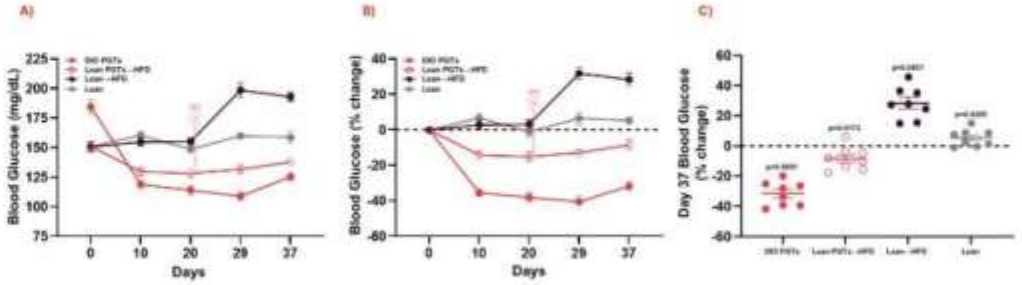


Figure 5. Single-Dose GLP-1 PGTx Reduced Blood Glucose in Diet-Induced Obesity Mice and Prevented Hyperglycemia in Lean Mice Challenged with High-Fat Diet. GLP-1 PGTx reduced blood glucose (BG) by 36% at day 20 (B) in diet-induced obesity (DIO) mice and maintained BG reductions through day 37 on high-fat diet (HFD) (-32%) (A, B and C; p<0.0001). In the Lean→HFD group, BG was increased by 28% at day 37 when switched to HFD (A, B and C; p<0.0001). However, in the Lean PGTx→HFD cohort, GLP-1 PGTx induced a BG reduction of 15% at day 20 (B) and prevented HFD-induced hyperglycemia as evidenced by a BG level 8% below baseline at day 37 (A, B and C; p=0.0173). Data are reported as mean absolute and percent change from baseline ± standard error of the mean, n=8 per group. HFD=high-fat diet.

Conclusions and Next Steps

These data demonstrate that single-dose GLP-1 PGTx can durably reduce weight and glycemia in DIO and prevent weight gain and hyperglycemia when treatment is initiated before HFD challenge.

Lean mice receiving GLP-1 PGTx did not exhibit excessive weight loss or hypoglycemia, suggesting a self-limiting mechanism that could enhance the PGTx safety profile.

PGTx has the potential to advance GLP-1 therapies by offering both reversal and prevention of obesity and type 2 diabetes (T2D), while minimizing risks in lean individuals.

Fractyl Health has submitted the first Clinical Trial Application module for RJVA-001 (human GLP-1 transgene and insulin promotor) in T2D to regulators.

Publications & Presentations | Fractyl.com | Contact Us | Email Alerts

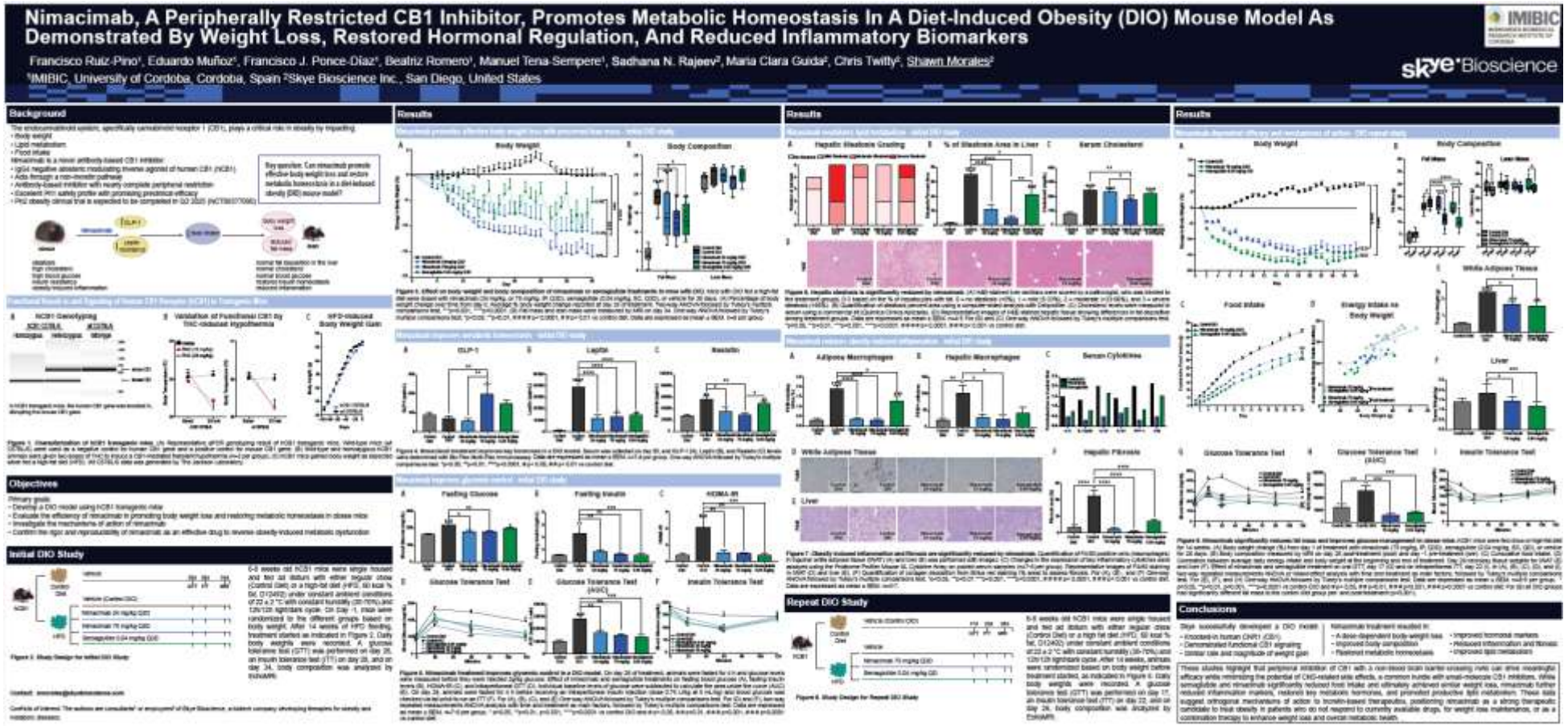
American Diabetes Association. 85TH SCIENTIFIC SESSIONS CHICAGO, IL | JUNE 20-23, 2025

Source: ADA Poster, June 2025

CB1 Drugs

Skye CB1 Shows Promising Preclinical Data at ADA

Importantly, Skye will have a POC readout in Q4 of this year for its promising CB1 mAb Nimacimab.



We saw Novo talk up the potential of its CB1 drug last year, only to disappoint when it press released findings (some unspecified CNS issues). We would note that Skye's CB1 antibody has high potential as it does not cross the blood-brain barrier and is set to report clinical data later this year.

This is an orthogonal MOA that could certainly be additive to the current armamentarium.

We will also see data from a small molecule drug candidate from Corbus later this year.

Given the high weight loss seen with Novo's monlunabant, our own view is that the CB1 class still has reasonable potential to be successful as an add-on therapy in today's incretin-heavy landscape.

Source: https://ir.skyebioscience.com/spotlight

High Potential Remains for Non-Brain Penetrant CB1 Strategy

Complementary, Not Competitive

CB1 impacts key metabolic pathways that complement existing products & strategies

	KEY TARGETS / MECHANISMS					
Key Targets Characteristics	GLP-1[1]	GIP[1]	Glucagon[1]	Amylin[2-4]	Myostatin[5-7]	CB1[8-9]
Decreases Appetite / Increases Satiety	✓	? *(limited)*	x	✓	x	✓
Delays Gastric Emptying	✓	x	✓ *(limited)*	✓	x	✓ *(limited)*
Stimulates Insulin Secretion	✓	✓	✓	x	x	✓ *(limited)*
Insulin Sensitivity	x	x	x	✓	✓	✓
Leptin Sensitivity	x	x	x	✓	✓ *(limited)*	✓
Lean Mass Preservation	x	x	x	x	✓	✓
GI Tolerability	x	x	x	x	?	✓
Key Safety Concerns	Nausea, vomiting, diarrhea	Nausea, vomiting, diarrhea	Increased heart rate, LFT, glucose	Nausea, vomiting, headache	Vascular side effects, erythema	Neuro-psychiatric symptoms[10]
Other Notable Considerations	Reduces glucagon secretion	Perceived synergistic in CNS w/ GLP1	Metabolic benefits/ mimic exercise	Reduces glucagon secretion	GLP-1 combination regimen	Complements incretin backbone

Opportunities for Nimacimab

- ✓ Magnitude and sustainability of weight loss
- ✓ Improved safety/tolerability profile (e.g. limited GI side effects)
- ✓ No neuropsychiatric symptoms observed in clinical trials
- ✓ Potential for reduced frequency of drug administration
- ✓ Maintenance dose/setting beyond GLP-1 RA
- ✓ Combinability with other mechanisms/agents

Prescribers/patients/payors will consider differentiated product attributes based on individual needs

Source: 1. Guggenheim Obesity Report; 2. Boyle. J Clin Med. 2022; 3. Dehestani. J Obes Metab Syndr. 2021; 4. Suh. J Bone Metab. 2020; 5. Roth. PNAS. 2008; 6. Choi. Am J Physiol Endocrinol Metab. 2011; 7. Schurgers. Cells. 2021; 8. RBC Capital Markets (February 2024); 9. Skye Internal Data 10. small molecule CB1 inhibitors

Corbus Pharmaceuticals Initiates Multiple Ascending Dose Portion of Phase 1 Study of CB1 Inverse Agonist CRB-913 for the Treatment of Obesity

NORWOOD, Mass., June 30, 2025 (GLOBE NEWSWIRE) -- Corbus Pharmaceuticals Holdings Inc. (NASDAQ: CRBP), a clinical-stage company focused on oncology and obesity, today announced the initiation of the multiple ascending dose (MAD) portion of its Phase 1 trial for CRB-913, a highly peripherally restricted CB1 inverse agonist for the treatment of obesity. This follows safety and pharmacokinetics (PK) data analysis of the single ascending dose (SAD) study launched in March. The MAD portion of this clinical study is scheduled for completion in the third quarter of this year.

The MAD portion of the Phase 1 trial is designed to test a once-daily dosing of CRB-913 for 7 days. Similarly to the SAD study, the MAD study is undertaken with healthy volunteers and focuses on safety, tolerability and PK of increasing doses of CRB-913. The study is being conducted in the United States.

“The data collected to date shows a satisfactory translation from pre-clinical models to the clinical settings,” said Yuval Cohen, PhD, CEO of Corbus. “An absence of treatment-related neuropsychiatric events was noted even at markedly higher doses than our modelling suggests would be required to achieve efficacy in clinical practice. We look forward to generating further clinical evidence in the multiple ascending dose cohorts before initiating a Phase 1b dose-range finding study in obese individuals later this year.”

The SAD/MAD portion of the Phase 1 trial is scheduled to be completed in Q3 of 2025, and the Company expects to commence a Phase 1b dose-range finding study in Q4 of 2025. The dose-range finding study is scheduled for completion in the second half of 2026.

About CRB-913

CRB-913 is an oral small molecule inverse agonist of the G-protein Coupled Receptor (GPCR) cannabinoid type-1 (CB1). This is a recognized mechanism of action for weight loss, but the previous class of such experimental drugs was abandoned due to potential neuropsychiatric adverse event risks. CRB-913 is a member of a new class of peripherally restricted CB1 inverse agonists designed to have reduced brain penetration.

Source: https://www.globenewswire.com/news-release/2025/06/30/3107418/0/en/Corbus-Pharmaceuticals-Initiates-Multiple-Ascending-Dose-Portion-of-Phase-1-Study-of-Highly-Peripherally-Restricted-CB1-Inverse-Agonist-CRB-913-for-the-Treatment-of-Obesity.html

GIP Blockers

The Promise of GIP Blockade

We have written enthusiastically about the potential of GIP inhibitors in past reviews of the obesity field.

This was one of the reasons we have been quite enthusiastic about Amgen's MariTide – perhaps our least well performing prognostication in the obesity area. We saw MariTide as a potent double whammy drug that could take out tirzepatide which has a *GIP agonist* component.

The argument for GIP inhibition is that GIP is upregulated with meals and signals to the pancreas that it's time to make a lot of insulin. Insulin in turn signals to adipocytes that they should pull glucose out of the circulation and store it as fat. Therefore, we reasoned that GIP antagonists should be a lot better than GIP agonists.

Further, the benefit of a pure GIP antagonist is that a patient can choose whether to take a GLP-1 agonist alone or to instead go with GIP receptor antagonist alone or to combine with another incretin agonist (e.g., amylin). This would allow patients to avoid the nausea inducing effect of GLP-1's if preferred. Given that 30% of GLP-1 users terminate use due to tolerability, the market for a monotherapy GIP agonist could be very large.

So far, the score is something like 5-0 against GIP antagonists. We have seen data from MariTide that was not as good as tirzepatide this year. Given that both molecules agonize GLP-1 it would seem that GIP agonism is a better strategy than antagonism.

Or, is it? Perhaps MariTide isn't that potent of a GIPr antagonist. And, further, there is good reason to think that GIPr agonists might actually be functional antagonists.

We touched on the evidence supporting this view in our review last year of MariTide where we noted that free insulin seemed *unaffected* in Amgen's phase 2a study. Interestingly, Amgen has published full results of its Phase 2b study in the last month but did not report what happened to free insulin with its drug. Puzzling. In contrast, there is clear evidence that tirzepatide knocks down insulin more than GLP-1 agonists alone, supporting the view that GLP/GIP agonists may actually be functional antagonists of GIP.

The June 2025 issue of *Diabetes* included two articles on the GIP debate. One article by Rosenkilde et. al., reviewed the overwhelming genetic, animal and clinical evidence in favor of GIP antagonism. A second article by Samms and Sloop takes the other side and argues that GIPR agonism attenuates nausea and suppresses appetite.

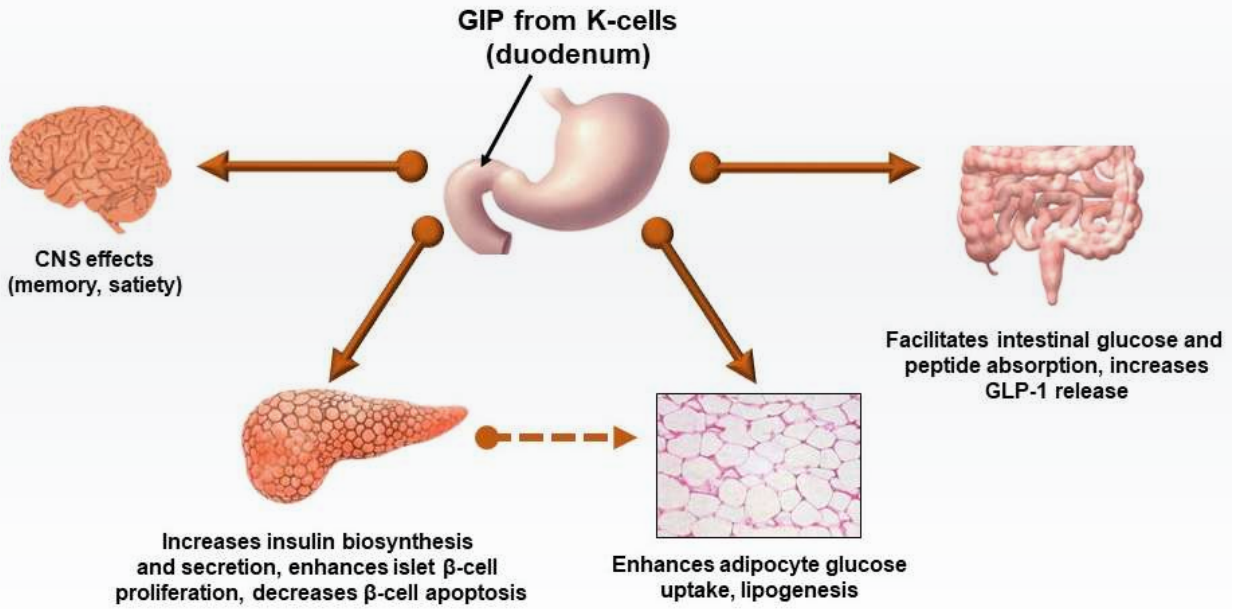
We will soon see some exciting and, hopefully, decisive data coming up on this debate. Specifically, Pfizer is well advanced with a GIPR antagonist drug, PF-07976016, which is in Phase 2a tests. This is a GIPR monotherapy trial that should, for once and for all, settle the matter. In addition, Helicore is testing a GIP ligand antibody and is in Phase 1 studies. Further, Helicore, perhaps noting Amgen's results, is souping up its pipeline by generating bispecifics of its GIP antibody with arms that agonize other key incretins such as amylin. Interesting indeed.

Finally, Antag's AT-7687 is a potent peptide GIP receptor antagonist. Antag has just started its Phase 1 studies so upcoming results should be quite interesting.

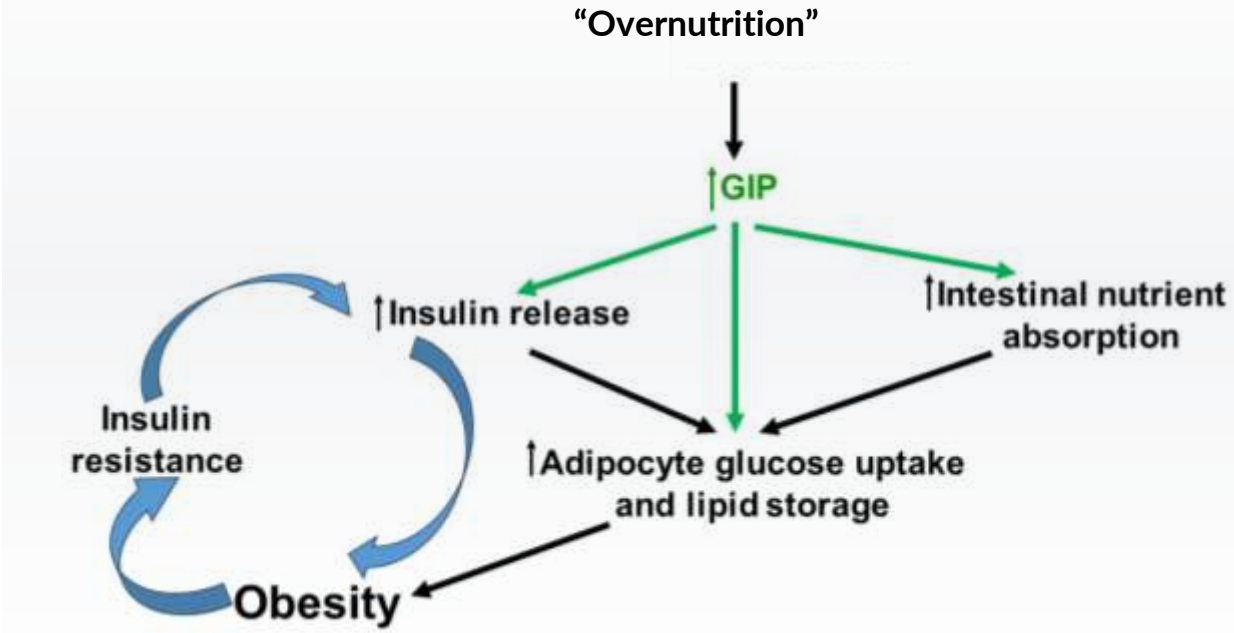
GIP in Health and Disease

*"Antagonizing GIP corrects vicious cycle and attenuates deleterious effects"**

Physiological Properties



Pathophysiology of Obesity



GIP overexpression leads *directly* to: (1) increased gut nutrient absorption, (2) enhanced adipocyte glucose uptake, and (3) enhanced adipocyte fat storage; Overexpression of GIP can lead to insulin resistance by causing obesity, leading to hyperinsulinemia and pre-diabetes and the development of a vicious cycle; (*Miyawaki K *et al. Nat Med* 2002;8:738-742)

GIP Blocker Pipeline

A year ago, just one or two assets on this page were in active development. There has been an explosion of development activity in muscle preservation associated with weight loss.

This area is very interesting but there are questions with the Activins (e.g., repro tox / black box / IV presentation).

Monotherapy myostatin inhibitors seem to have potential in preserving muscle. Importantly, Regeneron can administer this with a subcutaneous drug.

	Drug Category		
Current Phase of Development	**GIPR Antagonist**	**GIP Ligand Inhibitor**	**GIP antagonist dual therapy**
Phase 2 / Phase 3			AMGEN (MariTide)
Phase 1	ANTAG THERAPEUTICS (AT-7687) Pfizer (PF-07976016)	Helicore (HCR-188)	GMAXBio (GMA106)*
Pre-Clinical		Incregen Therapeutics	Helicore

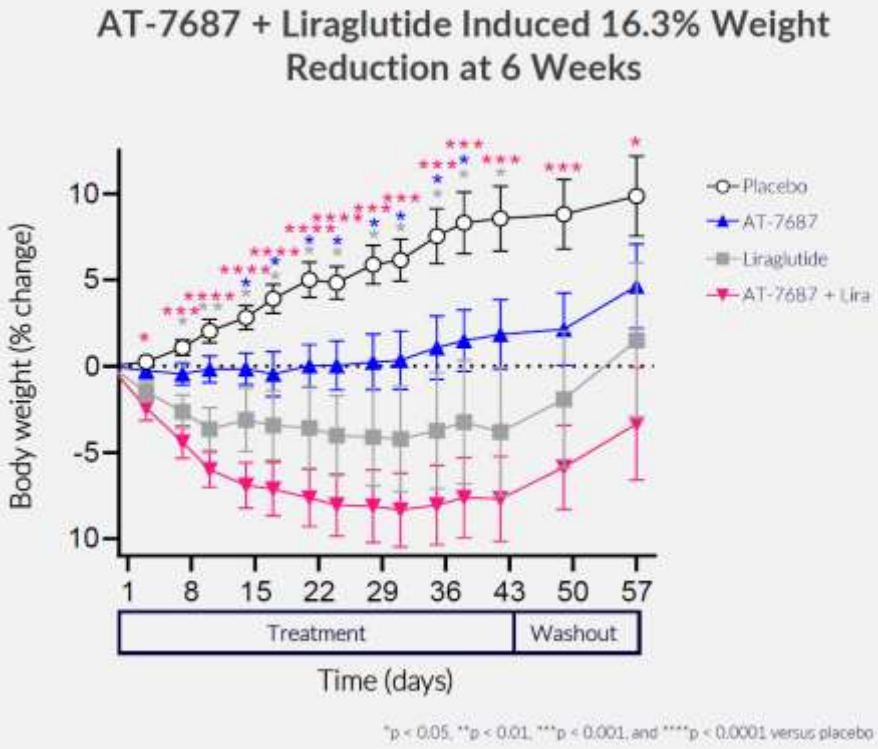
* GMAX has informed us that it has entered into an undisclosed outlicense of this compound to a third party.

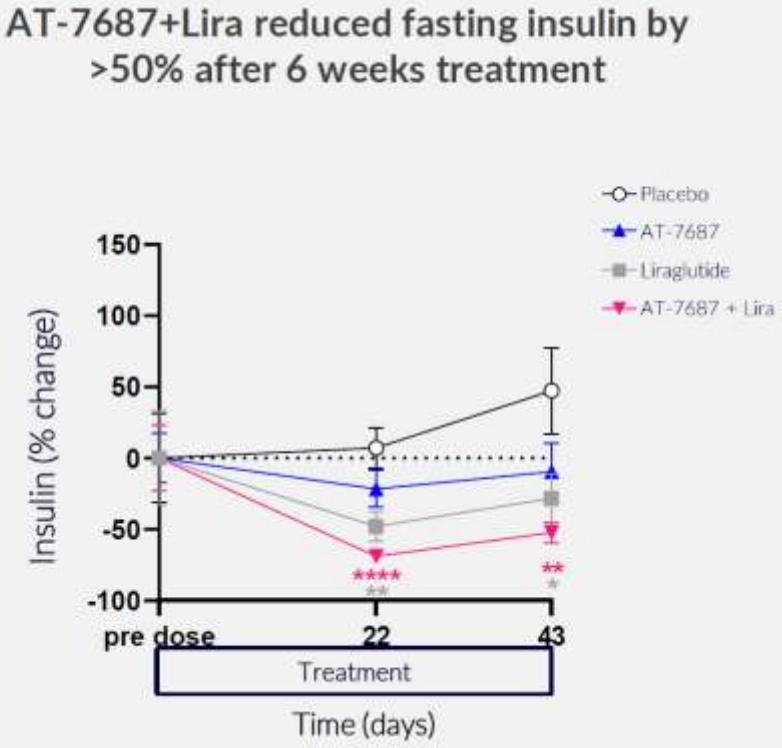
Source: Stifel Research and DealForma

Antag's GIP Blocker's Potential as an Alternative to GLP-1's

Antag's AT-7687 is a potent peptide GIP receptor antagonist. However, unlike MariTide, Antag's molecule does not agonize GLP-1. The result is that a patient can choose whether to take a GLP-1 agonist alone or to instead go with GIP receptor antagonist alone or to combine with another incretin agonist (e.g., amylin). This would allow patients to avoid the nausea inducing effect of GLP-1's if they prefer. Given that 30% of GLP-1 users terminate use due to tolerability, the market for a monotherapy GIP agonist could be very large.

Studies in non-human primates put on fatty diets show that Antag's GIP antagonist lowers insulin and results in much less weight gain:





Charts are from Antag.

Antag to Have Phase 1 Data for its GIPR Blocker in Q4 2025

ANTAG THERAPEUTICS

Antag Therapeutics initiates Phase 1a trial of AT-7687, a first-in-class GIPR antagonist designed to address key gaps in obesity treatment

- *First subjects dosed in double-blind, placebo-controlled trial assessing AT-7687's safety, tolerability, pharmacokinetics, and metabolic effects in healthy lean subjects and subjects living with obesity*
- *With strong genetic and clinical validation, AT-7687 aims to induce weight loss without gastrointestinal side effects, a major challenge in obesity management*

Copenhagen, Denmark, 2 April 2025 – Antag Therapeutics ("Antag" or "the Company"), a biopharmaceutical company pioneering novel treatments for obesity, today announces the initiation of its first-in-human Phase 1 clinical trial evaluating AT-7687, a first-in-class Glucose-Dependent Insulinotropic Polypeptide Receptor (GIPR) antagonist. AT-7687 is designed to offer a new approach to obesity treatment by targeting the GIPR, a mechanism with strong genetic and clinical validation for its potential to improve weight loss efficacy and tolerability of incretin-based therapies.

Source: https://antagtx.com/

Muscle Preservation

Why Revenues for Muscle Preserving Drugs Could be Huge

There are at least three use cases for a good SubQ or oral muscle enhancing drug: (1) avoiding the muscle loss side effect of GLP-1's, (2) preventing sarcopenia in the elderly and (3) generate aesthetic benefit. We believe that many men would pay up for muscle enhancing drugs from a pure aesthetic perspective. In the same sense that GLP-1's have generated very high demand from consumers in the DTC market we would expect $100bn+ in market potential in the aesthetic segment. Once a patient has conquered girth, muscling up tends to be the next priority. If you will, the next phase is going away from "Ozempic face" to having a truly great physique. Obviously, these drugs will need to be shown to be safe to justify this type of aesthetic use and will need to get through FDA.

Overweight Patient Before GLP-1 / GIP Drug

Patient After 18 Months on GLP-1 / GIP Drug

Patient After 18 Months on GLP-1 / GIP Drug and Muscle Preserving / Enhancing Drug

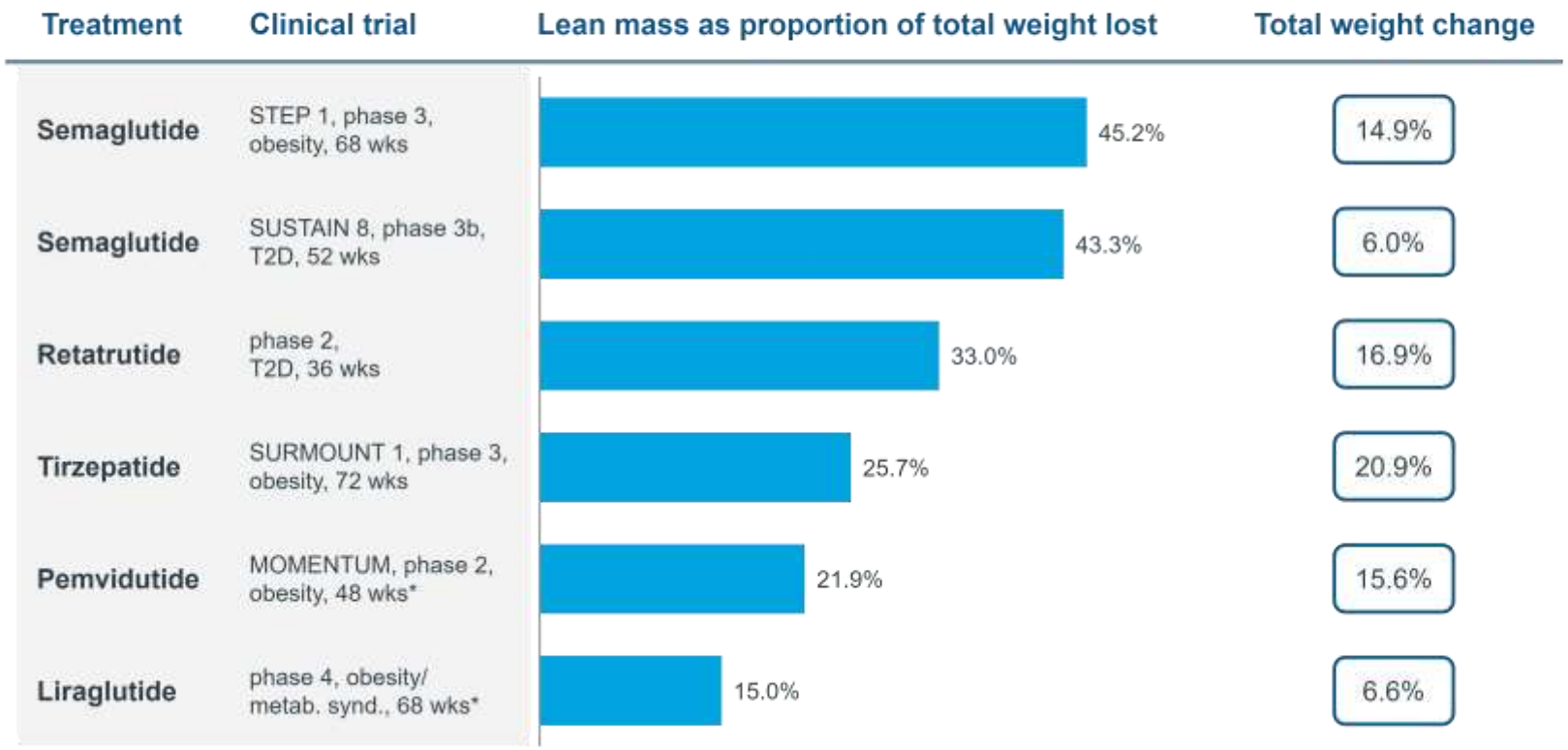
Significant Need to Manage Lean Mass Loss with GLP-1's

Markus Gores, "Beyond weight loss: Preserving muscle during pharmacotherapy of obesity," IQVIA Blog, July 3, 2025

Figure 1

Effect of AOM treatment on lean body mass

Selected clinical trials



* Lean mass in these trials estimated from MRI measured lean volume; DXA scans used in all other trials to measure lean mass
Source: Relevant scientific publication of trial results; IQVIA EMEA Thought Leadership analysis,

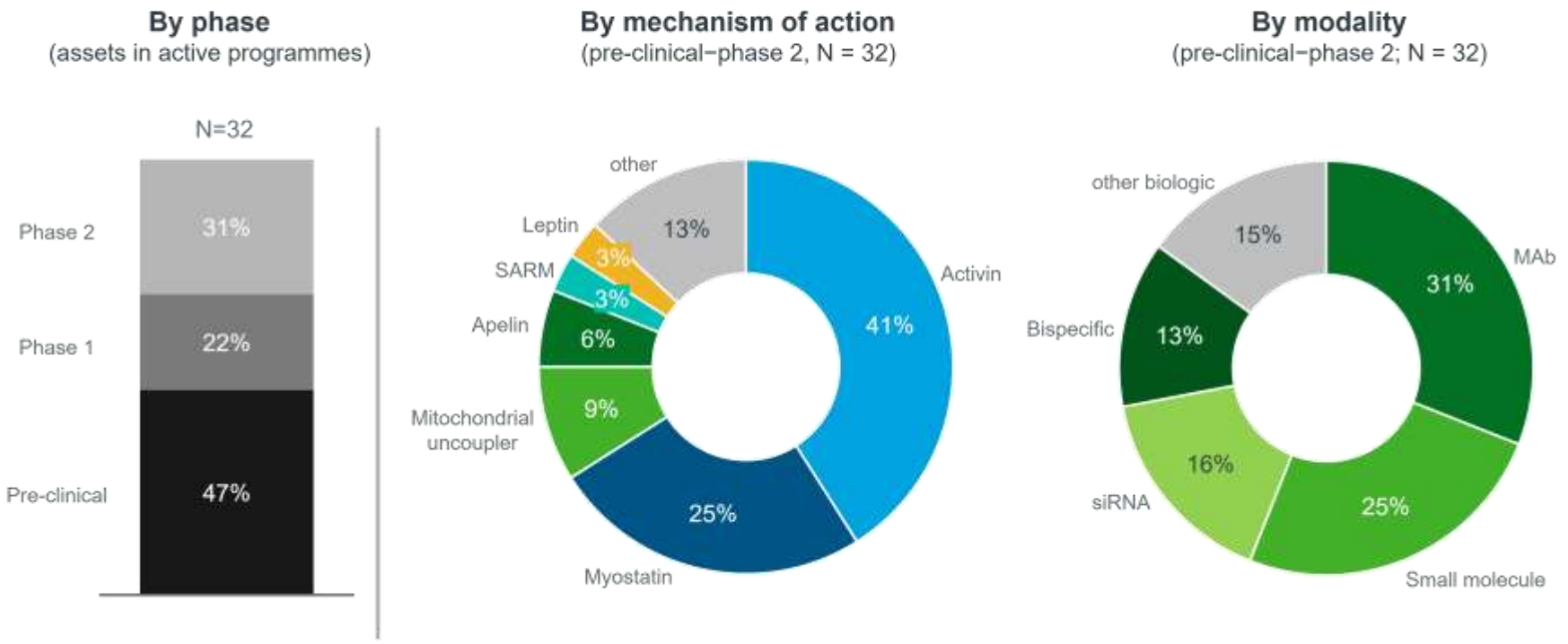
Source: https://www.iqvia.com/locations/emea/blogs/2025/06/beyond-weight-loss

Pipeline of Muscle Preserving Drugs Growing

Markus Gores, "Beyond weight loss: Preserving muscle during pharmacotherapy of obesity," IQVIA Blog, July 3, 2025

Figure 3

Pipeline: muscle-preserving therapies for obesity



Source: IQVIA Analytics Link; Clinicaltrials.gov; company reports, press releases, desk research; IQVIA EMEA Thought Leadership analysis

Source: https://www.iqvia.com/locations/emea/blogs/2025/06/beyond-weight-loss

Muscle Preservation Pipeline

Two years ago, just one or two assets on this page were in active development. There has been an explosion of development activity in muscle preservation associated with weight loss.

This area is very interesting but there are questions with the Activins (e.g., repro tox / black box / IV presentation).

Recent bimagrumab data show the potential of these drugs to avoid muscle loss when used with GLP-1's. Most interestingly, this was done with via a subQ formulation. A key unanswered question is what the FDA will want to see for an approval of a muscle drug. For example, will functional outcomes be needed?

	Drug Category			
Current Phase of Development	**Activin receptor II inhibitor**	**Myostatin Inhibitor**	**SARMs/Testosterone**	**Other Approaches**
Phase 2 / Phase 3	Lilly Bimagrumab	REGENERON Trevogrumab ScholarRock Apitegromab	LIPOCINE ENHANCING HEALTH Testosterone veru Enobasarm	biophytis LIVE LONGER, LIVE HEALTHIER BIO101 (MAS receptor activator) BIOAGE Azelaprag (Apelin)
Phase 1	REGENERON Garetosmab 35 Pharma AliveGen Live Stronger and Longer	KEROS THERAPEUTICS KER-065 ProGen PG-110		Juvena IGF-2 Fusion Protein
Pre-Clinical	biohaven Aldefgrobep alfa 35 Pharma iBio sixpeaks BIO	biohaven Taldefgrobep iBio PeptiDream ScholarRock SRK-439		Immunis Emmyon Metabolic Health REGERNA Therapeutics

Source: Stifel Research and DealForma

Muscle Preservation Drugs by Mode of Administration

Given that Lilly has shown good results with SubQ bimagrumab, we think it will be important that future muscle enhancing drugs either be SubQ or oral.

Indeed, a reasonable dosage volume delivered SubQ seems like the minimal price of admission to the muscle drug field in the future.

This chart identifies six candidates for SubQ delivery and three for oral. Presumably, Regeneron should be able to create SubQ versions of its leading drug candidates.

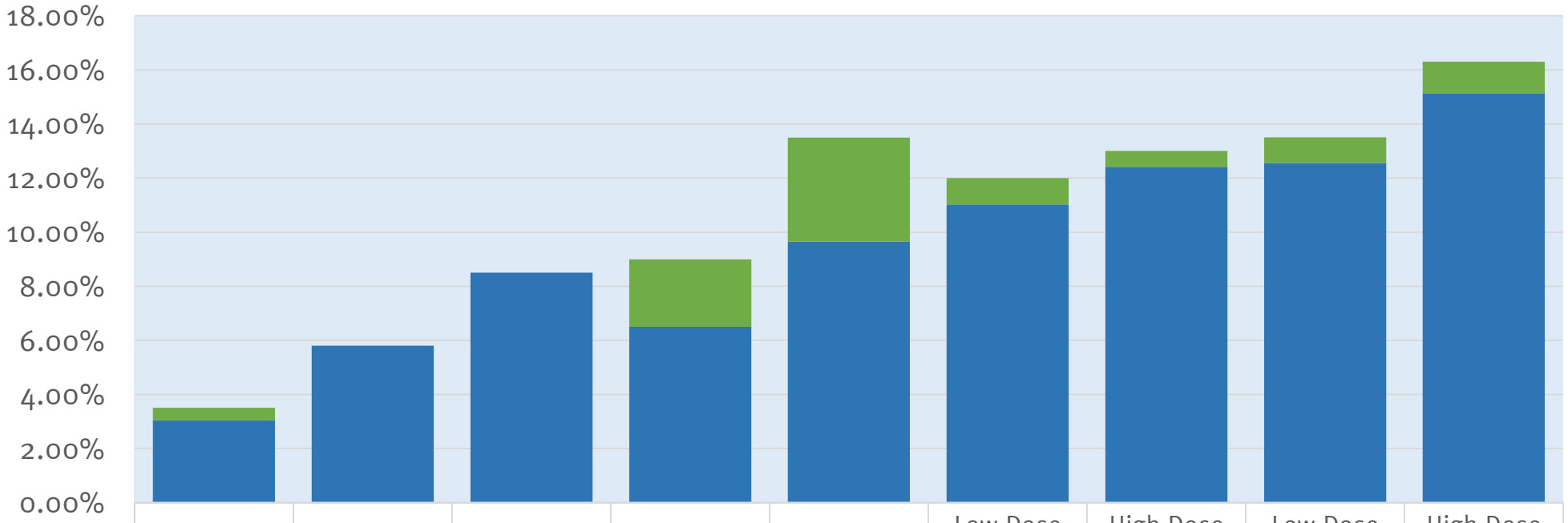
	Drug Category			
Current Phase of Development	**Activin receptor II inhibitor**	**Myostatin Inhibitor**	**SARMs/Testosterone**	**Other Approaches**
Oral			veru Enobasarm LIPOCINE ENHANCING HEALTH Testosterone	biophytis LIVE LONGER, LIVE HEALTHIER BIO101 (MAS receptor activator)
SubQ	Lilly Bimagrumab biohaven Aldefgrobep alfa	ProGen PG-110 biohaven Taldefgrobep PeptiDream iBio		Immunis
Intravenous	REGENERON Garetosmab KEROS THERAPEUTICS KER-065	REGENERON Trevogrumab ScholarRock Apitegromab	Juvena IGF-2 Fusion Protein	

Source: Stifel Research and DealForma

Summary of Improvements in Body Composition by Adding Bimagrumab to a GLP-1 Agonist

Inhibition of the Activin Type B Receptor Improves the Composition of Weight Loss

Results from the 48-Week BELIEVE Trial



	Placebo	Low-Dose Bimagrumab	High-Dose Bimagrumab	Semaglutide 1 mg	Semaglutide 2.4 mg	Low-Dose Bima + Sema 1 mg	High-Dose Bima + Sema 1 mg	Low-Dose Bima + Sema 2.4 mg	High-Dose Bima + Sema 2.4 mg
Lean Mass Reduction (% of BW)	0.46%	0.00%	0.00%	2.50%	3.85%	0.98%	0.58%	0.95%	1.16%
Fat Mass Reduction (% of BW)	3.05%	5.80%	8.50%	6.50%	9.65%	11.02%	12.42%	12.56%	15.14%

Source: BELIEVE Trial, ADA 2025

Regeneron Phase 1 Data for Trevogrumab at ADA (2024)

OR: CLINICAL THERAPEUTICS—OTHER THERAPEUTIC AGENTS | JUNE 14 2024

34-OR: The Effect of Combined Activin A and Myostatin Blockade on Body Composition—A Phase 1 Trial FREE

DINKO GONZALEZ TROTTER; STEPHEN DONAHUE; CHRIS WYNNE; SHAZIA ALI; PRODROMOS PARASOGLOU; ANITA BOYAPATI; KUSHA MOHAMMADI; BRET J. MUSSER; PRETTY MEIER; JASON MASTAITIS; EVELYN GASPARINO; JESUS TREJOS; JOHN D. DAVIS; GARY A. HERMAN; ROBERT PORDY

Introduction: Preclinical data suggest myostatin and activin A are important negative regulators of muscle mass. Trevogrumab (a monoclonal antibody [mAb]) binds and blocks myostatin signalling, while garetosmab (a mAb) binds and blocks activin A, AB and AC signalling. Here, the effects of administering trevogrumab and garetosmab, alone or in combination, on body composition in healthy participants was assessed.

Methods: This Phase 1, double-blind, placebo-controlled study randomized healthy males and postmenopausal females to single-dose or multiple-dose parts of the study. For single-dose, females received: trevogrumab 6 mg/kg (n=6); garetosmab 10 mg/kg (n=6); combination trevogrumab 6 mg/kg and garetosmab (1 mg/kg, n=6; 3 mg/kg, n=6; 10 mg/kg, n=12); or placebo (PBO; n=12). For multiple-dose, females received: garetosmab 10 mg/kg every 4 weeks (Q4W; n=6) or PBO (n=2); combination trevogrumab 6 mg/kg and garetosmab 10 mg/kg every 2 weeks (n=6) or PBO (n=4). In the multiple dose part, males received garetosmab 10 mg/kg Q4W (n=8) or PBO (n=8).

Results: **Thigh muscle volume (TMV) increased from baseline 7.7% with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (nominal P<0.001 vs PBO) and 4.6% with trevogrumab 6 mg/kg (nominal P<0.05 vs PBO) 8 weeks after single-dose. Total fat mass and android fat mass (AFM) decreased from baseline with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (-4.6% and -6.7%; both nominal P<0.05 vs PBO).** After multiple-dose, TMV initially increased after 3 doses of trevogrumab 6 mg/kg + garetosmab 10 mg/kg but decreased to similar levels as PBO at Week 28; AFM and visceral fat mass decreased from baseline by 14.3% and 20.1%, respectively (both nominal P<0.05 vs PBO). No safety concerns were identified in any active treatment groups.

Strong data!

Source: ADA 2024 Website, https://diabetesjournals.org/diabetes/article/73/Supplement_1/34-OR/154774/34-OR-The-Effect-of-Combined-Activin-A-and

Regeneron (Jun 2, 2025): Phase 2 COURAGE Trial Data

Interim Results from Ongoing Phase 2 COURAGE Trial Confirm Potential to Improve the Quality of Semaglutide (GLP-1 receptor agonist)-induced Weight Loss by Preserving Lean Mass

June 2, 2025 at 7:00 AM EDT

PDF Version

Trial demonstrated that approximately 35% of semaglutide-induced weight loss was due to loss of lean mass

Combining semaglutide with muscle-preserving antibodies protected lean mass – sparing approximately 50%-80% of the lean mass lost with semaglutide alone – while also increasing loss of fat mass

TARRYTOWN, N.Y., June 02, 2025 (GLOBE NEWSWIRE) -- Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced interim results from the ongoing Phase 2 COURAGE trial investigating novel combinations of semaglutide (GLP-1 receptor agonist) and trevogrumab (anti-GDF8/anti-myostatin) with or without garetosmab (anti-activin A) for the treatment of obesity. The trial demonstrated that approximately 35% of semaglutide-induced weight loss was due to loss of lean mass, and further demonstrated that combining semaglutide with trevogrumab with or without garetosmab helped preserve lean mass while increasing loss of fat mass. The interim analysis was conducted when 50% of patients reached week 26 in the trial. The combination of semaglutide with trevogrumab was generally well-tolerated; the triplet combination of semaglutide with both antibodies had a substantially higher rate of discontinuations due to tolerability issues and other adverse events, consistent with the safety profile previously seen with garetosmab alone.

Source: https://investor.regeneron.com/news-releases/news-release-details/interim-results-ongoing-phase-2-courage-trial-confirm-potential

Much Improved Preservation of Lean Mass When Regeneron Molecule Used

	Semaglutide monotherapy (n=151)	Lower-dose combo (n=149)	Higher-dose combo (n=152)	Triplet (n=147)
Lean mass				
Change in lean mass (SE), in lbs (% of total weight loss)	-7.9 (0.64) lbs (-34.5%)	-3.7 (0.64) lbs*** (-17.0%)	-4.2 (0.66) lbs*** (-16.8%)	-2.0 (0.75) lbs*** (-6.6%)
% preservation of lean mass (compared to semaglutide monotherapy)	---	50.8%	51.3%	80.9%
Fat mass				
Change in fat mass (SE), in lbs (% of total weight loss)	-15.3 (0.90) lbs (-66.3%)	-16.9 (0.90) lbs (-78.1%)	-18.9 (0.93) lbs* (-76.3%)	-25.4 (1.06) lbs*** (-84.4%)
% increase in fat loss (compared to semaglutide monotherapy)	---	17.8%	15.1%	27.3%
Body weight				
Change in body weight (SE), in lbs (% change in body weight)	-23.0 (1.12) lbs (-10.4%)	-21.6 (1.15) lbs (-9.9%)	-24.8 (1.15) lbs (-11.3%)	-30.0 (1.26) lbs*** (-13.2%)

*** = statistically significant at 0.01 or better probability.

Source: https://investor.regeneron.com/news-releases/news-release-details/interim-results-ongoing-phase-2-courage-trial-confirm-potential

Some Tolerability Issues with Regeneron Products

The lower dose combo improves muscle condition without having a worse tolerability profile than semaglutide alone. The high dose combo doesn't buy much extra muscle mass but appears to substantially worsen tolerability. The 9% discontinuation rate seen with the Bimagrumab/Sema combo is in line with the high dose combo shown here. Our sense is that the products are fairly similar in AE's. An important distinction is that both trevogrumab and garetosmab are administered as IV infusions in their clinical programs. There is no public indication that subQ formulations are imminent from Regeneron.

Participants with at least one:	Semaglutide monotherapy (n=151)	Lower-dose combo (n=148)	Higher-dose combo (n=151)	Triplet (n=149)
TEAE	64.9%	68.2%	68.2%	77.2%
Severe TEAE	2.0%	1.4%	3.3%	10.1%
TE-SAE	0.7%	0.7%	1.3%	6.7%
TEAE leading to treatment discontinuation	**4.6%**	**4.1%**	**10.6%**	**28.3%**
Treatment-related TEAE	47.0%	48.6%	56.3%	63.8%

Source: https://investor.regeneron.com/news-releases/news-release-details/interim-results-ongoing-phase-2-courage-trial-confirm-potential

Scholar Rock Apitegromab Worked Nicely to Preserve Muscle When Used Alongside Tirzepatide

OBESITY

EMBRAZE Demonstrated Improved Overall Body Composition with Apitegromab

EMBRAZE

Study achieved goals

54.9%
STATISTICALLY SIGNIFICANT LEAN MASS PRESERVATION COMPARED TO GIP/GLP-1 MONOTHERAPY (p=0.001)

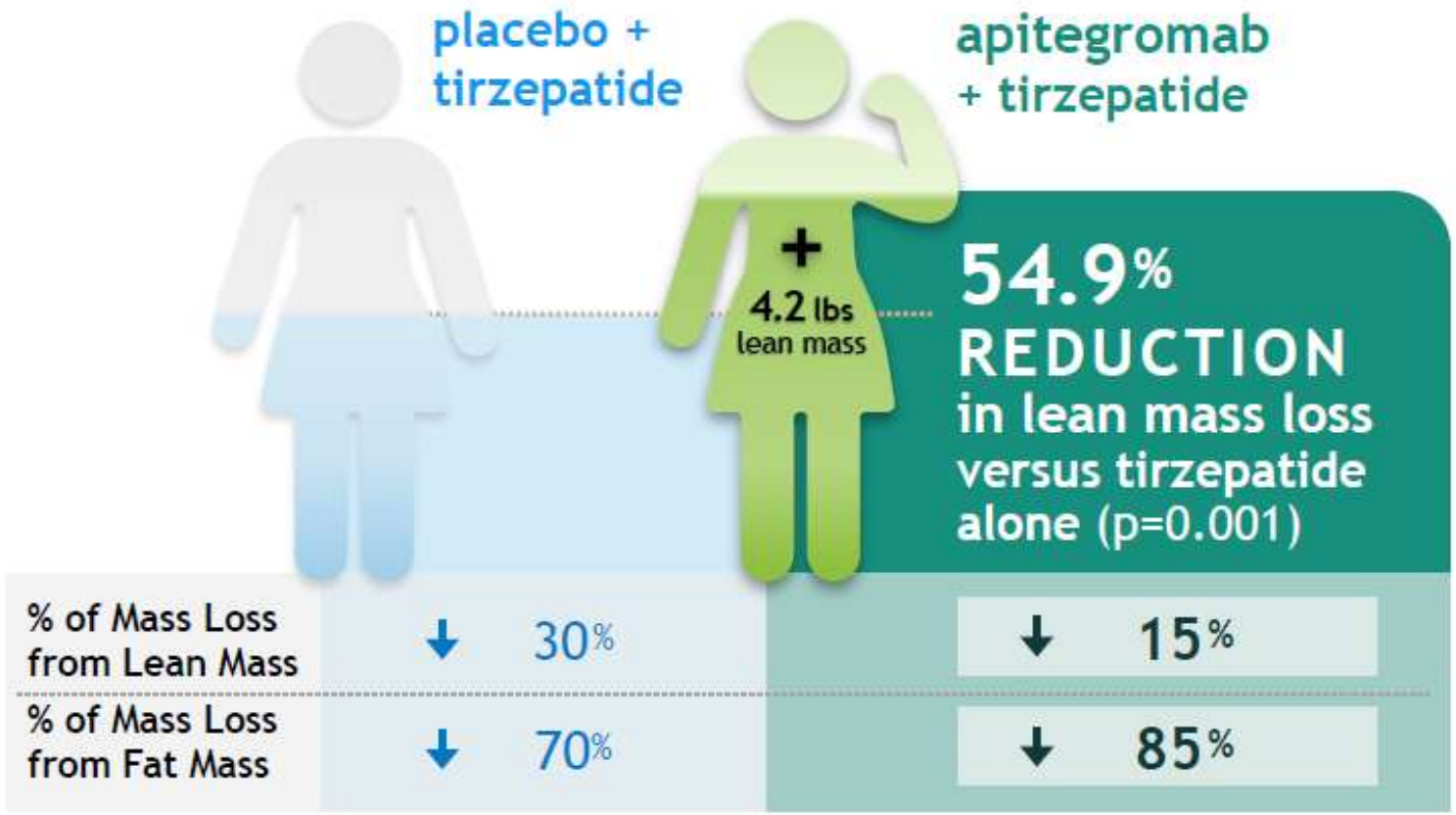
WEIGHT & FAT MASS LOSS CONSISTENT WITH GIP/GLP-1 MONOTHERAPY

ENCOURAGING SAFETY PROFILE

Trial demonstrated ~30% of tirzepatide-induced weight loss was due to lean mass loss

Source: https://investors.scholarrock.com/static-files/ee81c6fd-aeef-4a5a-9457-b73496b68aa3

Apitegromab Associated with a Big Improvement in Lean Muscle Loss



There is much to like about the Scholar Rock myostatin inhibitor approach to muscle preservation.

The company ran the right study – looking at how the molecule could improve the quality of weight loss for patients on tirzepatide.

Apitegromab is nearing a BLA approval for its benefits for SMA.

Unfortunately, with the recent Bimagrumab data from Lilly, this molecule does not look competitive.

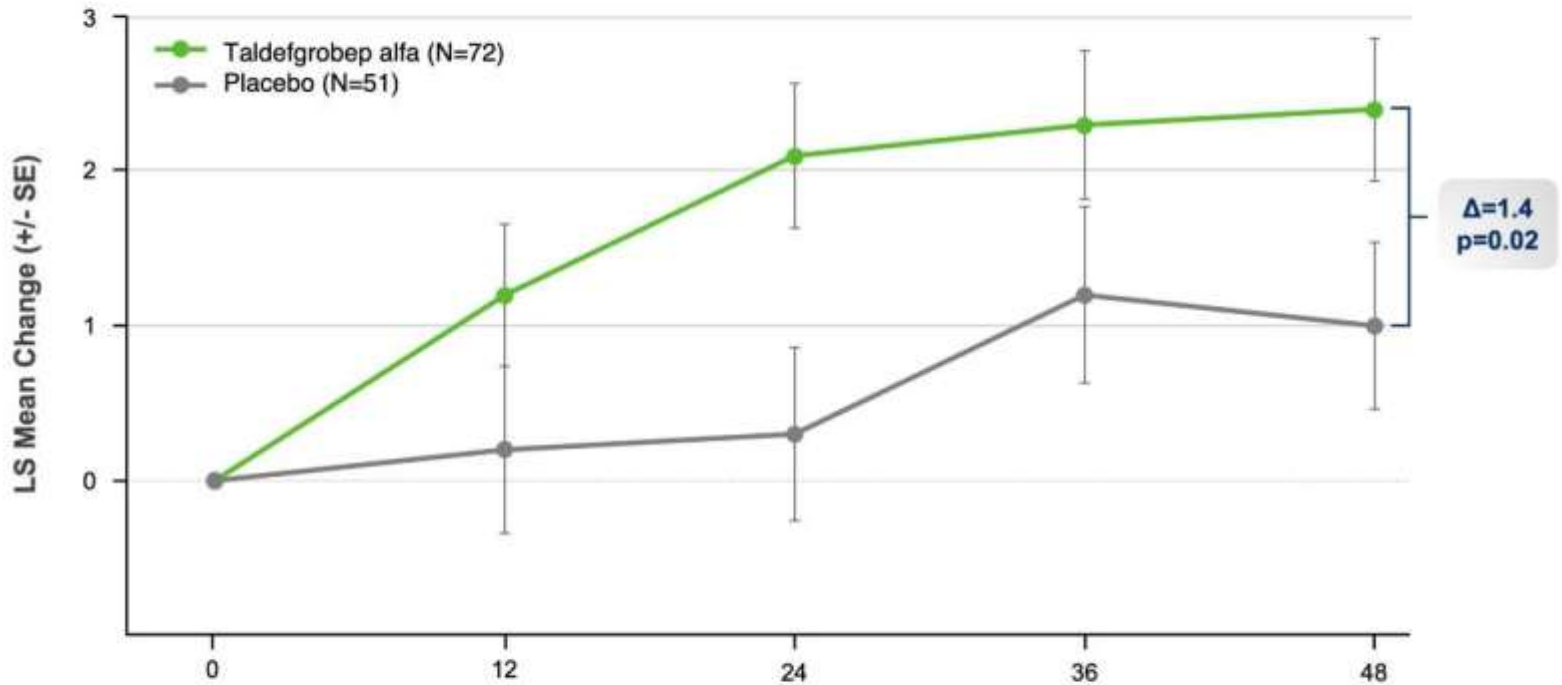
The reason is that Apitegromab is an IV delivered drug that will have a rare disease pricing scheme.

There does not appear to be a commercial pathway with which to take this molecule into the obesity market.

Source: https://investors.scholarrock.com/static-files/ee81c6fd-aeef-4a5a-9457-b73496b68aa3

Biohaven in Phase 2 Studies with Taldefgrobep Alfa with a Product in an Autoinjector

Figure 1: MFM-32 Total Score Change from Baseline in Caucasian Subjects with Measurable Free Myostatin Levels Present at Baseline



Taldefgrobep alfa	72	68	68	70	68
Placebo	51	51	49	50	50

LS, least squares; MFM-32, 32-Item Motor Function Measure; SE, standard error

Source: https://ir.biohaven.com/news-releases/news-release-details/biohaven-provides-update-taldefgrobep-alfa-development-program

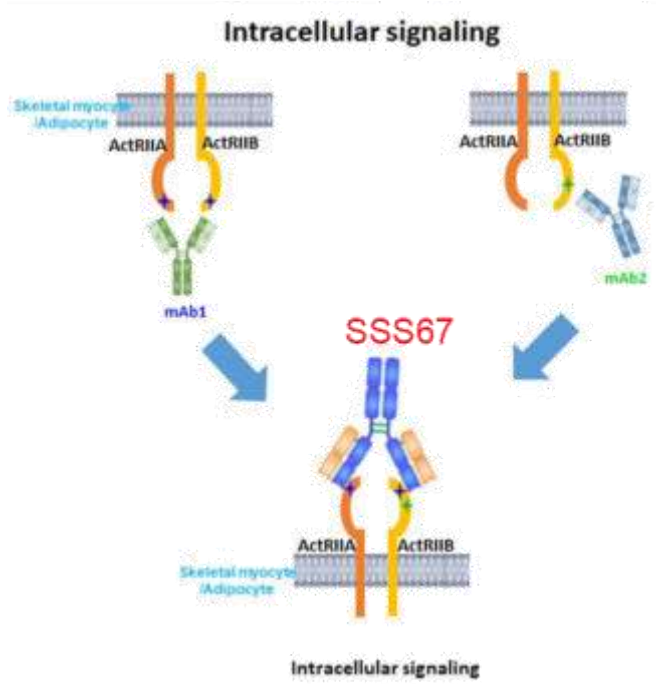
3SBio Developing a Muscle Drug to Compete vs. Bima

3SBIO SSS67 is an ActRIIA and ActRIIB inhibitor

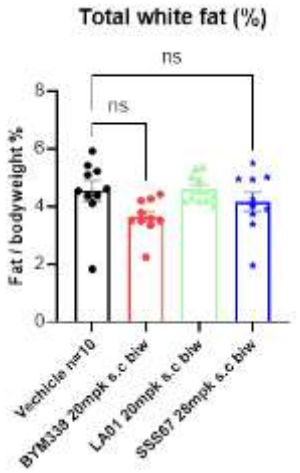
SSS67 is a preclinical bispecific antibody made of two distinct mAbs:

- mAb1 simultaneously binds to ActRIIA and ActRIIB (**blue stars in diagram beow**)
- mAb2 binds only to ActRIIB at one binding site (**green star**) distinct form that of mAb1 This allows SSS67 to essentially bind to three different epitopes on two receptors, two of which are on ActRIIB and allows ActRIIB to accommodate two antibodies at the same time

Targeting two distinct domains of a single receptor by a bispecific antibody showed enhanced inhibitory effects in the clinic as demonstrated by Zymeworks' zanidatamab



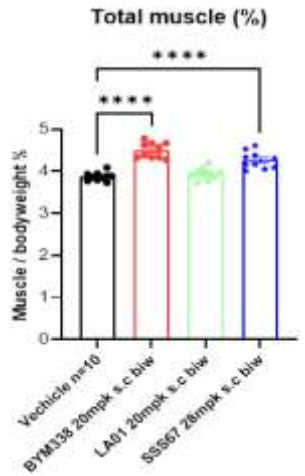
SSS67 showed comparable muscle gain and fat loss to bima *in vivo*



SSS67 showed apparent tendency to **reduce white fat** in SCID mice on par with that of bimagrumab, and both were better than that of LA01

White fats included:

- Inguinal fat
- Perirenal fat
- Epididymal fat
- Retroperitoneal fat



SSS67 showed significant ability to **increase muscle** in SCID mice on par with that of bimagrumab, whereas LA01 failed to do so

Muscles included:

- Pectoralis
- Quadriceps
- femoris
- Tibialis anterior
- Gastrocnemius

Source: 3SBio Presentation on SSS67

Progen (South Korea) Shares Details on PG-110 at ADA

PG-110, a Novel Bispecific Antibody Targeting ActRII and Myostatin, Enhances Fat-Specific Weight Loss and Improves Bone Health in Combination with GLP-1 Agonist Therapy

ProGen

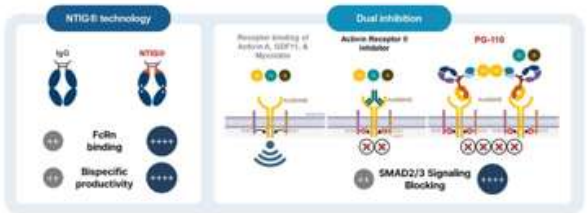
Younglim Son[1], Seung-Ah Lee[1], Jong-Gyun Kim[1], Sang-In Yang[1,2], Young Chul Sung[2]
[1]ProGen. Co., Ltd., Seoul, South Korea; [2]SL Bigen. Co., Ltd., Incheon, South Korea.

1690-P

BACKGROUND

Fist-in-class Bispecific Antibody Simultaneously Targeting Activin Type II Receptor (ActRII) & Myostatin

- **Triple Ligand Blockade**
  : Inhibits Activin, Myostatin, and GDF-11 by targeting ActRII
- **Affinity Enhancement**
  : Improves binding avidity via clustering with myostatin homodimers
- **Improved Target Selectivity and Safety Profile**
  : Selectively inhibits Myostatin in muscle tissue to minimized off-target effects



OBJECTIVES

To investigate the mode of action (MoA) and the therapeutic efficacy of PG-110, a novel bispecific antibody targeting ActRII and myostatin, in enhancing fat-specific weight loss, preserving lean muscle mass, and improving bone health when combined with the GLP-1 agonist semaglutide in a diet-induced obese (DIO) mouse model.

RESULTS

Study 1. *In Vitro* Mode of Action

Category	Purpose	Cell	Analysis method
	Direct fat-lowering effect	- Murine pre-adipocytes (3T3-L1)	- Oil Red O staining - Thermogenic gene expression
	Myostatin-induced signal blockade	- Murine myoblast (C2C12)	- Detection of p-Smad2 levels - Atrophy-related gene expression
	Increased osteoblast differentiation potential	- Human osteogenic cells (FOB1.19)	- Expression of osteoblast-specific marker genes - Alkaline phosphatase (ALP) staining

PG-110 more effectively reduces lipid accumulation and increases energy expenditure than mono-targeted agents in adipocyte cells

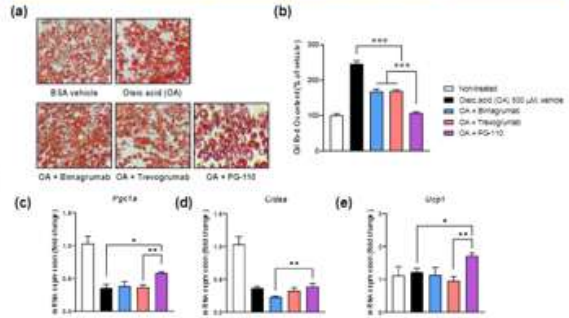


Figure 1. Effect of PG-110 on lipid accumulation in adipocytes. 3T3-L1 preadipocytes were differentiated and treated with 500 μM oleic acid to induce lipid accumulation. Cell were then treated with PG-110 for 24 h. Lipid content was visualized using Oil Red O staining. **(a)** Representative images show a marked reduction in intracellular lipid droplets upon PG-110 treatment compared to other comparator-treated groups. **(b)** Quantification of Oil Red O staining confirms the fat-reducing effect of PG-110. Data are presented as mean ± SEM (n=3–6/group). **(c-e)** mRNA expression levels of thermogenesis-associated genes, *Pgc1α*, *Cidea*, and *Ucp1* were measured by qPCR and normalized to *18S*. n=4-6 per group. All values are mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

PG-110 outperforms mono-inhibitors in reversing myostatin-induced blockade of osteoblast differentiation in human osteogenic cells

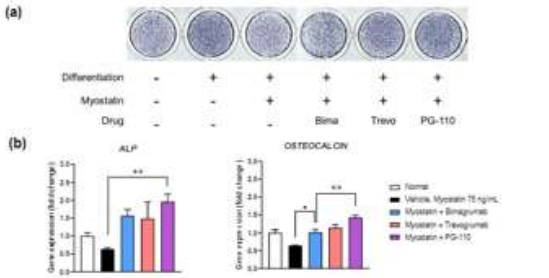


Figure 2. Effects of PG-110 treatment on osteoblast differentiation *in vitro*. FOB1.19 human pre-osteoblasts were seeded in 24-well plates and treated with differentiation medium containing 10 mM β-glycerophosphate, 0.25 mM L-ascorbic acid, and 0.1 μM dexamethasone in the presence or absence of 100 nM drug and 75 ng/mL myostatin for 5 days. **(a)** Alkaline phosphatase (ALP) staining was performed to assess early osteoblast differentiation. Representative ALP staining images are shown. **(b)** mRNA expression levels of osteoblast markers *ALP* and *OSTEOCALCIN* were measured by qPCR. n=4-5 per group. All values are mean ± SEM. *$p < 0.05$, **$p < 0.01$.

PG-110 blocks myostatin-induced Smad2/3 signaling and effectively suppresses the expression of atrophy-related genes in muscle cells

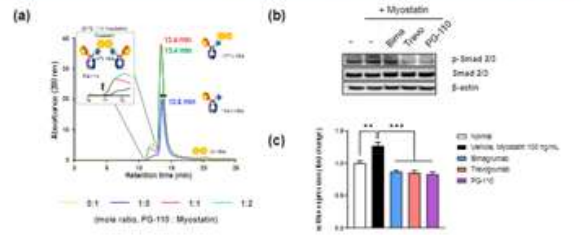
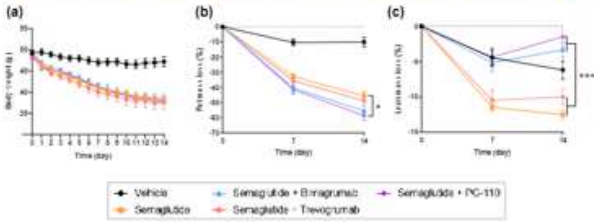


Figure 3. Effects of PG-110 on atrophy-induced muscle cells. (a) Binding avidity of PG-110 by myostatin homodimer was measured by size-exclusion chromatography (SEC-HPLC). C2C12 mouse myoblasts were seeded in 12-well plates and differentiated using medium supplemented with 2% horse serum (HS) in the presence or absence of 100 nM drug and 100 ng/mL myostatin for 4 days. **(b)** Western blotting was performed to detect phosphorylated Smad2/3 (p-Smad2/3). **(c)** The mRNA expression levels of atrophy-related gene, *Atrogin-1*, were quantified by qPCR. n=4-5 per group. All values are mean ± SEM. **$p < 0.01$, ***$p < 0.001$.

Study 2. *In Vivo* Efficacy: Combination with Semaglutide

PG-110 shows comparable fat loss to bimagrumab & trevogrumab, with a favorable trend in preserving lean mass in combination with semaglutide



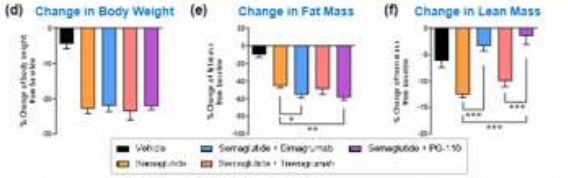


Figure 4. Effects of semaglutide-based combination therapies on body weight, fat mass, and lean mass in diet-induced obese (DIO) mice. DIO mice were treated with semaglutide alone or in combination with bimagrumab, trevogrumab, or PG-110. **(a)** Time course of body weight change over 14 days. **(b)** Percent change in fat mass and **(c)** lean mass from baseline to day 14 as measured by DEXA. **(d-f)** Quantitative bar graph showing percent changes in body weight **(d)**, fat mass **(e)**, and lean mass **(f)** at day 14 for each treatment group. Data are presented as mean ± SEM (n=6/group).

PG-110 outperforms mono-inhibitors by enhancing bone health through Greater improvements in bone mineral density and content

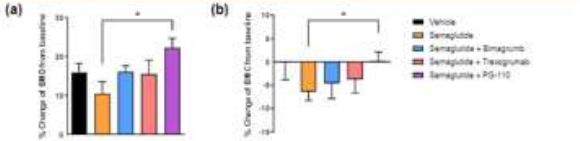


Figure 5. Effects of combination therapies on bone health. Final hind limb bone mineral density (BMD) **(a)** and bone mineral content (BMC) **(b)** measured at the end of the experiment (day 14). Data are presented as mean ± SEM (n=6/group). *$p < 0.05$.

SUMMARY & CONCLUSION

Molecule	Vehicle	Semaglutide	Semaglutide & Bimagrumab	Semaglutide & Trevogrumab	Semaglutide & PG-110
Construct					
Fat Mass Loss	10 %	45.8 %	55.5 %	48.9 %	58.6 %
Lean Mass Loss	8.2 %	12.5 %	3.3 %	9.9 %	1.5 %
Bone Mineral Density Change	15.9 %	10.4 %	16.1 %	15.5 %	22.3 %

- Due to its ability to selectively reduce fat, preserve muscle mass, enhance bone density, and support osteoblast activity while inhibiting muscle atrophy pathways, **PG-110 is expected to offer superior functional benefits in metabolic and musculoskeletal health.**

American Diabetes Association – 85th Annual Scientific Sessions; Chicago, IL; 20-23 June 2025

Laekna Shows Phase 1A Data for SubQ Muscle Drug At ADA

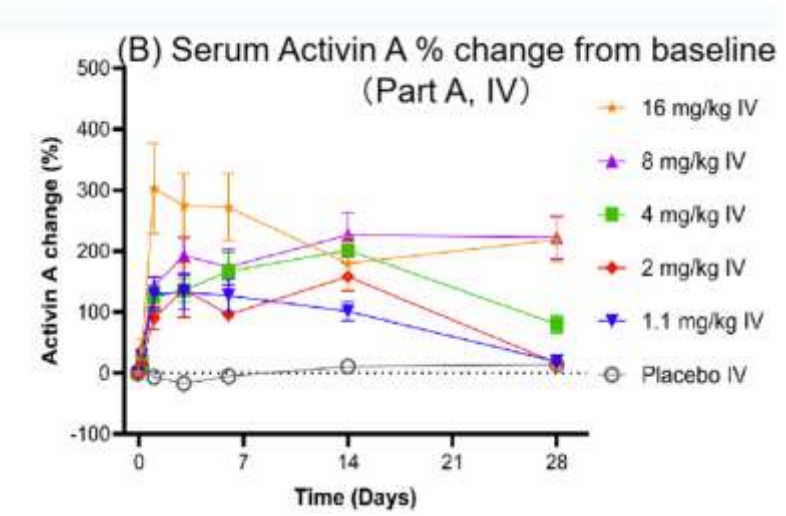
First-in-Human Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LAE102 in Healthy Volunteers

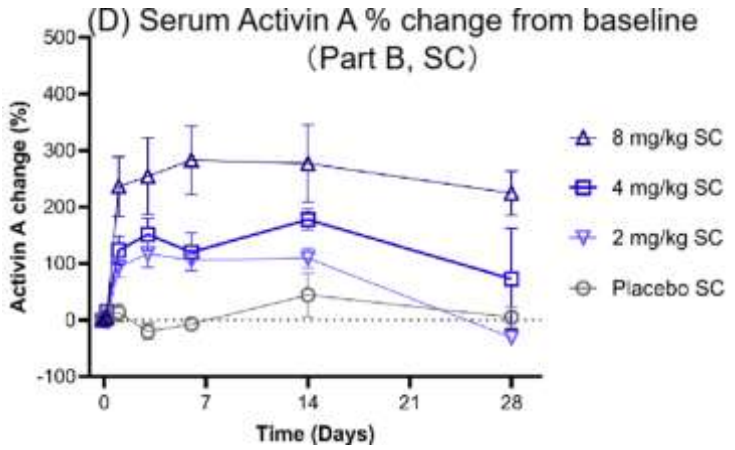
Introduction and Objective: LAE102 is the first anti-ActRIIA (activin receptor type IIA) monoclonal antibody in clinical development to increase muscle mass and reduce fat mass. This first-in-human study reported the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of single ascending doses of LAE102 in healthy participants.

Methods: This randomized, double-blind, placebo-controlled, Phase 1 study enrolled 64 participants who were randomized to receive a single dose of LAE102 or placebo (6:2 ratio) intravenously (Part A: 1.1, 2, 4, 8, or 16 mg/kg, IV) or subcutaneously (Part B: 2, 4, or 8 mg/kg, SC).

Results: LAE102 was well tolerated, with the majority of treatment-emergent adverse events (TEAEs) being mild, asymptomatic laboratory test abnormalities. No serious adverse events or TEAEs leading to study discontinuation were reported. LAE102 demonstrated dose-dependent increases in serum concentration, non-linear PK and target-mediated drug disposition profile. Significant increases in serum activin A levels were observed across all groups. At the 8 mg/kg SC and the 8 and 16 mg/kg IV doses, the increased activin A levels were maintained over the 28-day follow-up period.

Conclusion: A single dose of LAE102 IV or SC demonstrated a favorable safety profile in healthy participants. Robust PK/PD correlation indicate potential efficacy and support clinical development of LAE102 SC in overweight and obese population.





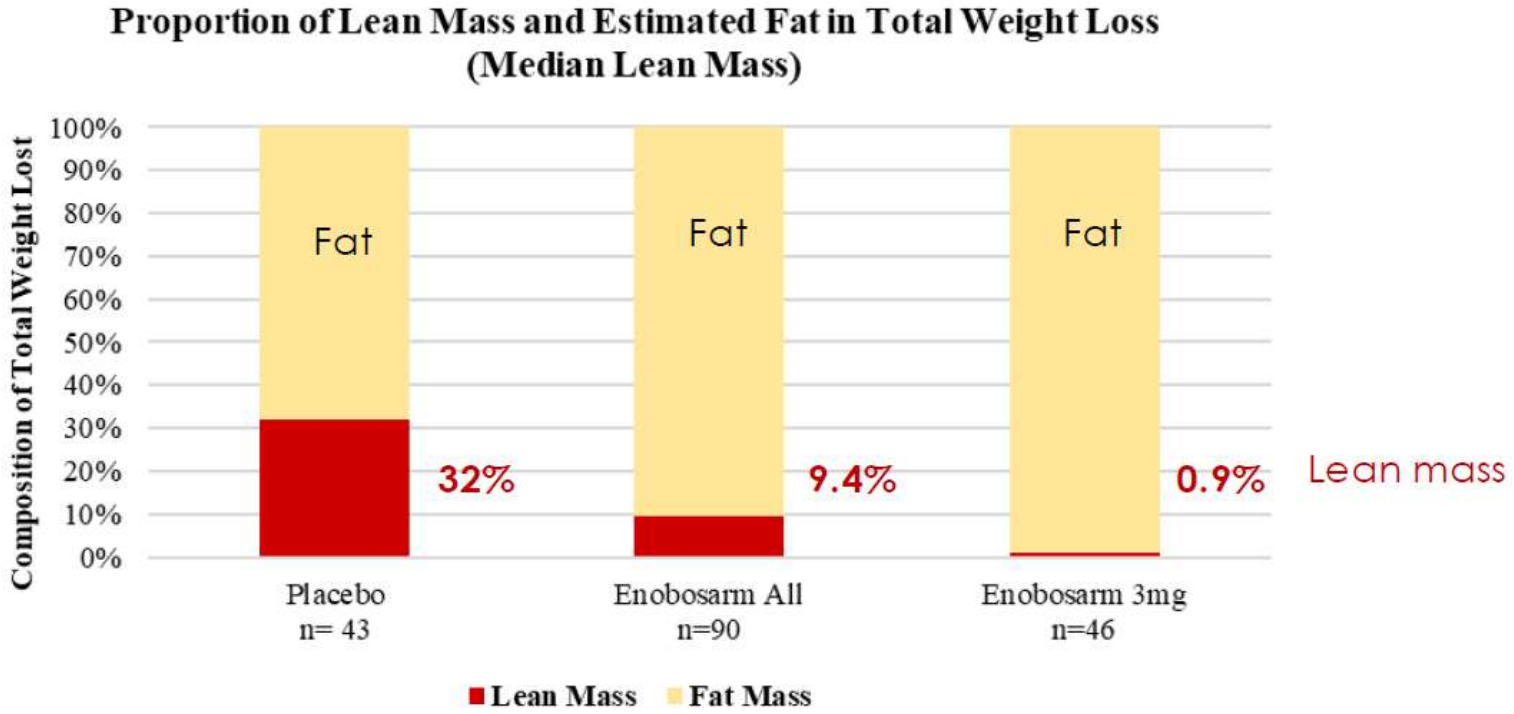
Source: https://www.businesswire.com/news/home/20250623952873/en/ADA-2025-Laekna-Presented-Clinical-and-Pre-clinical-Studies-Results-of-LAE102-LAE103-and-LAE123

Veru Reports Positive Results from Phase 2b QUALITY and Maintenance Extension Study Showing Enobosarm Significantly Reduced Body Weight Regain, Prevented Fat Regain, and Preserved Lean Mass After Semaglutide Discontinuation

MIAMI, FL, June 24, 2025 (GLOBE NEWSWIRE) -- Veru Inc. (NASDAQ: VERU), a late clinical stage biopharmaceutical company focused on developing innovative medicines for the treatment of cardiometabolic and inflammatory diseases, today announced positive topline efficacy and safety results from the maintenance extension portion of the Phase 2b QUALITY clinical study. The Phase 2b Maintenance Extension clinical trial demonstrated that in 12 weeks after stopping semaglutide, the placebo monotherapy group regained 43% of body weight that was previously lost during the Phase 2b QUALITY study, while enobosarm monotherapy reduced weight regain by 46% in the enobosarm 3mg group and completely prevented fat regain and preserved lean mass in both enobosarm dose groups compared to placebo after semaglutide discontinuation. Enobosarm treatment also led to up to 93% greater loss of fat mass and 100% preservation of lean mass compared to the placebo group at the end of the study. Enobosarm monotherapy maintained a positive safety profile, with essentially no gastrointestinal side effects observed during the maintenance period… After completing the efficacy dose-finding portion of the Phase 2b QUALITY clinical trial, 148 participants continued to the Phase 2b Maintenance Extension study, a double-blind study, where all patients discontinued semaglutide treatment, but continued receiving placebo, enobosarm 3mg, or enobosarm 6mg as monotherapy for 12 weeks.

Source: https://ir.verupharma.com/news-events/press-releases/detail/236/veru-reports-positive-results-from-phase-2b-quality-and

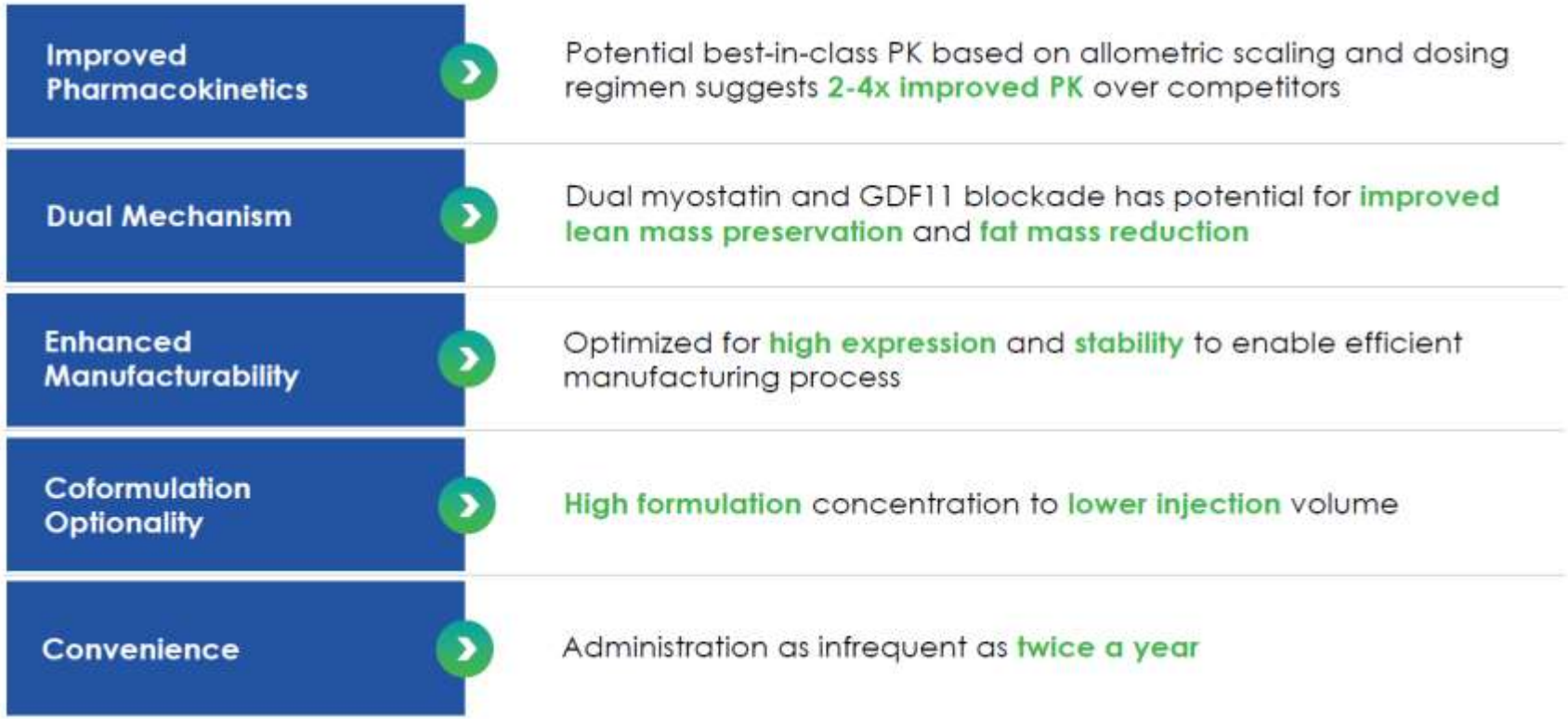
Phase 2b QUALITY clinical trial topline results
Adding enobosarm to semaglutide therapy retained lean mass and total weight loss shifted to SELECTIVE greater loss of adiposity (fat mass)



- **Tissue composition of the total weight loss shifted to greater loss of adiposity (fat mass)**
  - The median percentage of total body weight loss that is due to lean mass is 32% in the placebo + semaglutide group, versus 9.4% in the All enobosarm + semaglutide group and 0.9% for enobosarm 3mg dose group
- **Enobosarm + semaglutide improved body composition during weight reduction which resulted in more selective and greater loss of adiposity than in subjects receiving placebo + semaglutide alone**

Source: https://d1io3yogooux5.cloudfront.net/_adf8398df5650257e4bod59639e35455/verupharma/db/2224/21079/pdf/Veru+Presentation+-+Jones+Healthcare+and+Technology+Innovation+Conference+April+2025.pdf

IBIO-600: A Differentiated Long Acting Anti-Myostatin Program



We like the iBio myostatin inhibitor program. IBIO-600, developed with AstralBio, inhibits myostatin and GDF11 to enhance muscle preservation.

By driving high concentration it should be possible to deliver this molecule subcutaneously.

Importantly, the long-acting formulation will allow for infrequent administration. The idea here is that the patient goes on their obesity drug of choice, say tirzepatide, orforglipron, etc. Then, once a quarter or, perhaps, once every six months gets a shot of IBIO-600.

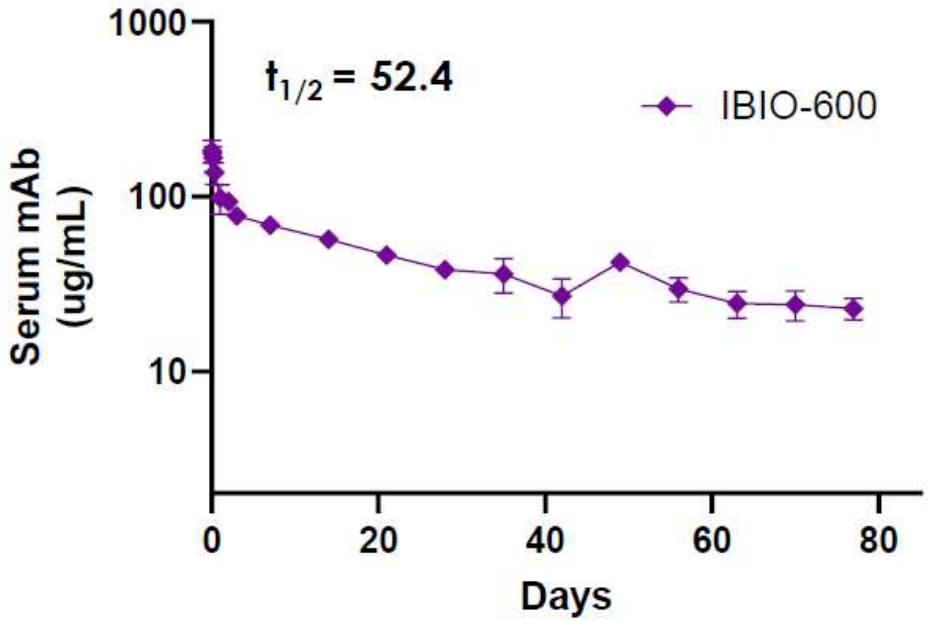
Investors seem to have missed this company as its market cap is under $15mm.

IBIO is also developing a first-in-class Activin E inhibitor program.

Source: https://d1io3yogooux5.cloudfront.net/_711e47ff9d8bfc92c7db6bb3db6ee6fo/ibioinc/db/344/3383/presentation/Investor+Call+Presentation+June+2025.pdf

IBIO-600 Fc Engineering Drives Extended Half-Life in Obese NHPs

12 Week Pharmacokinetics Data[1]



Study Details:
- Obese, aged NHPs
- Monthly DEXA scan for body composition
- Periodic PK sampling

IBIO-600 Fc Engineering Results in Enhanced FcRn Binding

Clone	Fc	Fold increase over standard IgG
IBIO-600 FAB	Standard IgG4	**1.0**
IBIO-600	Engineered IgG4	**16.5**

IBIO-600 Demonstrates Extended Half-Life in NHPs

Dose	$t_{1/2}$ (days)
5 mg/kg, I.V.	**52.4**

Study Design:
- N=3 per group
- 5mg/kg single I.V. dose

Source: https://d1io3yogooux5.cloudfront.net/_711e47ff9d8bfc92c7db6bb3db6ee6fo/ibioinc/db/344/3383/presentation/Investor+Call+Presentation+June+2025.pdf

ADA Poster on iBio Anti Activin E Antibody

Activin E-Blocking Antibody for Treatment of Metabolic Diseases

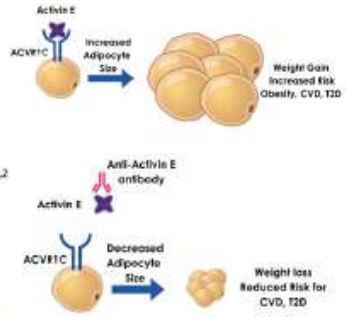
Cory Schwartz[1], Cody Moore[1], Alexander Taguchi[1], Hongyu Zhang[1], Tam Phuong[1], Tom Hsu[1], Matthew Dent[1], Courtney Wood[1], Patrick Crutcher[2], Justin DiMartino[2], Martin B. Brenner[1]

1. iBio, Inc., 11750 Sorrento Valley Rd. Suite 200, San Diego, CA, 92121; 2. AstralBio Inc., 867 Boylston St., Boston, MA, 02116

Therapeutic Targeting of Activin E

Why Target Activin E?

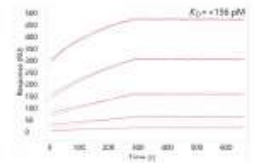
- Activin E: Liver-derived TGFβ-family hepatokine[1,2]
- Strong genetic evidence links Activin E signaling to adiposity, diabetes, and cardiovascular disease[1,2]
- Genetic loss-of-function reduces fat accumulation and disease risk[1,2]
- Validated by preclinical RNA-targeting therapies
- Challenging target for antibody discovery due to difficulties working with active recombinant protein, overcome by iBio AI-enabled discovery platform

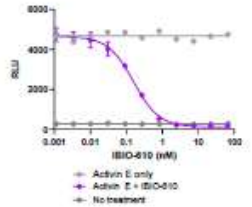


Antibody Testing and Engineering

Lead Activin E antagonist antibody (IBIO-610) has high affinity binding to Activin E

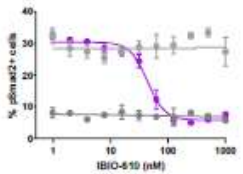
K_D < 156 pM





Potent neutralization of Activin E-mediated signaling in cell-based reporter assay

IC_{50} ≈ 150 pM *(treated with 200 pM Activin E)*

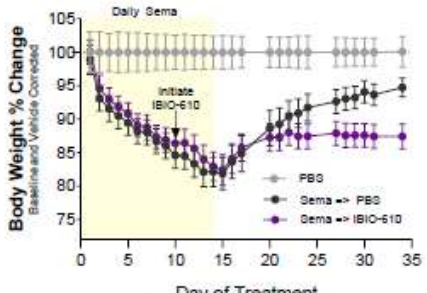


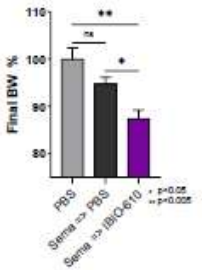
Potent neutralization of Activin E-mediated signaling in human adipocytes

IC_{50} ≈ 150 pM *(treated with 200 pM Activin E)*

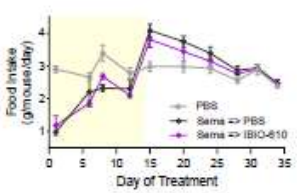
Synergism with GLP-1

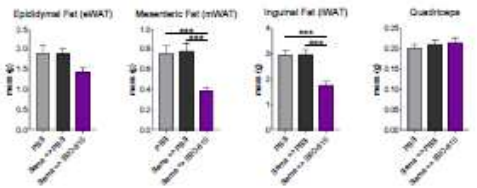
Prevention of Weight and Fat Regain after GLP-1 Cessation



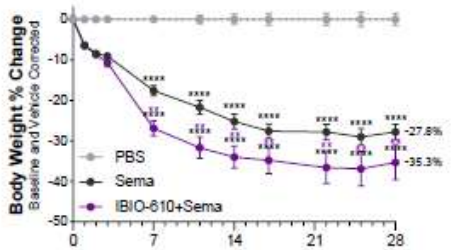


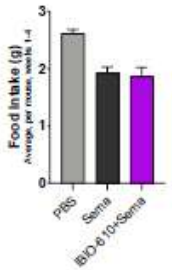
DIO mice, 14-20 week HFD induction, N=10 per group, antibody dosed BIW 10 mg/kg S.C. starting on day 10, semaglutide daily for days 1-14, 10 nmol/kg, 2-way ANOVA





Combination with GLP-1 for Enhanced Weight Loss



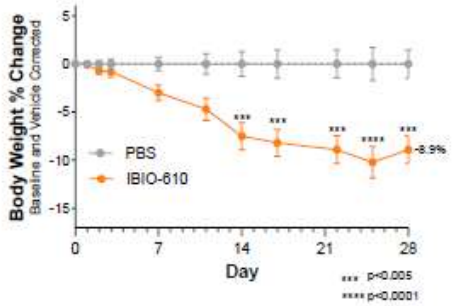


DIO mice, 14-20 week HFD induction, N=10 per group, antibody dosed BIW 10 mg/kg S.C., Sema daily 10 nmol/kg, 2-way ANOVA

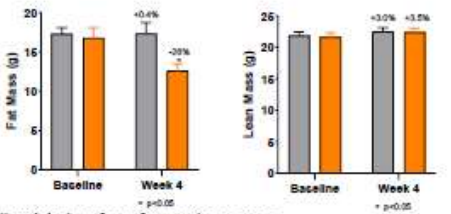
*** p<0.005 vs. PBS
**** p<0.0001 vs. PBS
** p<0.01 vs. Sema

Monotherapy Weight Loss

Fat-Selective Weight Loss



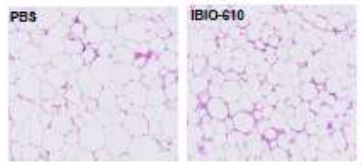
DIO mice, 14-20 week HFD induction, N=10 per group, BIW dosing, 10 mg/kg S.C., Non-responder outlier mice removed from data, 2-way ANOVA

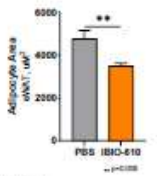


All weight loss from fat, not lean, mass

Body composition measured via DEXA

Impact on Adipose Tissue

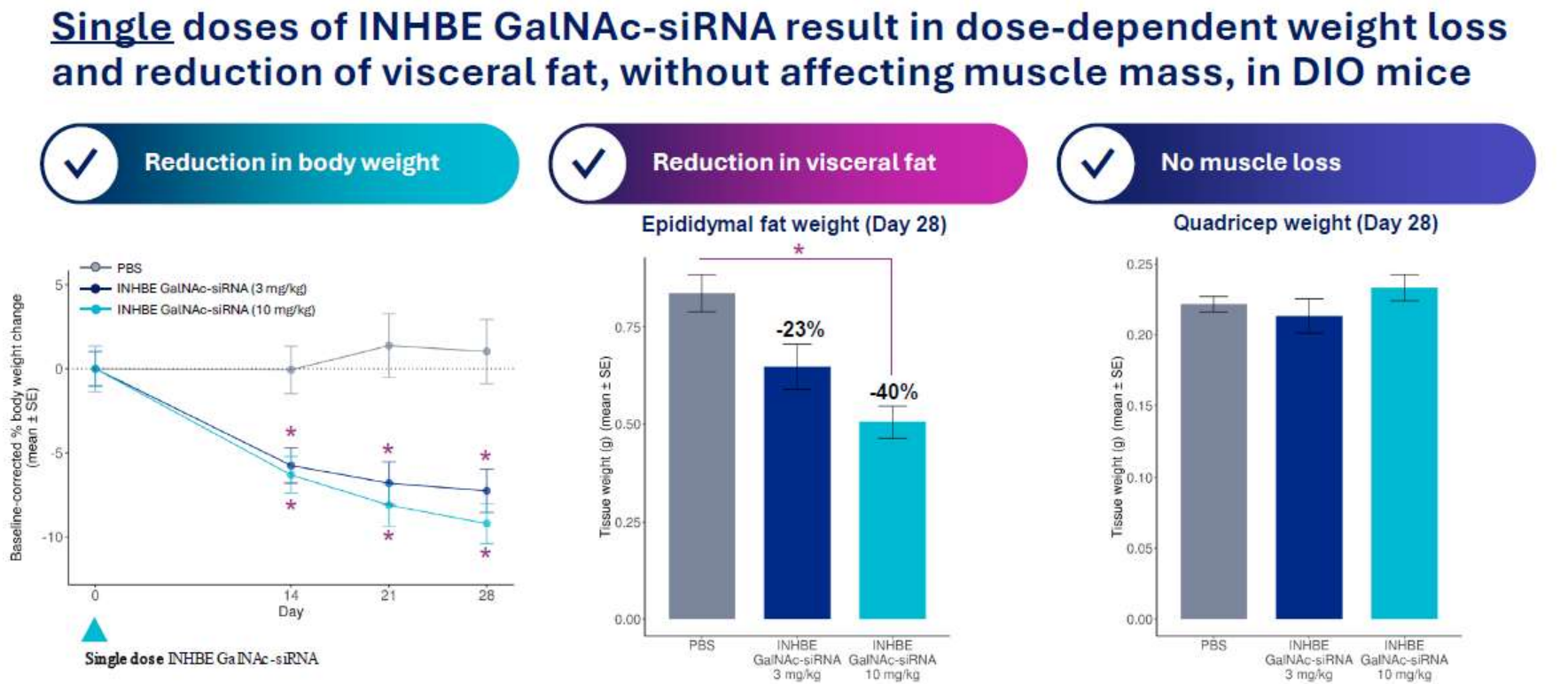




Leptin Expression

Source: https://ibioinc.com/media-events/presentations/

ADA: Wave Life Sciences Shows Impressive In Vivo Data on its INHBE siRNA Therapy (Human Data in H2 2025)



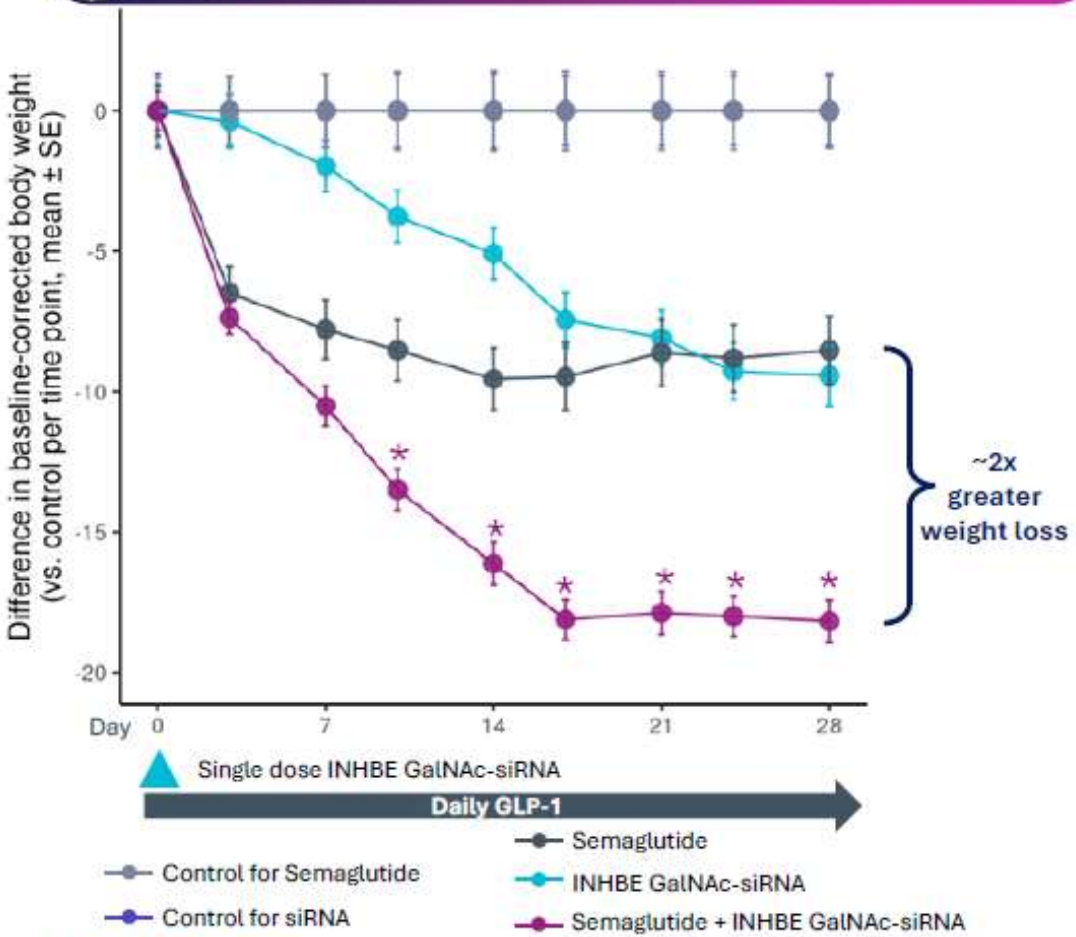
Note: Wave's INHBE program is closely linked with Activin E antagonism approaches to muscle preservation. The cognate receptor for INHBE (which forms Activin E, a hepatokine) is the activin receptor **ALK7**, encoded by the gene **ACVR1C**. Research shows that Activin E signals via ALK7 on adipocytes to suppress lipolysis through SMAD2/3 signaling, and human genetic studies link loss-of-function mutations in both INHBE and ACVR1C with favorable metabolic traits—supporting ALK7 as the primary receptor for INHBE-derived Activin E*

* See https://www.nature.com/articles/s41467-022-31757-8

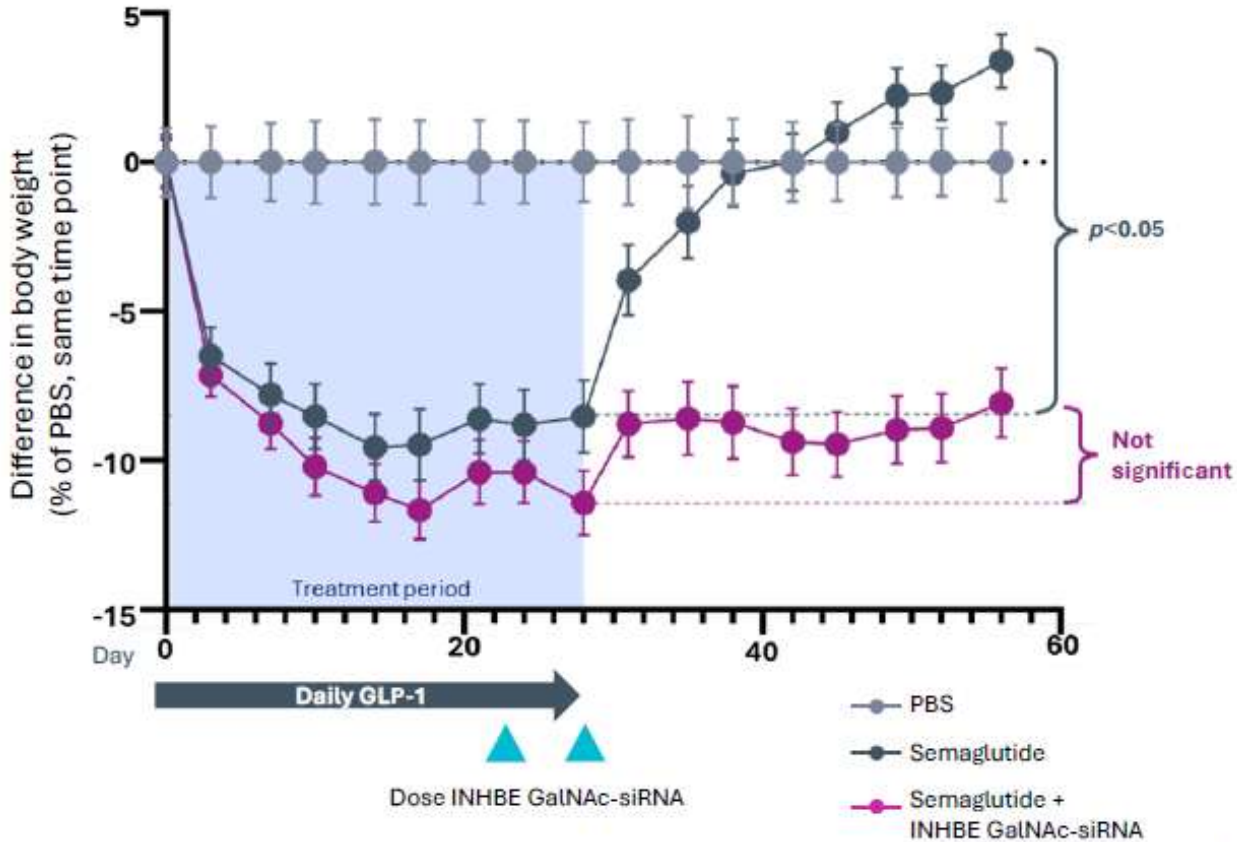
Source: https://ir.wavelifesciences.com/static-files/b873fdfd-8f68-4ead-bf5d-fb4146b6413a

INHBE GalNAc-siRNA can be used synergistically with GLP-1s or to curtail weight regain after the cessation of treatment with GLP-1

~2x greater overall weight loss when added to GLP-1



Curtails weight regain after the cessation of GLP-1



WAVE LIFE SCIENCES

Data from preclinical studies conducted in DIO mice; Left: 10nmol/kg in mouse is equivalent to therapeutic dose of GLP-1s in human. Stats: Linear Mixed Effects ANOVA with post hoc comparisons of marginal treatment effects of Semaglutide vs. Semaglutide + INHBE GalNAc-siRNA per time point * $p < 0.05$; Right Stats: Linear Mixed Effects ANOVA with post hoc comparison of Day 28 vs. Day 56 marginal effects per treatment * $p < 0.05$

Rivus HU6 Molecule Associated with Pure Fat Reduction in MASH Setting

Rivus Pharmaceuticals Announces Positive Topline Results from Phase 2 M-ACCEL Trial of HU6 Showing Significant Reductions in Liver Fat in Patients with MASH

– Study met primary endpoint, with a statistically significant reduction in liver fat observed in all HU6 treatment groups –

– Treatment with HU6 significantly reduced body weight, body fat and abdominal visceral fat with preservation of skeletal muscle mass versus placebo and was well tolerated –

CHARLOTTESVILLE, Va., and SOUTH SAN FRANCISCO, Calif., June 24, 2025 – Rivus Pharmaceuticals, Inc., a clinical-stage biopharmaceutical company dedicated to treating obesity and the resulting cardiometabolic diseases, today announced that its Phase 2 M-ACCEL clinical trial of HU6 in patients with metabolic dysfunction-associated steatohepatitis (MASH) met its primary endpoint, with statistically significant reductions in liver fat content at 6 months compared with placebo ($p<0.01$) in each of the three treatment groups. The proportion of responders, defined as experiencing a greater than 30% reduction in liver fat, was also statistically significant ($p<0.01$) in all treatment groups.

Source: https://www.rivuspharma.com/wp-content/uploads/2025/06/Rivus_M-ACCEL_topline-results_press-release_final_6.23.pdf

Rivus' HU6 is a prodrug of DNP and has high potential to reduce weight and to impact mitochondrial function.

We like the MOA and approach.

While this company has been around for awhile, they have yet to run a trial in obesity directly. In addition, they would benefit by running a trial where they see if their drug can add value on top of an existing obesity drug like tirzepatide or semaglutide.

OrsoBio TLC-6740 Mitochondrial Protonophore Also Looks Promising

MENLO PARK, Calif. – June 20, 2025 – OrsoBio, Inc. ("OrsoBio" or "the Company"), a clinical-stage biopharmaceutical company developing treatments for obesity and obesity-associated disorders, today announced new preclinical data being presented at the 85th Scientific Sessions of the American Diabetes Association (ADA) being held June 20-23, 2025, in Chicago, Ill. The Company will present three abstracts highlighting the efficacy of its mitochondrial protonophores to induce weight loss and provide glycemic benefits while preserving lean mass in diet-induced obese (DIO) mice. The studies demonstrate the potential of TLC-6740 and TLC-1180—as monotherapy and in combination with the glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide—for both the induction and maintenance of weight loss following incretin treatment.

"The mechanism of our mitochondrial protonophores to increase energy expenditure complements that of incretins to enhance and sustain weight loss and provide additive metabolic benefits," said Mani Subramanian, MD, PhD, Chief Executive Officer of OrsoBio. "These preclinical findings mark an important step in fulfilling our mission to develop innovative, effective, oral therapies for obesity that preserve muscle and support cardiometabolic health."

OrsoBio is advancing a pipeline of novel therapies targeting obesity through mechanistically distinct and complementary approaches. The Company's lead candidates include TLC-6740 and TLC-1180, both mitochondrial protonophores that promote weight loss by increasing energy expenditure. In addition, OrsoBio is developing TLC-3595, a selective inhibitor of acetyl-CoA carboxylase 2 (ACC2), designed to enhance fat oxidation.

"GLP-1 receptor agonists have transformed obesity treatment but are limited by gastrointestinal side effects and loss of muscle mass," said Rob Myers, MD, Chief Medical Officer of OrsoBio. "Our preclinical data show that our mitochondrial protonophores drive sustained, fat-selective weight loss and metabolic benefits when combined with or sequenced after GLP-1 receptor agonists. These findings support our ongoing Phase 1b study of TLC-6740 in combination with tirzepatide (NCT05822544)."

We recently met with OrsoBio and learned about the potential of their small molecule drug candidate to preserve muscle using a mitochondrial protonophore.

The company will be reporting out phase 1b data of the drug in combination with tirzepatide versus tirzepatide alone shortly.

This strikes us as an important readout as it may validate a distinct small molecule approach to muscle preservation with GLP-1's.

Presumably, one could use this drug in combination with an oral GLP-1 to achieve excellent weight loss while preserving muscle.

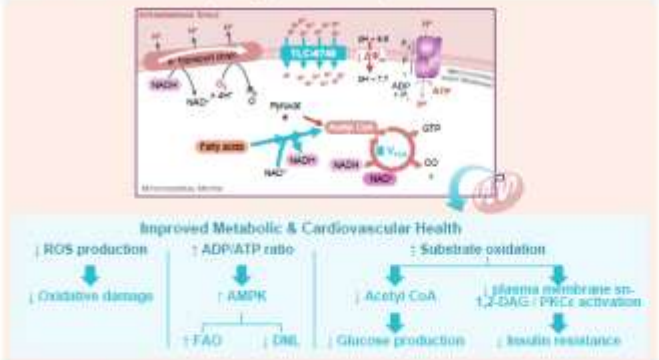
Source: https://orsobio.com/orsobio-to-present-preclinical-data-on-mitochondrial-protonophore-portfolio-in-models-of-obesity-at-the-american-diabetes-associations-85th-scientific-sessions/

TLC-6740, a potent liver-targeted mitochondrial protonophore, has multiple metabolic benefits in preclinical models

Archana Vijayakumar[1], Leigh Goedeke[2,3], Eisuke Murakami[1], Steve Weng[1], Robert P. Myers[1], G. Mani Subramanian[1], Gerald I. Shulman[2]
[1]OrsoBio, Inc., Palo Alto, CA, USA; [2]Yale University School of Medicine, New Haven, CT, USA; [3]Icahn School of Medicine at Mount Sinai, New York, NY, USA

Introduction

- Futile cycling of protons across the inner mitochondrial membrane by uncoupling dissociates oxidative phosphorylation from ATP synthesis, leading to heat production and enhanced tricarboxylic acid (TCA) cycle flux and β-oxidation to meet energy demands[1]
- Mitochondrial uncoupling using synthetic protonophores such as 2,4-dinitrophenol (DNP) is a validated approach for weight loss; however, safety concerns due to excessive systemic uncoupling (e.g., hyperthermia) have limited clinical development[2]
- Mild mitochondrial uncoupling has multiple potential metabolic benefits[1]
- Various approaches to increase the therapeutic window of DNP (e.g., controlled-release formulations and prodrugs) have shown promise[3,4]



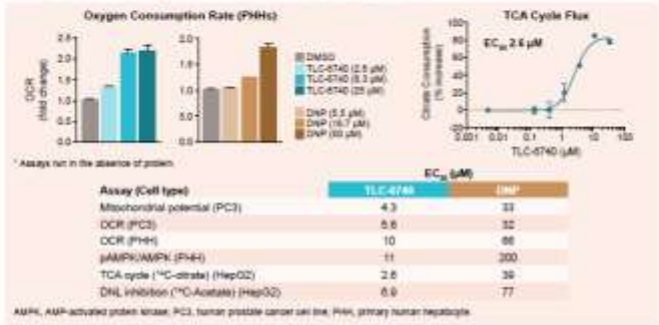
- **TLC-6740 is a novel mitochondrial protonophore with distinct pharmacology to DNP and its derivatives—namely, high hepatic extraction—that may afford a greater therapeutic margin**
- **Here, we characterize the potency, preclinical activity (target engagement and efficacy), and preliminary safety of TLC-6740 in a variety of rodent models**

Methods

- In vitro assays:
  - Oxygen consumption rate (OCR) was evaluated using Seahorse XF Analyzers
  - TCA cycle flux and *de novo* lipogenesis (DNL) inhibition were evaluated using radiolabeled tracers
- In vivo studies:
  - Pharmacokinetics (PK) studies: Overnight fasted, male Sprague-Dawley (SD) rats or cynomolgus monkeys were dosed orally with TLC-6740 30 mg/kg or 5 mg/kg, respectively. Plasma and liver TLC-6740 concentrations were measured using LCMS
  - Acute PINTA studies: Overnight fasted, male SD rats were dosed orally with vehicle or TLC-6740, and after 20 min, received 2-hour infusions of stable isotope tracers to measure *in vivo* hepatic mitochondrial fat oxidation by Positional Isotopomer NMR Tracer Analysis (PINTA)[5]
  - Efficacy studies: Zucker Diabetic Fatty (ZDF) rats were fed a high-fat, high-cholesterol diet (HFHCD) for 2 or 8 weeks and treated with TLC-6740 (90 mg/kg b.i.d or 120 mg/kg in diet) for 7 days or 6 weeks, respectively. Diet-induced obese (DIO) mice were fed a high-fat diet (HFD) for 18 weeks and treated with TLC-6740 in diet for 6 weeks. Liver and plasma lipids were measured biochemically. Body temperature was measured using rectal thermometers. Oral glucose tolerance test (OGTT) was performed after a brief 4–6 hour fast.
- Data analysis
  - Data are presented as mean ± SEM. Statistical analyses were performed using Prism 9.4.1 (*p<0.05 vs vehicle; #p≤0.05 vs baseline, within the same group)

Results

In vitro Potency of TLC-6740 and DNP



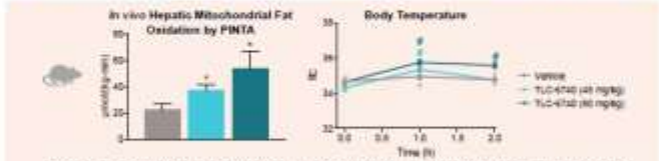
* Assays run in the absence of protein

Assay (Cell type)	EC_{50} (μM) TLC-6740	DNP
Mitochondrial potential (PC3)	4.3	33
OCR (PC3)	5.6	92
OCR (PHH)	10	66
pAMPK/AMPK (PHH)	11	200
TCA cycle (^{14}C-citrate) (HepG2)	2.6	39
DNL inhibition (^{14}C-Acetate) (HepG2)	6.9	77

AMPK, AMP-activated protein kinase; PC3, human prostate cancer cell line; PHH, primary human hepatocyte

- Mild mitochondrial uncoupling has pleiotropic metabolic benefits in multiple cell types
- TLC-6740 is 6 to 18-fold more potent than DNP *in vitro*

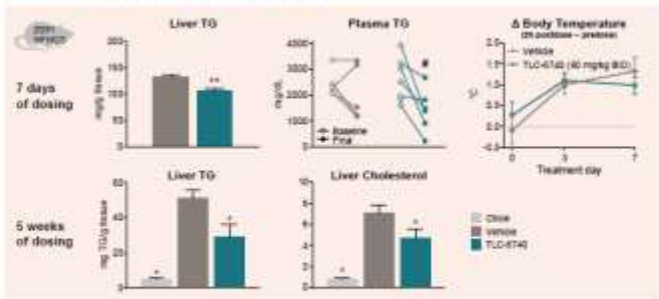
Target Engagement with TLC-6740 and in vivo Pharmacology



Species	TLC-6740 Dose	Time Post Dose	Liver Concentration	Plasma Concentration	Liver:Plasma Ratio
Monkey	30 mg/kg	6 h	38.6 μM	1.0 μM	39x
Rat	5 mg/kg	4 h	39.4 μM	0.92 μM	43x

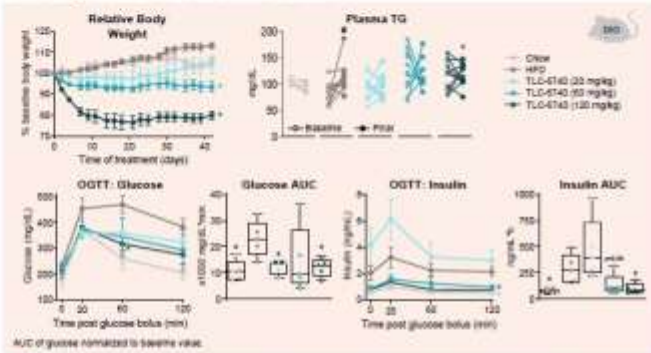
- TLC-6740 dose-dependently increases *in vivo* hepatic mitochondrial fat oxidation by 2–3x
- TLC-6740 demonstrates preferential hepatic distribution in rats and cynomolgus monkeys

Efficacy of TLC-6740 in ZDF Rats



- In HFHCD-fed ZDF rats, TLC-6740 significantly improves liver and plasma TG, without increasing body temperature

Efficacy of TLC-6740 in DIO Mice



AUC of glucose normalized to baseline value

- TLC-6740 dose-dependently decreases body weight and plasma TG, and improves glucose tolerance in DIO mice

Safety Pharmacology and Preliminary Toxicology*

- No human ether-à-go-go-related gene (hERG) inhibition or off-target activity observed in *in vitro* screening studies
- No effects on radiotelemetry or echocardiography endpoints observed after a single dose in rats (≤15 mg/kg)
- Dose-range finding, 14-day toxicology study completed in beagle dogs dosed with TLC-6740 (5, 20, and 45 mg/kg QD)
  - At the NOAEL (20 mg/kg QD), large safety margins (>30x) estimated relative to the projected efficacious dose in humans
  - >80x difference between projected human efficacious dose and thermogenic dose
- **IND-enabling toxicology studies initiated in Sept 2022**

* Unpublished data.

Conclusions

- TLC-6740 is a novel, liver-targeted, mitochondrial protonophore that demonstrates multiple metabolic benefits in dysmetabolic rodents including body weight loss, and improvements in liver and plasma TG and glucose homeostasis
- No evidence of excessive systemic uncoupling (i.e., thermogenesis) was observed in these pre-clinical models, likely due to active hepatic uptake of TLC-6740
- TLC-6740 is projected to demonstrate large safety margins (>80x) between efficacious and thermogenic doses in humans and is currently being evaluated in IND-enabling toxicology studies
- These data support the evaluation of TLC-6740 in metabolic diseases such as lipodystrophies, NASH, obesity, and diabetes; a first-in-human study with TLC-6740 is targeted for 2023

References: 1. Goedeke & Shulman, Molecular Metab 2021; 2. Poole FE, et al. JAMA 1934; 3. Perry RJ, et al. Science 2015; 4. Perry RJ, et al. Cell Metab 2014; 5. Perry RJ, et al. Nat Commun 2019.
Disclosures: A Vijayakumar, E Murakami, S Weng, RP Myers, GM Subramanian, OrsoBio; L Goedeke, OrsoBio, Bain Capital Life Sciences; GI Shulman: OrsoBio, Equator Therapeutics and holder of intellectual property regarding mitochondrial protonophores.
Acknowledgments: Poster production assistance was provided by BioScience Communications, New York, NY and funded by OrsoBio.

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Presented at AASLD: The Liver Meeting®, November 4–8, 2022, Washington, DC

Scholar Rock Preclinical Data for SRK-439 Impressive

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Jun. 24, 2024-- Scholar Rock (NASDAQ: SRRK), a late-stage biopharmaceutical company focused on advancing innovative treatments for spinal muscular atrophy (SMA), cardiometabolic disorders, and other serious diseases where protein growth factors play a fundamental role, today announced that the first participants were dosed in the Phase 2 EMBRAZE proof-of-concept trial, designed to assess the safety and efficacy of apitegromab, an investigational, highly selective myostatin inhibitor, to preserve lean muscle mass in individuals living with obesity and on background therapy of a GLP-1 receptor agonist (GLP-1 RA). The trial will also evaluate the effects of apitegromab on the durability of weight loss upon withdrawal of GLP-1 RA therapy. The results from this trial will inform the development of SRK-439, a novel investigational selective myostatin inhibitor optimized for the treatment of cardiometabolic disorders, including obesity.

The Company also presented new preclinical data that support the potential of SRK-439 to increase lean mass and contribute to a favorable body composition following withdrawal from GLP-1 RA treatment. These data were presented by Melissa Fulham, PhD, of Scholar Rock, at the American Diabetes Association's 84th Scientific Sessions on June 23rd in Orlando, Florida.

"We are happy to share the exciting news that we've dosed the first participants in our EMBRAZE clinical trial ahead of schedule and to have new preclinical data with SRK-439, our highly selective anti-myostatin, featured at the American Diabetes Association Scientific Sessions," said Jay Backstrom, M.D., MPH, President and Chief Executive Officer at Scholar Rock. "SRK-439 preclinical data to date have demonstrated preservation of lean mass with GLP-1 RA-induced weight loss, attenuation of fat mass regain following GLP-1 RA withdrawal, and greater potency compared to an anti-ACTRII antibody. Together, these data continue to support a best-in-class potential for healthy weight loss management and could be transformative for the management of weight loss. We are looking forward to providing additional updates on our cardiometabolic program as we advance SRK-439, as well as the EMBRAZE trial."

Shown below are results for body composition at baseline (6 days before semaglutide treatment), the end of semaglutide treatment (at 4 weeks), and at the end of the semaglutide withdrawal period (at 8 weeks):

Endpoint (units)	IgG control + semaglutide	SRK-439 + semaglutide	P value
Absolute lean mass (g) at baseline	24.8	25.5	n.s.
Absolute lean mass (g) at 4 weeks	22.3	26.4	P<0.001
Absolute lean mass (g) at 8 weeks	25.1	29.4	P<0.0001
Absolute fat mass (g) at baseline	11.8	10.3	n.s.
Absolute fat mass (g) at 4 weeks	5.9	3.8	n.s.
Absolute fat mass (g) at 8 weeks	12.7	8.3	n.s.
Relative lean mass (%) at 8 weeks	57.1%	65.8%	P<0.001
Relative fat mass (%) at 8 weeks	28.7%	18.0%	P<0.01

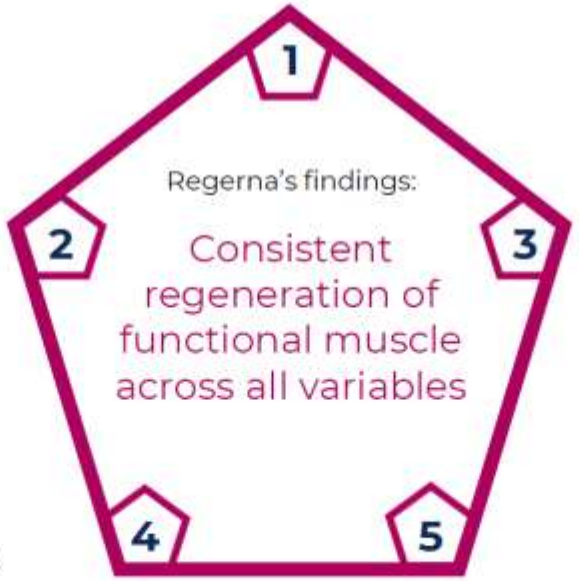
"These new preclinical data provide compelling evidence that SRK-439 contributed to lean muscle preservation during GLP-1 RA-induced weight loss and attenuated fat mass rebound following discontinuation of semaglutide," said Mo Qatanani, PhD, Chief Scientific Officer at Scholar Rock. "Mice receiving SRK-439 treatment had significantly more lean mass at the end of the semaglutide withdrawal period. These exciting data continue to support the differentiated profile of SRK-439 and its potential to contribute to healthier weight management and long-term metabolic benefits during and after GLP-1 RA treatment."

Source: https://investors.scholarrock.com/news-releases/news-release-details/scholar-rock-announces-new-srk-439-preclinical-data-showing

Regerna Developing AUF1 Therapies to Restore Muscle

AUF1 consistently regenerates functional muscle across disease states, mode of delivery, and timing of administration

Disease/injury model
DMD, disuse atrophy, sarcopenia, injury, obesity



Delivery technologies
AAV8 gene therapy and LNP delivery

Route of delivery
Systemic and intramuscular delivery

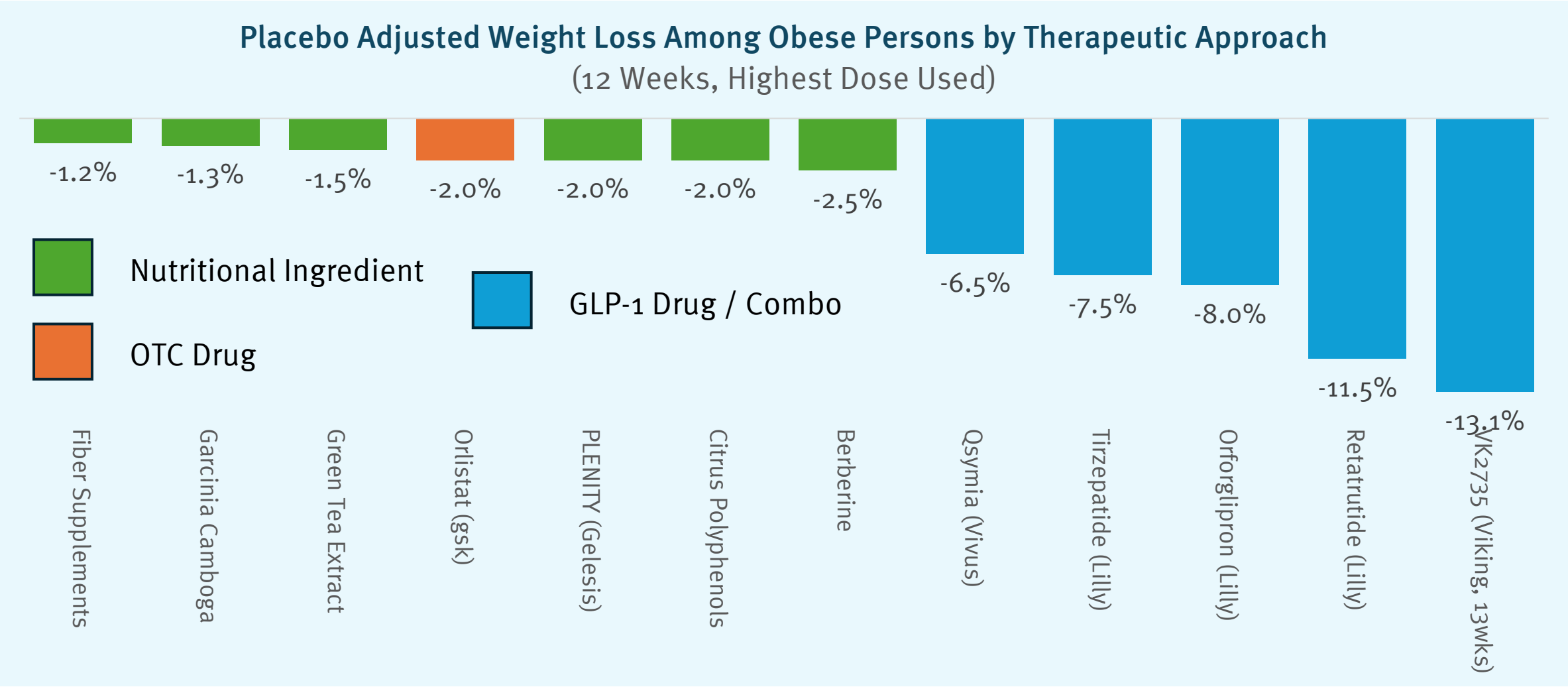
Species
Mouse, human cells, rat (in process). AUF1 is biologically conserved.

Timing of administration
Before, during, or after muscle injury or initiation of disuse atrophy

Source: Regerna Corporate Presentation, June 2025

Consumer Friendly

Today's Supplement Solutions for Weight are Marginal Compared to GLP-1's



Source: Stifel compilation of scientific research studies.

Key Need: An OTC Drug or Nutritional That Really Works

Five years ago, drugs could get you to 8% weight loss in a year while the best OTC solution (Alli®) could cause you to lose 4% in a year.

Total sales in the category were less than $1bn. Now, with weight loss of 15% to 20% in a year, sales have jumped to $50 billion and are growing fast.

There was a step change in buying behavior once we saw weight loss go over 15%.

We think that an OTC or supplement that can get an obese person to 10%+ weight loss in a year would be a multi-billion dollar a year product.

This is because many consumers would prefer not to deal with a physician in obtaining self-care.

Several Emerging and Attractive Approaches To Reaching the Consumer Weight Loss Market with an Effective Product

Multi-Ingredient Combo Pill

GRAS/OTC type supplements that work include Plenity, lipase inhibitors, thermogenic agents like caffeine, acarbose, an alpha-glucosidase inhibitor.

Empros Pharma combined two of these (acarbose/lipase inh) and got up to around 6.5% weight loss. The idea is to keep adding on until on hits the magic 10%+ weight loss number.

We believe that this is **doable** today.

Metabolic Ingredients

Brightseed is a leading AI nutritional bioactives company. Their Bio Metabolism ingreatient uses proprietary NCT / NFT bioactives modulating key master metabolic regulator; operates in the less crowded claims space with visceral and abdominal fat loss claims.

Clinical studies backing these claims are quite promising.

Consumer Combo Pill Opportunity

Based on the data in this presentation it looks like most of the small molecule GLP-1's can get to 15% to 22% weight loss in a year (based on orforglipron's 14.7% average weight loss at 9 months).

With small molecule manufacturing economics, one could turn either one of these drug types into a $10 billion+ drug in the self-pay market alone.

Obviously, one can combine them and compete on efficacy and, probably, charge more. There is obvious potential to offer regular, premium and supreme options to the consumer.

There are obvious powerful incentives to take some of the more derisked small molecule classes (e.g,. GLP-1's or CB1's) and get an FDA approval in order to be able to sell the drugs to the self-pay market.

An intriguing area is for non-GLP-1 oral options, particularly those that would be available through the OTC or nutritional channel. In this case the consumer need not access a physician get to get the desired therapies.

Empros Pharma EMP16 Drug Gets to 6% Weight Loss at Six Months

empros pharma

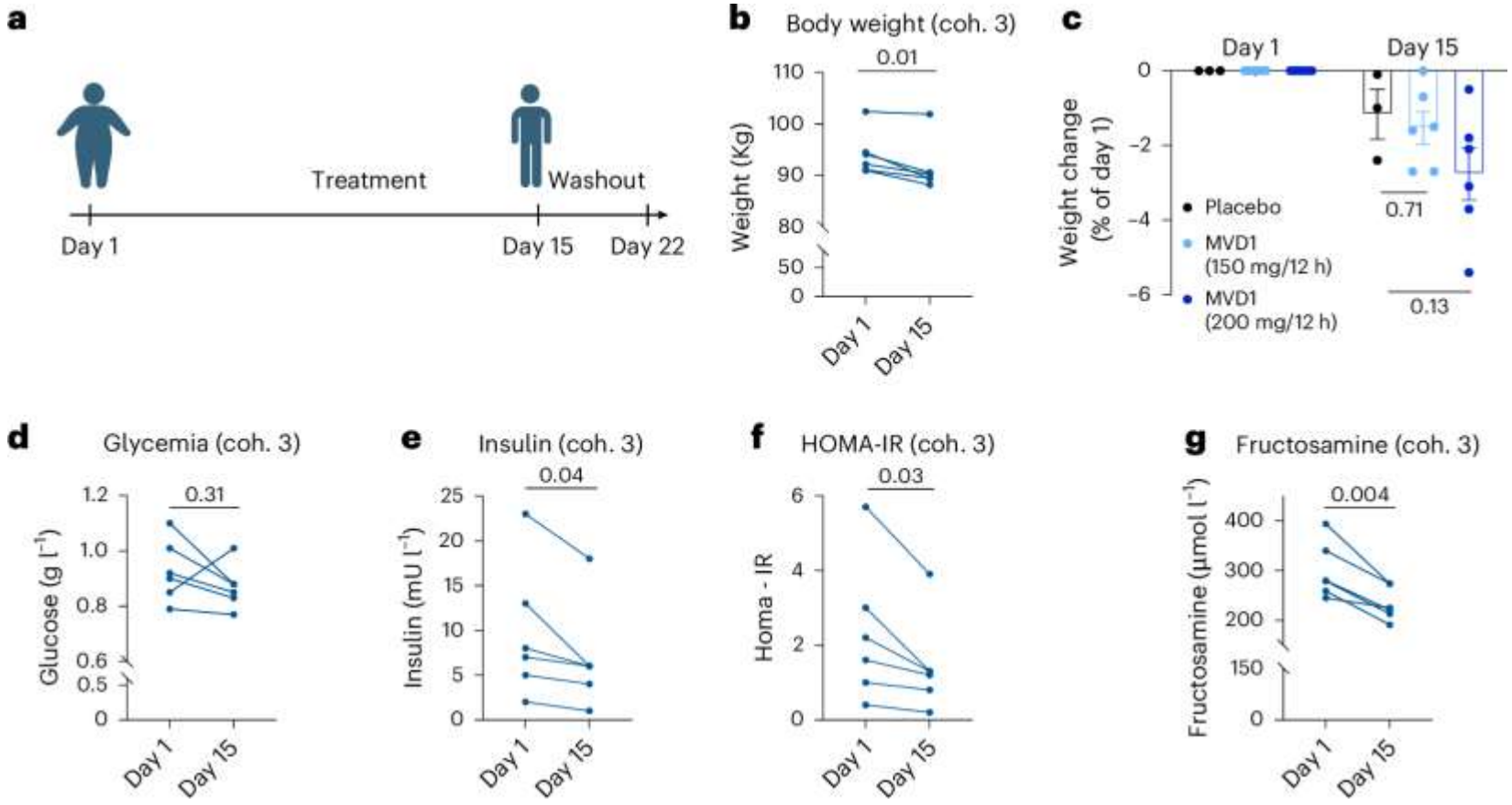
EMP16 target patient groups

Stand-alone treatment for patients with moderate obesity related health risks	**Effective**	✓ For responders (1/3rd of the population), the weight loss is on par with most marketed GLP-1's
Combination with GLP-1's to boost effect and mitigate AEs.	**Mutual benefits**	✓ Reducing GLP-1 related constipation ✓ Low cal diet will mitigate any EMP16 related AE
Sustained weight management, Stand-alone treatment at full or half dose	**For life: Affordable Convenient**	✓ Oral drug nudging for healthy diet ✓ Low monthly cost ✓ Dose can be adjusted on daily basis
Geriatric, pediatric	**Undisputable safety**	✓ Orlistat and acarbose has been in use for decades ✓ Non-systemic ✓ Low muscle mass loss
Possible market: consumer health	**OTC**	✓ EMP16-60/20 can become OTC

Source: Empros Pharma corporate presentation, June 2024

Eolo Pharma's Salicylate Derivative Leads to 0.7% Placebo-Adjusted Weight Loss at 14 Days

Cal, K., Leyva, A., Rodríguez-Duarte, J. *et al.* A nitroalkene derivative of salicylate, SANA, induces creatine-dependent thermogenesis and promotes weight loss. *Nat Metab* June 2025.



Source: https://www.nature.com/articles/s42255-025-01311-z Also see https://www.wired.com/story/new-obesity-pill-may-burn-fat-without-suppressing-appetite/

Brightseed: Using AI to Design Customized Nutritionals

	Bio Gut Fiber	Bio Gut	Bio Metabolism	Bio Liver
Key opportunity insight	1 in 2 consumers who prioritize gut health are dissatisfied with food solutions	1 in 2 consumers who prioritize gut health are dissatisfied with supplement solutions	9/10 adults have tried to lose weight, only 28% keep it off	Fatty liver disease is rapidly becoming #1 reason for liver transplants
Target consumer audience	Consumers who want regularity and gut strength via food	Consumers with chronic GI issues and take supplements	Consumers who want to lose belly fat, including 50% US pop who is pre-diabetic	Metabolically unhealthy population
Market opportunity	$3B in gut-food and supplements	$3B in gut-food and supplements	$7.4B size of US Weight and Glucose Mgmt supplement market	No drugs treat it, expected to be $27B market size
Launch or out-license date target	Q4 2022	Q2 2025	H2 2025	H1 2025 Target out-license date
Expected peak rev / yr	$14M	~$40M	~$40 to $80M+	$4-10M+ (license)

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