Obesity Drug Review

Market Update – July 1, 2023

Source: Getty Images.

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Executive Summary

The recent American Diabetes Association conference was one of the most exciting scientific meetings that we can remember. This report summarizes studies released at ADA on novel obesity drugs and compares results from novel agents highlighted at the conference to other agents in development. We also discuss the evolution of the obesity drug market and the growing importance of the image conscious consumer.

Retatrutide Data at ADA

Retatrutide (RETA) from Lilly, a triple incretin drug, reported stunning 48-week weight loss data with 22% placebo-adjusted weight loss. On average, this corresponded to 58 pounds for study participants. There are some side effects that will need to be tracked as this agent goes through Phase 3 trials.

Remarkably, Lilly's RETA, its tirzepatide molecule and newly introduced orforglipron jointly position Lilly as the market leader in weight loss efficacy at 24 weeks.

The story behind Lilly's success involves persistence, focus and speed. A backgrounder on Lilly's efforts in the *Wall Street Journal* was illuminating.

When one starts to look at agents that are earlier in development it is far from clear that either tirzepatide or retatrutide will emerge as the long-term winners in the market.

(continued on next page)

Executive Summary (Continued)

There are four earlier stage agents with strong data from 4-week and 12-week obesity studies that have caught our eye: Amgen's AMG133, Viking's VK2734, Carmot's CT-268 and Sun's GL0034. All are incretin modulators, and each has potential to be outcompete retatrutide, tirzepatide and semaglutide.

AMG133

Amgen's is a GLP-1 agonist fused to a GIPr antagonist. The weight loss seen with this agent corresponds to going from 250 pounds to 215 pounds in three months.

AMG133 is the first pharmacologic agent to beat bariatric surgery for weight loss.

Unmet Needs in the Market and Emerging Pipeline

Despite recent successes, the obesity market remains wide open to competition. New agents are needed by patients that can deliver one or more of the following traits: (1) avoidance of nausea, (2) avoidance of the "rebound effect", (3) reduced cost, (4) oral delivery, (5) avoidance of muscle loss, (6) less frequent dosing and (7) delivery via direct-to-consumer models.

There are a number of exciting agents in development. Both Structure Therapeutics and Pfizer are developing oral agents to compete with Novo's oral semaglutide and Lilly's orforglipron. Other promising oral approaches in development include AZ/Regeneron's GPR75 modulator, Inversago's CB1r agonist, Glaceum's mitochondrial drug and Kallyope's gut-brain axis drugs. A number of companies are working on approaches that would selectively eliminate fat mass while preserving muscle. Of particular interest are Rivus and Versanis, which is using an antibody to attack a target selectively expressed on adipocytes.

The Changing Market and Opportunity

Interest in the modern GLP-1 agonists like Ozempic® is off the charts. A recent STAT / Harris Poll survey indicated that 16% of Americans would be willing to pay more than $500 a month out of pocket for these obesity drugs. One of the remarkable differences between today's obesity market and that of the past is how important the consumer's direct participation has become. Because of shortages with semaglutide, consumers have increasingly gone online to buy drugs directly.

The market opportunity is obviously a large one. After conducting some analysis, we conclude that current estimates of ultimate market size ($30 billion to $100 billion peak sales) appear conservative. There is both a gigantic private pay market opportunity and a reimbursed market opportunity – unlike anything we have seen before in the pharma sector. The latter will depend on upcoming readouts from outcomes studies.

Lilly's Retatrutide Stuns the Market Last Week

Source: Getty Images.

Lilly's Retatrutide Associated with 24.2% Weight Loss in Eleven Months (58 Pounds, on Average)

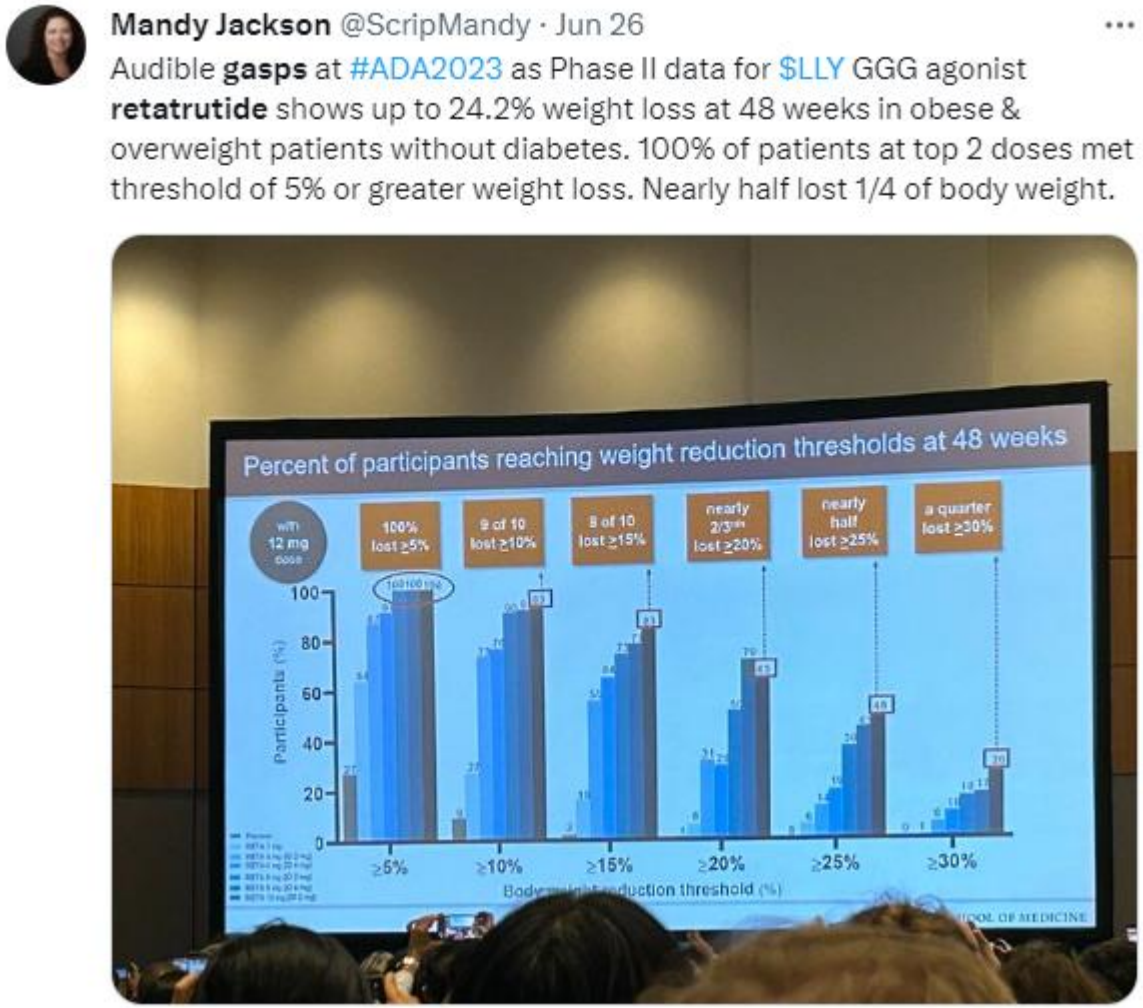
INDIANAPOLIS, June 26, 2023 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today new phase 2 data from retatrutide, Lilly's investigational molecule being studied for the treatment of obesity. At 24 weeks, retatrutide (1 mg, 4 mg, 8 mg or 12 mg) met the primary endpoint for the efficacy estimand in participants living with obesity or overweighti without diabetes, demonstrating a mean weight reduction up to 17.5% (41.2 lb. or 18.7 kg)ii. In a secondary endpoint, retatrutide demonstrated a mean weight reduction up to 24.2% (57.8 lb. or 26.2 kg)ii at the end of the 48-week treatment duration. The results were presented in a symposium at the American Diabetes Association's® 83rd Scientific Sessions and were simultaneously published in The New England Journal of Medicine (NEJM).

The safety profile of retatrutide was similar to other incretin-based therapies. Gastrointestinal side effects were the most commonly reported adverse events, were generally mild-to-moderate in severity, and usually occurred during the dose escalation period.

"Obesity is a treatable chronic disease with a complex underlying biology. We are now in the midst of a rapidly expanding therapeutic landscape of potential highly effective treatment options for individuals with obesity," said Ania Jastreboff, MD, Ph.D., Associate Professor of Medicine & Pediatrics, Endocrinology & Metabolism, at Yale School of Medicine; Director, Yale Obesity Research Center (Y-Weight); and co-Director of the Yale Center for Weight Management. "Participants treated with the highest dose of retatrutide achieved a mean **weight reduction of 24.2%; this translates to an average absolute weight reduction of about 58 pounds over 11 months** of the study. Given that participants had not yet reached a weight plateau at the time the study ended, it appears that full weight reduction efficacy was not yet attained. Longer duration phase 3 trials will enable comprehensive evaluation of efficacy and tolerability of this potential pharmacotherapeutic for the treatment of obesity."

Source: https://www.prnewswire.com/news-releases/lillys-phase-2-retatrutide-results-published-in-the-new-england-journal-of-medicine-show-the-investigational-molecule-achieved-up-to-17-5-mean-weight-reduction-at-24-weeks-in-adults-with-obesity-and-overweight-301863690.html

Audience at ADA Stunned by Retatrutide Data



Lilly's retatrutide presentation at ADA was not an everyday industry event.

Source: https://twitter.com/ScripMandy

The New Weight Loss “Godzilla” Has Arrived

Better than Mounjaro? New Drug Sees Highest Weight Loss Results Seen in Studies Yet, *Diatribe*, June 27, 2023

“This is really a ‘wow’ kind of a reaction because we haven't reached this degree of weight loss in people with type 2 diabetes before,” said Julio Rosenstock [Professor of Medicine at UT Southwestern].

Right now, tirzepatide is the gold standard for weight loss. With these promising new findings, retatrutide could present a whole new generation of treatments for weight loss management.

“We know that tirzepatide is the King Kong of the GLP-1s,” said Rosenstock. “And when I look at retatrutide, I think that there is no question that Godzilla is smiling."

Godzilla Has Arrived

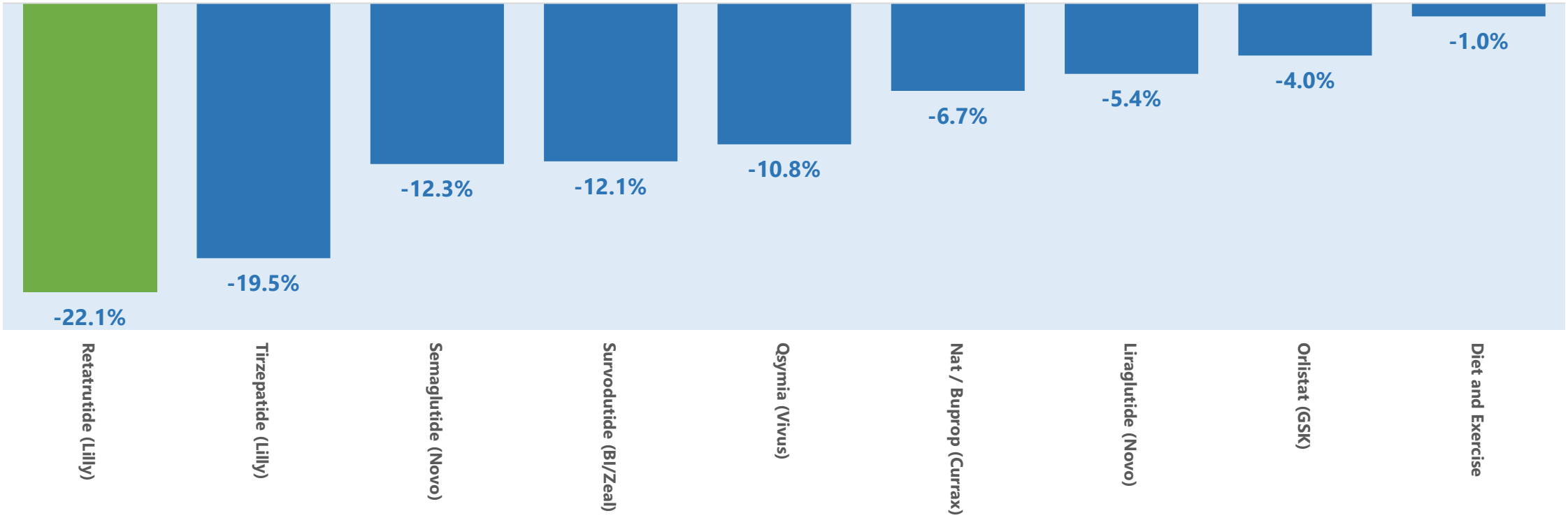
Source: https://diatribe.org/better-mounjaro-new-drug-sees-highest-weight-loss-results-seen-studies-yet. Photo sourced from Getty Images.

Retatrutide Sets the New Benchmark for 48 Week Weight Loss

Unlike some of our previous analyses this chart shows placebo-adjusted weight loss at the same timepoint in order to enhance comparability. The results speak for themselves: Lilly's retatrutide has edged out tirzepatide – another Lilly product. It's important, of course, to note that none of these agents were compared head-to-head and, indeed, study designs can influence outcomes.

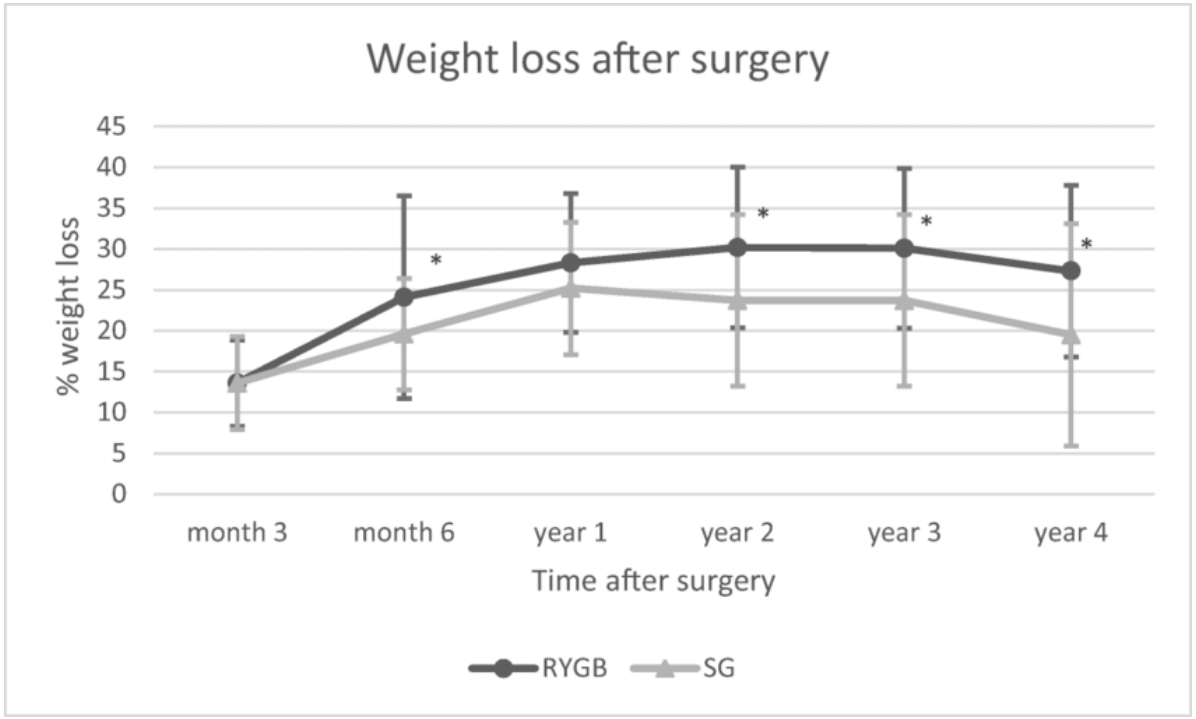
Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(48 Weeks, Highest Dose Used)



Source: Stifel analysis of study results for various agents.

Retatrutide Weight Loss at 12 Months is Competitive With Bariatric Surgery



A pharma industry holy grail has been to match the effect of bariatric surgery with a drug.

Roux-en-Y Gastric Bypass and Sleeve Gastrectomy surgery are associated with 14% weight loss at 90 days, with 28% weigh loss at one year and, ultimately, get to 30% weight loss at year 2.

Retatrutide's 22% weight loss result is within shouting distance of gastric surgery.

There are major disadvantages of bariatric surgery including potential nutritional deficiencies. Chronic complications include but are not limited to strictures, bone loss, internal hernias, fistulae, gallstones and dumping syndrome.

There is one major benefit of gastric surgery versus obesity drugs: the **weight loss is permanent**. While there is some rebound gain it is quite limited versus what's seen with GLP-1s to date

Source: Cadart O, Degrandi O, Barnetche T, Mehsen-Cetre N, Monsaingeon-Henry M, Pupier E, Bosc L, Collet D, Gronnier C, Tremollieres F, Gatta-Cherifi B. Long-Term Effects of Roux-en-Y Gastric Bypass and Sleeve Gastrectomy on Bone Mineral Density: a 4-Year Longitudinal Study. *Obes Surg.* 2020 Sep;30(9):3317-3325.

NAFLD Sub Study with Retatrutide Also Impressive

ADA Press Release, June 26, 2023

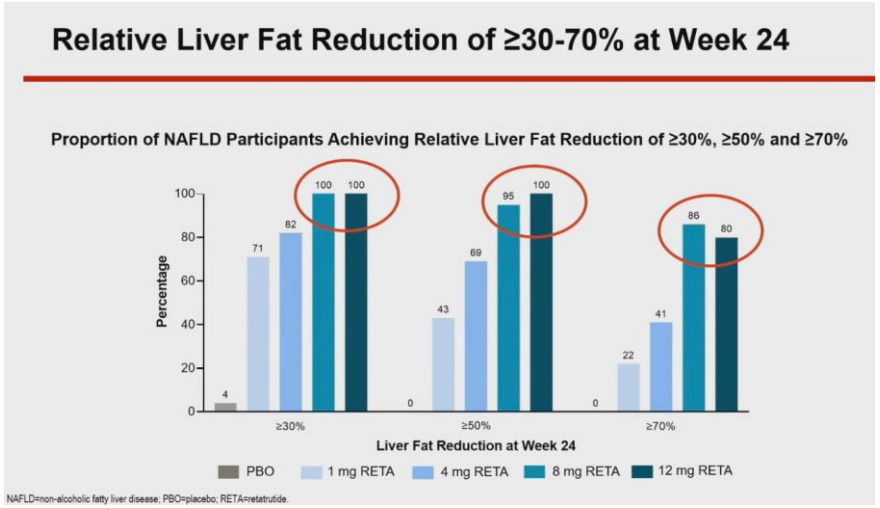
The phase 2 obesity study included a NAFLD substudy, which sought to evaluate how the use of retatrutide in patients with obesity and NAFLD would affect the amount of fat in the liver. The substudy evaluated 98 patients with obesity and NAFLD who underwent magnetic resonance imaging (MRI) of their livers and had biomarkers of liver injury and fibrosis (scarring) measured in their blood.

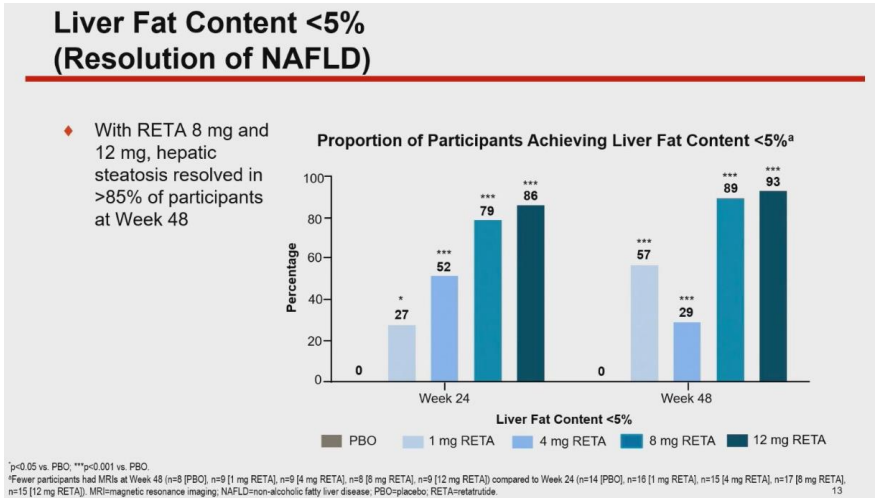
Findings showed that in those with NAFLD, the **amount of fat in the liver normalized in 9 out of 10 patients after 48 weeks treatment with the two highest doses of retatrutide**. These data indicate that retatrutide has the potential to resolve NAFLD.

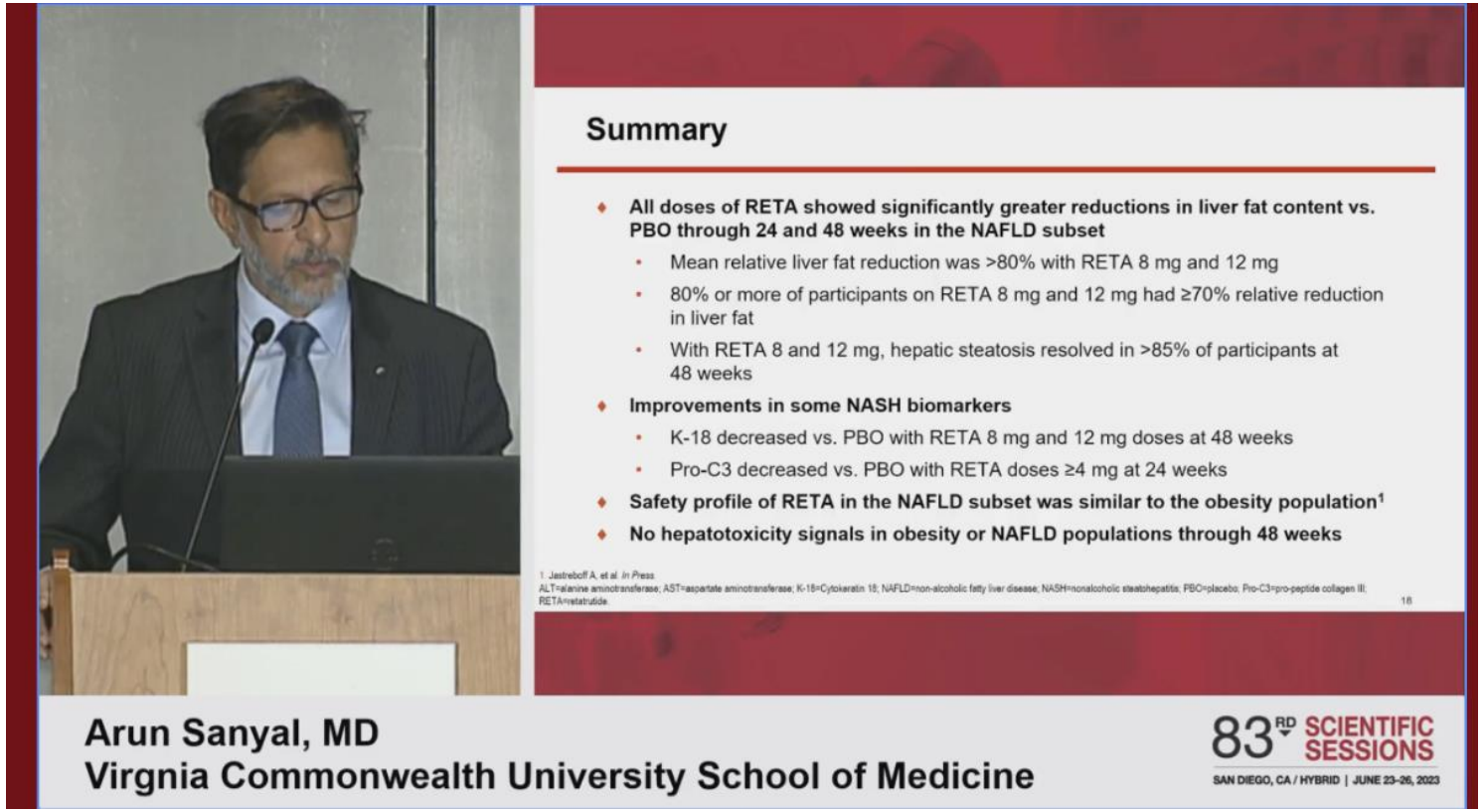
"This study raises the possibility that in the early stages of liver disease, it is possible to 'de-fat' the liver, which could in turn help to reduce the long-term cardiac, metabolic, renal, and liver-related harm from obesity. We are encouraged by these results and how they can potentially help tackle a disease that is currently without any approved therapies," said Arun J. Sanyal, MD, Director of the Stravitz Sanyal Institute for Liver Disease and Metabolic Health, Professor of Medicine, Physiology, and Molecular Pathology and Interim-Chair of the Gastroenterology, Hepatology, and Nutrition Division at Virginia Commonwealth University.

Source: https://diabetes.org/newsroom/press-releases/2023/american-diabetes-association-highlights-novel-agent-retatrutide-results-substantial-weight-reduction-people-with-obesity-type-2-diabetes-during-late-breaking-symposium

Impressive Reductions in Liver Fat with Retatrutide







These findings mirror a well-known phenomenon – that NAFLD largely resolves with meaningful weight loss. It remains to be seen how competitive weight loss drugs will be to FGF21 analogues and other competitors in the NASH field.

Source: ADA slides from Dr. Sanyal

Some Safety Items to Track with Retatrutide

Will be important to track arrhythmias in subsequent development.

Will be important to track severe GI events in subsequent development.

Adverse Events of Special Interest

Participants with AEs, n, %	PBO N=70	RETA 1 mg N=69	RETA 4 mg [ID 2 mg] N=33	RETA 4 mg [ID 4 mg] N=33	RETA 8 mg [ID 2 mg] N=35	RETA 8 mg [ID 4 mg] N=35	RETA 12 mg [ID 2 mg] N=62	Total (N=337)
Antidrug antibodies	1 (1.5)	3 (4.4)	4 (12.1)	5 (15.6)	5 (15.6)	2 (5.9)	11 (18.3)	31 (9.2)
Hypersensitivity	2 (2.9)	7 (10.1)	1 (3.0)	2 (6.1)	3 (8.6)	7 (20.0)	8 (12.9)	30 (8.9)
Hyperaesthesia/related	1 (1.4)	1 (1.4)	2 (6.1)	2 (6.1)	1 (2.9)	5 (14.3)	8 (12.9)	20 (5.9)
Cardiac arrhythmias	2 (2.9)	3 (4.3)	0	2 (6.1)	0	5 (14.3)	7 (11.3)	19 (5.6)
Hepatic disorders	2 (2.9)	5 (7.2)	1 (3.0)	0	1 (2.9)	2 (5.7)	2 (3.2)	13 (3.9)
Injection site reactions	0	1 (1.4)	0	1 (3.0)	0	1 (2.9)	5 (8.1)	8 (2.4)
Severe GI AEs	0	0	0	1 (3.0)	1 (2.9)	1 (2.9)	4 (6.5)	7 (2.1)
Renal events	1 (1.4)	1 (1.4)	1 (3.0)	0	0	1 (2.9)	0	4 (1.2)
Biliary disorders	0	0	0	0	1 (2.9)	2 (5.7)	0	3 (0.9)
MACE	0	2 (2.9)	0	0	0	0	0	2 (0.6)
MDD/suicidal ideation	1 (1.4)	0	0	0	0	0	0	1 (0.3)
Pancreatitis	0	0	0	0	0	0	1 (1.6)	1 (0.3)

No cases of clinically significant hypoglycemia, medullary thyroid cancer, or C-cell hyperplasia were reported.

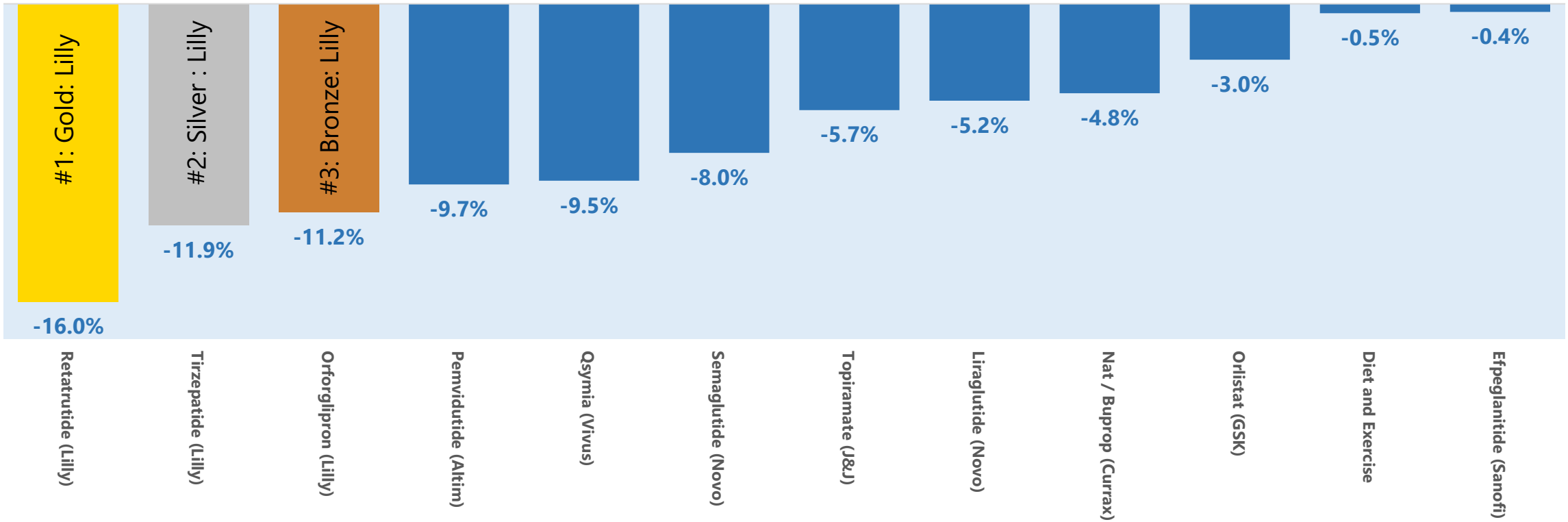
Source: ADA, Company data

Lilly Sweeps All Three Top Spots in 24-Week Weight Loss Rankings

To be able to drop 16% of body weight with retatrutide in less than a half year is stunning and important therapeutic option for persons who are overweight. It's interesting to note that the three agents with the best weight loss at this time period all come from Eli Lilly. We are reminded of Jamaica's medal sweep in the women's 100 meters at the 2020 Olympics.

Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

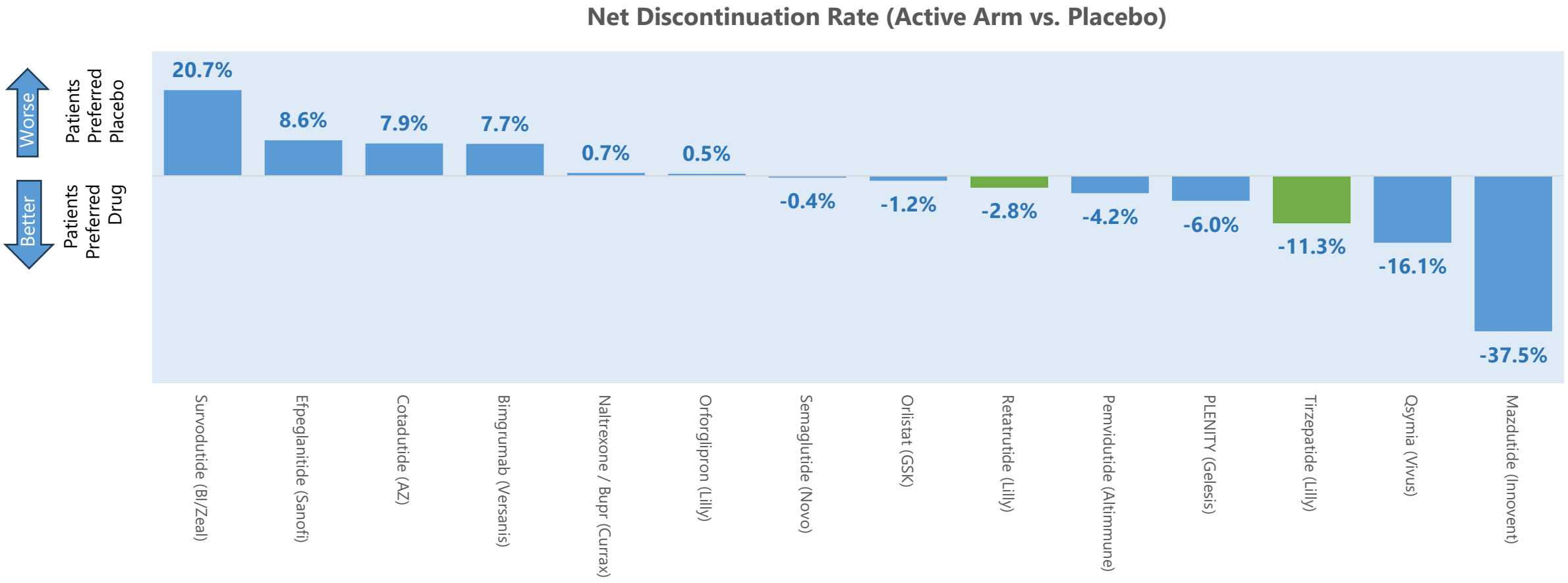
(24 Weeks, Highest Dose Used))



Source: Stifel analysis of study results for various agents.

The Difference Between Tirzepatide and Retatrutide Narrows When One Compares Discontinuation Rates

Both retatrutide and tirzepatide are preferred by patients over placebo. But tirzepatide had a more favorable net discontinuation rate. Of course, studies are not comparable, and a head-to-head comparison could find a different result.



Source: Stifel analysis of study results for various agents.

How Has Lilly Gotten So Good in Obesity Drugs?

Peter Loftus, *Wall Street Journal*, "The 'King Kong' of Weight-Loss Drugs Is Coming," April 3, 2023

Eli Lilly's Mounjaro could outpace Ozempic as the most powerful treatment on the market. To develop it, the drug company needed to overhaul long-held but failing practices.

"Dr. Skovronsky recommended Lilly pursue drug projects where it best understood the science and lean less on commercial sales estimates. Lilly was not very good at predicting a drug's sales over time anyway, he concluded, but could better predict the scientific probability of a drug's success.

Lilly jettisoned research on diseases where it was tougher to deliver an advance, including osteoporosis and psychiatric conditions, and doubled down in areas where it had expertise: diabetes, oncology and Alzheimer's disease."

Focus on Science Early On

Source: https://www.wsj.com/articles/ozempic-mounjaro-weight-loss-drug-wegovy-eli-lilly-66f2906

Key Lilly Insight: Believe in Mouse Models. They Predict Efficacy of Obesity Drugs in Humans

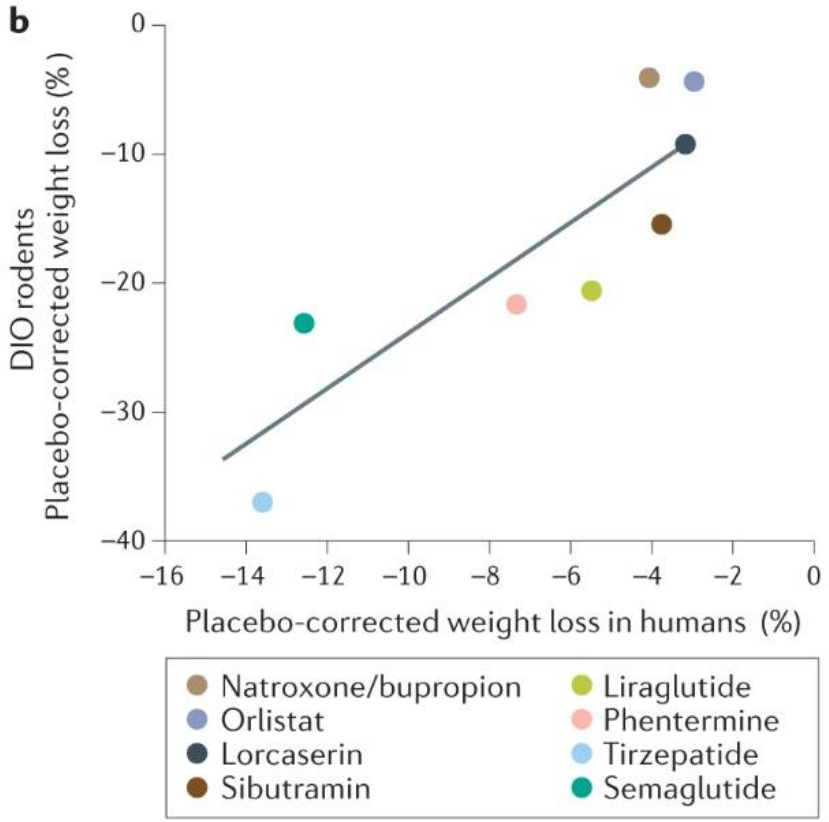
Peter Loftus, *Wall Street Journal*, "The 'King Kong' of Weight-Loss Drugs Is Coming," April 3, 2023

"Lilly scientists expressed hope their drug candidate [Mounjaro] could do much more than that. The experimental drug combined a synthesized GLP-1 gut hormone like the one in Trulicity with a cousin called GIP, which the scientists theorized could produce even more insulin and suppress appetite further.

Two weeks after starting to get the compound, chubby laboratory mice given the compound lost 20% to 25% of their weight.

Despite the unknowns, Lilly went ahead and greenlighted the experimental drug for human testing. "It was the largest degree of weight loss I had ever seen in a mouse model of obesity. It felt pretty compelling," Dr. Skovronsky said."

Timo D. Müller, Matthias Blüher, Matthias H. Tschöp & Richard D. DiMarchi, Anti-obesity drug discovery: advances and challenges," *Nature Reviews Drug Discovery*, 2022: **"weight loss effects generally translate from rodents to humans"**



Sources: (1) left: https://www.wsj.com/articles/ozempic-mounjaro-weight-loss-drug-wegovy-eli-lilly-66f2906, (2) right: https://www.nature.com/articles/s41573-021-00337-8/.

Key Consideration from an IRA Perspective

Like Tirzepatide, Retatrutide is a 39-amino acid peptide. The good news is that it can be made synthetically. The bad news is that from an IRA perspective, it is a small molecule – not a biologic. The threshold to file a BLA on a peptide is that a drug needs to have 40 or more amino acids.* This means that this drug will be eligible for IRA negotiation rather soon after its approach. Obviously, Lilly developed this drug well before the IRA was passed.

Jalan and Kopath, American Chemical Society, 2023

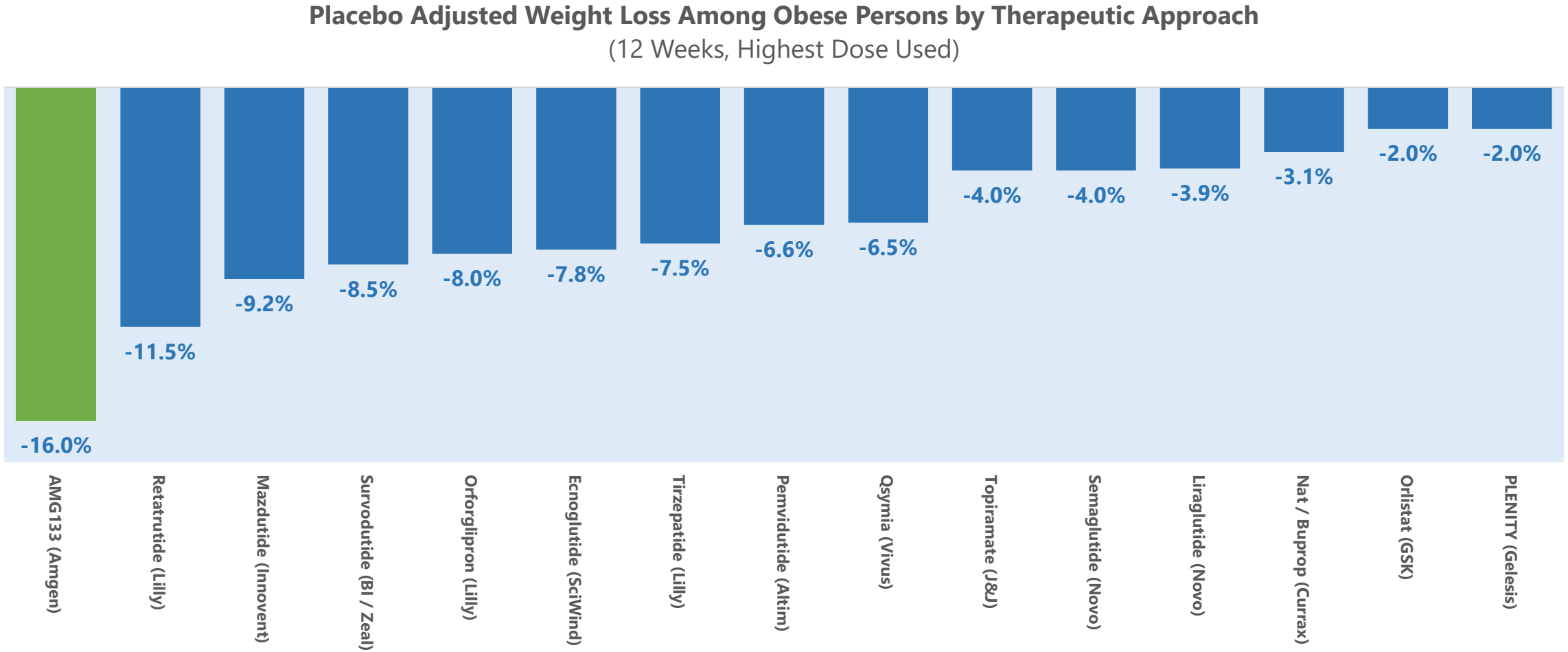
"Synthetic chemistry has provided access to a wide class of peptides and proteins which was out of bound several decades ago, particularly peptides containing more than 10-15 amino acids. With the advent of solid phase peptide synthesis (SPPS), peptides longer than 20 amino acids could be readily built on a solid support through either Boc/Bzl or Fmoc/*t*-Bu strategies. However, it was still challenging to synthesize peptides containing 50 or more amino acids by the linear SPPS because of lower yields and reduced purities with increasing peptide length. Thus, the convergent hybrid strategy becomes highly attractive wherein high purity peptide fragments can be coupled together in solution phase to overcome the drawbacks of the linear SPPS. Some of the shortcomings of this strategy are the need for tight control over epimerization because of the limited non-epimerizable coupling junctions, and the decreasing solubility of the growing protected peptide chain in organic solvents. The introduction of native chemical ligation (NCL) in 1994 has helped immensely in the synthesis of numerous large peptides and proteins, which were inaccessible earlier. **Retatrutide, a 39-amino acid synthetic peptide**, is a once-weekly novel GIP (glucose-dependent insulinotropic polypeptide), GLP-1 (glucagon-like-peptide-1) and glucagon receptor agonist and is currently in phase 2 clinical trials for diabetes and obesity. Herein, we have developed an NCL synthesis where two unprotected peptide fragments are coupled in aqueous media without any epimerization to yield retatrutide cysteine analogue, which is then subjected to desulfurization with water soluble radical initiators to chemoselectively give retatrutide."

Source: https://acs.digitellinc.com/sessions/531874/view

* See https://www.fda.gov/about-fda/economic-impact-analyses-fda-regulations/definition-term-biological-product-final-regulatory-impact-analysis

Picture With 12 Week Data Gets More Complicated

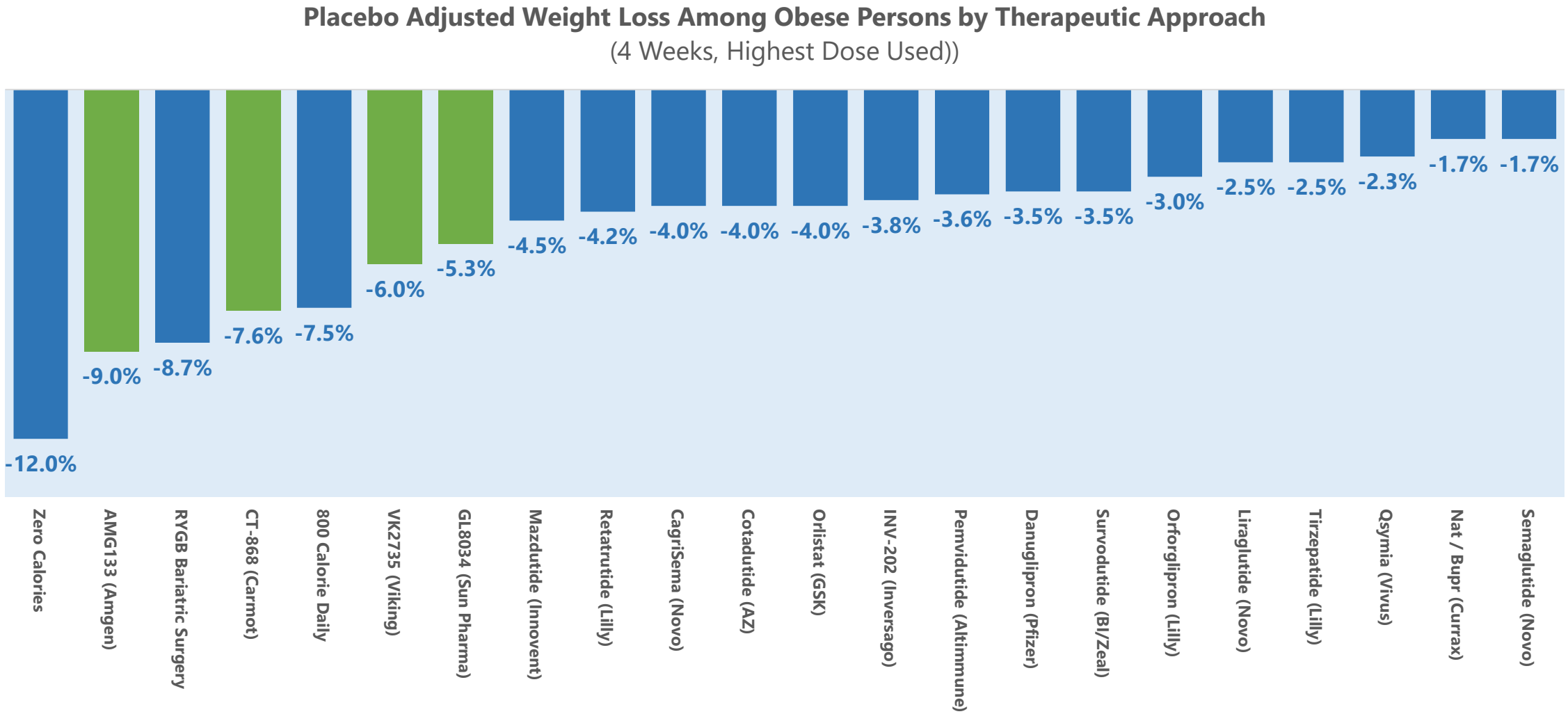
Recall that Retatrutide is associated with 16% weight loss at 24 weeks. Amgen is seeing the *same* level of weight loss in half the time and is by far the leader at this point. Amgen has not yet reported data for AMG133 beyond 12 weeks. Based on weight loss curves over time for other agents, we expect 48-week weight loss with AMG133 to be on the order of 30% to 35% of starting weight.



Source: Stifel analysis of study results for various agents.

Multiple Agents Showing Game-Changing 4 Week Weight Loss

Amgen has reported 9% placebo-adjusted weight loss with AMG133 at four weeks. Carmot Therapeutics, Viking and Sun Pharma have also shown game changing four-week weight loss data.



Source: Stifel analysis of study results for various agents.

Carmot Therapeutics Dual Incretin, CT-268, Showing Highly Impressive 4-Week Weight Loss at ADA

SAN DIEGO, Calif., June 23, 2023 (GLOBE NEWSWIRE)

Poster No. 75-LB: CT-388, a novel once-weekly dual GLP-1 and GIP receptor modulator, is safe, well-tolerated, and produces more than 8% weight loss in 4 weeks in overweight and obese adults

As part of a larger Phase 1/2 clinical trial, the Phase 1 results presented at ADA comprised single ascending doses (SAD; 0.5-7.5 mg) and multiple ascending doses (MAD; 5-12 mg) for 4 weeks administered to overweight/obese adults. The primary objective, safety and tolerability of CT-388, was evaluated across a total of 64 participants who received at least one dose of CT-388 or placebo. The results were as follows across the three MAD cohorts:

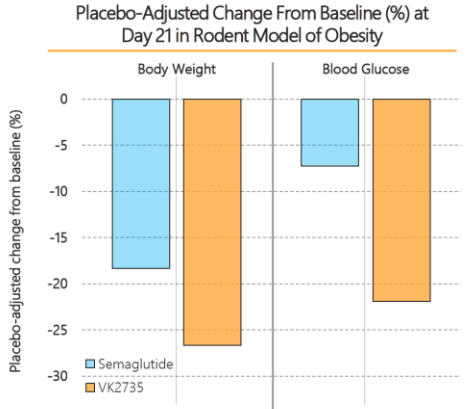
- Favorable tolerability profile in both overweight and obese participants with most common adverse events (AEs) being GI-related, consistent with the incretin class. No temporal patterns for AEs around dose up-titration periods.
- Pharmacokinetic (PK) profile supports once weekly dose administration.
- CT-388 dosed at 5/8/12/12 mg produced 8.4% weight loss (7.7 kg, ~17 lbs) accompanied by a decrease in waist and hip circumference, and improvement in markers of insulin sensitivity (HOMA-IR). Initial profile suggests that obese patients might benefit the most given the higher weight loss and more favorable tolerability.
- These data warrant further clinical evaluation of CT-388, possibly with minimal to no titration, for the treatment of obesity, type 2 diabetes and other weight-related comorbidities. Carmot has designed the Phase 1/2 CT-388 clinical trial to evaluate not only higher doses across longer treatment durations (e.g. 12-24 weeks), but also cohorts with minimal to no titrations. Carmot expects data from these additional cohorts in the first half of 2024. Additional Phase 2 clinical trials in overweight and obese adults are planned to commence in 2023.

Source: https://carmot.us/carmot-therapeutics-highlights-clinical-data-from-its-pipeline-of-treatments-for-obesity-and-diabetes-at-the-83rd-american-diabetes-association-scientific-sessions/

Strength of Viking's VK2735 at Four Weeks

VK2735: Novel Dual Agonist of GLP-1 and GIP Receptors

- GLP-1 receptor activity similar to known agonist semaglutide (<300nM)
- GLP-1/GIP binding ratio <1
- Robust reduction in body weight, blood glucose in rodent models
- Data support additive benefit of GIP-agonist activity on top of GLP-1 activation



	Body Weight	Blood Glucose
Semaglutide	-18%	-7%
VK2735	-27%	-22%
p-value vs. semaglutide	<0.0001	<0.0001

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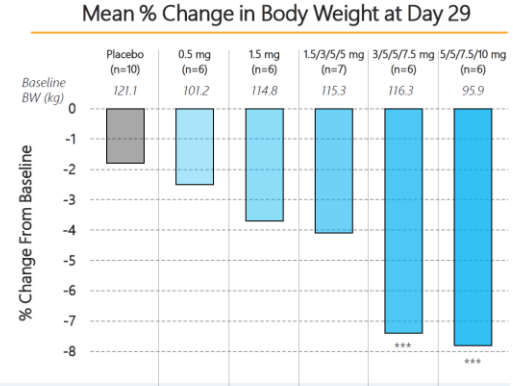
VK2735 Phase 1 MAD Results: Weight Change After 28 Days

- Reduction in body weight observed in all VK2735 dosing cohorts
- Dose dependent effect observed across VK2735 cohorts
- Significant reduction vs. placebo observed at higher VK2735 doses



	Placebo (n=10)	0.5 mg (n=6)	1.5 mg (n=6)	1.5/3/5/5 mg (n=7)	3/5/5/7.5 mg (n=6)	5/5/7.5/10 mg (n=6)
% Change in BW:	-1.8%	-2.5%	-3.7%	-4.1%	-7.4%	-7.8%
Placebo-adjusted:	-	-0.7%	-1.9%	-2.3%	-5.6%	-6.0%
p-value vs placebo	-	0.64	0.17	0.09	0.0003	0.0002

Notes: Baseline BMI ≥30 in all MAD subjects. ***p<0.001

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Most common AEs to date Number of subjects reporting (%)	Placebo (n=10)	0.5 mg (n=6)	1.5 mg (n=6)	1.5/3/5/5 mg (n=7)	3/5/5/7.5 mg (n=6)	5/5/7.5/10 mg (n=6)
GERD	1 (10%)	0 (0%)	0 (0%)	3 (43%)	4 (67%)	1 (17%)
Nausea	5 (50%)	2 (33%)	4 (67%)	5 (71%)	5 (83%)	2 (33%)
Vomiting	1 (10%)	2 (33%)	0 (0%)	2 (29%)	1 (17%)	1 (17%)
Abdominal pain	1 (10%)	0 (0%)	1 (17%)	3 (43%)	4 (67%)	2 (33%)
Diarrhea	3 (30%)	1 (17%)	1 (17%)	2 (29%)	0 (0%)	0 (0%)
Constipation	0 (0%)	1 (17%)	1 (17%)	2 (29%)	1 (17%)	0 (0%)

GERD: Gastroesophageal reflux disease.

- Majority of all reported AEs (98%) mild or moderate
- Mechanism-based mild (89%) to moderate (11%) nausea observed
- No discontinuations related to GI adverse events

There is a lot to like about Viking's story. Unlike Amgen's drug there were no discontinuations at the high dose.

Unlike Carmot's story, patients in the MAD portion had BMI's under 30 (Carmot's high dose group had a starting BMI average of 34.9). It is well known that percentage weight loss tends to be lower when baseline BMI is lower.

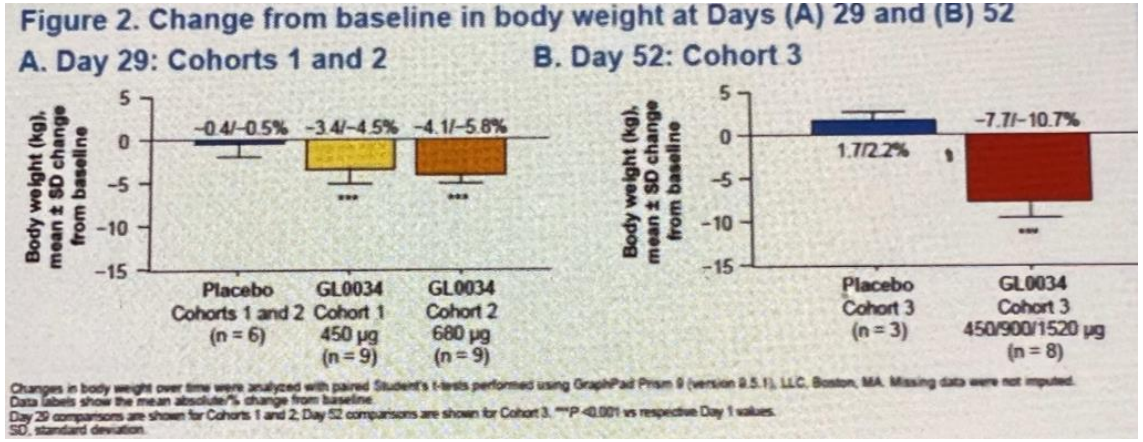
We see Viking as a relatively tolerable dual competitor in the market.

Source: https://www.prnewswire.com/news-releases/viking-therapeutics-announces-results-from-phase-1-clinical-trial-of-dual-glp-1gip-receptor-agonist-vk2735-301782861.html

Sun Pharma's Long-acting GLP-1 Receptor Agonist

A Single-Ascending Dose Study of The Novel GLP-1 Receptor Agonist GL0034 (Utreglutide) in Obese Individuals Without Diabetes. [Poster # 765-P, Sunday, June 25, 2023, 11:30am – 12:30pm PT, Hall B-C, Presented by Dr. Rajamannar Thennati]

- Participants (n=24; BMI ≥30 kg/m^2) were randomized 3:1 to treatment with GL0034 or placebo. The cohorts achieved mean percent changes in body weight, ranging from -1.9% at the 2000 µg dose ($p<0.01$) to -2.5% at the highest dose (2520 µg; $p<0.001$) at Day 8 and sustained beyond initial treatment exposure through Day 22, compared to 0.3% at Day 8 and -0.1% at Day 22 in placebo-treated participants.
- Triglyceride levels were significantly decreased from baseline in participants treated with GL0034 2000 µg and 2520 µg with mean percent changes of -40.7% (2000 µg; $p<0.01$) and -28.0% (2520 µg; $p<0.05$) at Day 8, compared to an increase of 9.9% in placebo-treated individuals.
- The most common AEs occurring in ≥5 participants receiving GL0034 were decreased appetite, early satiety, nausea, dyspepsia, and vomiting.



Sun's new GLP-1 agonist at ADA was a surprise to us.

10.7% weight loss at 52 days is highly competitive and it's far from clear that Sun has yet optimized dose. Nausea rates with the drug were quite low and their Phase 1 only included male subjects who tend to experience lower weight loss than females with GLP-1's, on average.

Sun is a low-cost manufacturer and is willing to compete on price.

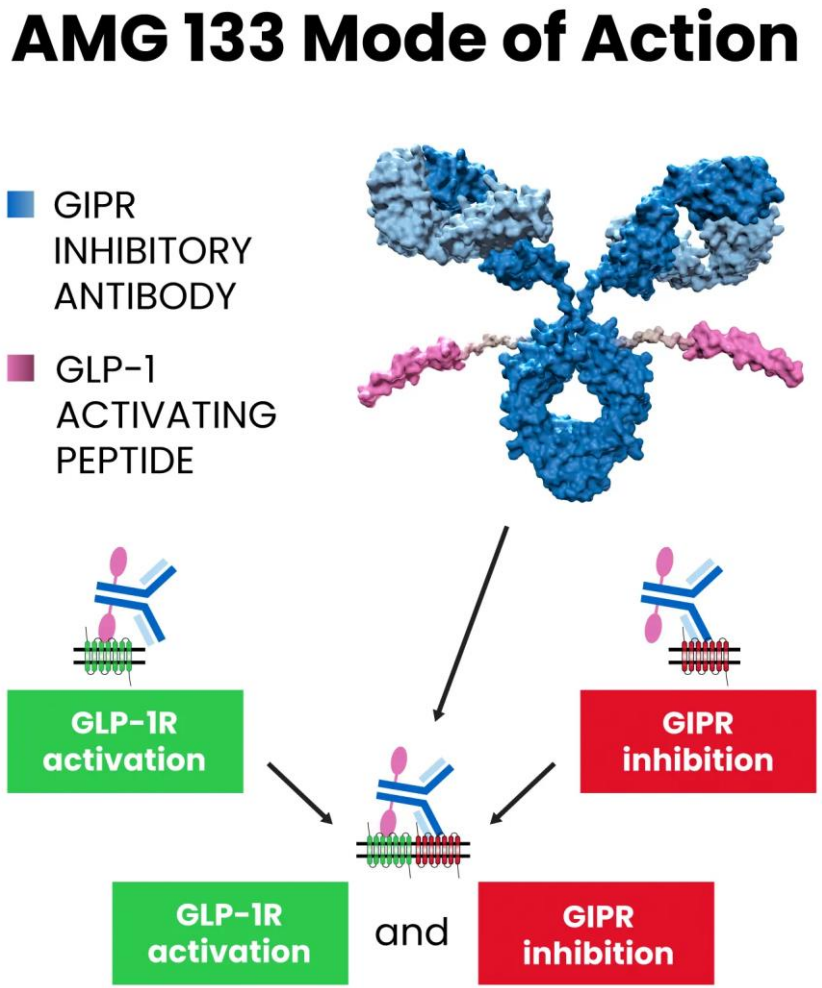
They could be a very interesting addition to the U.S. obesity market which is in dire need of price competition.

Source: https://www.prnewswire.com/news-releases/sun-pharma-presents-data-from-first-in-human-phase-1-studies-of-gl0034-at-the-american-diabetes-association-83rd-scientific-sessions-301861402.html, ADA presentation.

Details on Amgen's AMG133

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

AMG 133 Antagonizes GIP and Agonizes GLP-1



To create AMG 133, Amgen researchers started with an antibody that blocks GIPR (GIP Receptor).

To this antibody backbone, they then added two modified GLP-1 peptides that activate the GLP-1 receptor.

Preclinical research at Amgen confirmed that this dual action, or bifunctionality that targets these two key metabolic pathways, seemed to have a stronger effect on weight loss than either GLP-1 or GIPR antibodies alone.

Gastric inhibitory polypeptide (GIP) is a 42-amino acid hormone made in K-cells localized to the proximal gut, and it is secreted after eating food containing glucose and fat.

Although originally named as an acid blocker, the principal property of GIP is the stimulation of insulin release from pancreatic islet β-cells in the presence of glucose. Accordingly, GIP is also known as "glucose-dependent insulinotropic polypeptide".

GIP enhances gut nutrient absorption, and it increases uptake of glucose into fat cells. Importantly, GIP increases insulin release which further improves nutrient uptake and storage.

Source: https://www.amgen.com/stories/2022/12/targeting-obesity-using-biology-not-behavior

Amgen Work on GIP Receptor Motivated by Rare Genetic Variants Seen in GWAS Studies by its deCODE Subsidiary

"Further obesity research at Amgen and Icelandic subsidiary deCODE Genetics began looking at the effects of rare genetic changes, called variants, on Body Mass Index (BMI), a measure of body fat based on height and weight. The Centers for Disease Control and Prevention (CDC) defines obesity as having a BMI of 30 or higher. deCODE looked for variants associated with low BMI in human data accumulated from hundreds of thousands of individuals across biobanks from several countries, with the idea that these could be valuable drug targets.

The deCODE work and other research uncovered variants in the GIPR (Gastric Inhibitory Polypeptide Receptor) gene that were particularly interesting. GIP and its receptor are involved in regulating insulin levels after eating. Individuals with specific variants in this gene that reduced its activity had lower BMIs. Further analysis by Amgen researchers confirmed this finding."

Source: https://www.amgen.com/stories/2022/12/targeting-obesity-using-biology-not-behavior

Amgen cites to GWAS work

1. Nature Genetics 2012; 44 (3):302-6
2. Nature Genetics 2010; 42 (11):937-48 (deCODEis collaborator)
3. Nature Genetics 2013; 45 (5):501-12 (deCODEis collaborator)
4. Science 2021; 373 (6550)

Mice With Loss-of-Function Mutations in GIPR Gain Only a Third of Weight of Normal Mice When Fed High Fat Diets

Normal mouse 3x heavier at 36 weeks

GIPr KO mouse gains weight but only modestly despite HF diet

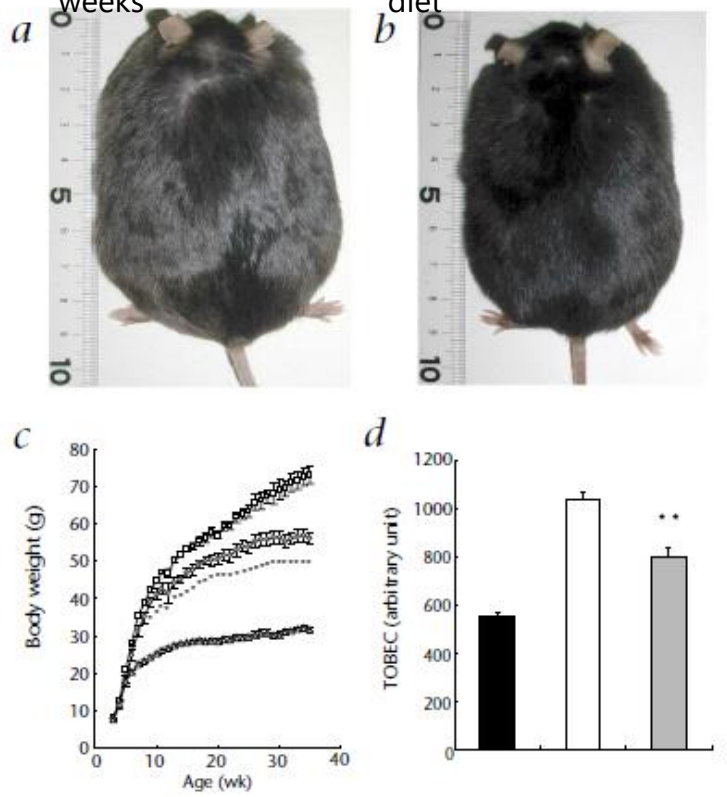


Fig. 2 Inhibition of GIP signal prevents hyperphagia-induced obesity. ***a*** and ***b***, Gross appearance of *Lep*ob/*Lep*ob (*a*) and *Gipr*–/– *Lep*ob/*Lep*ob (*b*) mice. ***c***, Body weight of WT (), *Lep*ob/*Lep*ob () and *Gipr*–/– *Lep*ob/*Lep*ob mice () at 35 wk of age. *n* = 4; *, *P* < 0.05, compared with *Lep*ob/*Lep*ob mice. ***d***, TOBEC of WT (), *Lep*ob/*Lep*ob () and *Gipr*–/– *Lep*ob/*Lep*ob () mice at 35 wk. *n* = 4; **, *P* < 0.01, compared with *Lep*ob/*Lep*ob mice.

"Secretion of gastric inhibitory polypeptide (GIP), a duodenal hormone, is primarily induced by absorption of ingested fat. Here we describe a novel pathway of obesity promotion via GIP.

Wild-type mice fed a high-fat diet exhibited both hypersecretion of GIP and extreme visceral and subcutaneous fat deposition with insulin resistance.

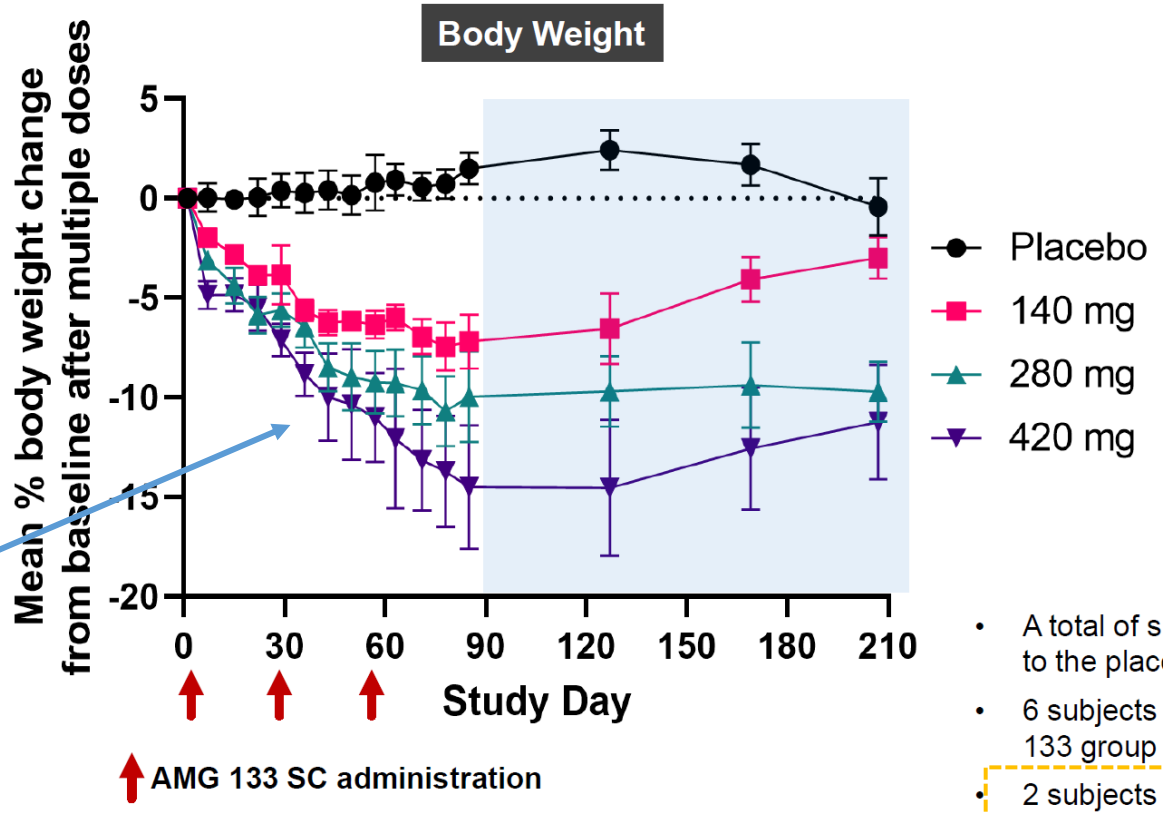
In contrast, mice lacking the GIP receptor (Gipr(-/-)) fed a high-fat diet were clearly protected from both the obesity and the insulin resistance. Moreover, double-homozygous mice (Gipr(-/-), Lep(ob)/Lep(ob)) generated by crossbreeding Gipr(-/-) and obese ob/ob (Lep(ob)/Lep(ob)) mice gained less weight and had lower adiposity than Lep(ob)/Lep(ob) mice. The Gipr(-/-) mice had a lower respiratory quotient and used fat as the preferred energy substrate, and were thus resistant to obesity. **Therefore, GIP directly links overnutrition to obesity and it is a potential target for anti-obesity drugs."**

Source: https://pubmed.ncbi.nlm.nih.gov/12068290/

The Scale of Weight Loss Seen with AMG133 Has Never Been Seen Before with a Pharmacological Agent

The observed weight loss with a GLP1 agonist and GIPr antagonist corresponds to going from 250 pounds to 215 pounds in three months.

The weight loss slope at the 420mg dose is extreme. Patients lost 1% of their body weight *every four* days.



- A total of six subjects were randomized to the placebo group across cohorts
- 6 subjects were randomized to the AMG 133 group at each dose level
- 2 subjects were replaced in the 420 mg dose group

SC = subcutaneous; mg = milligram.

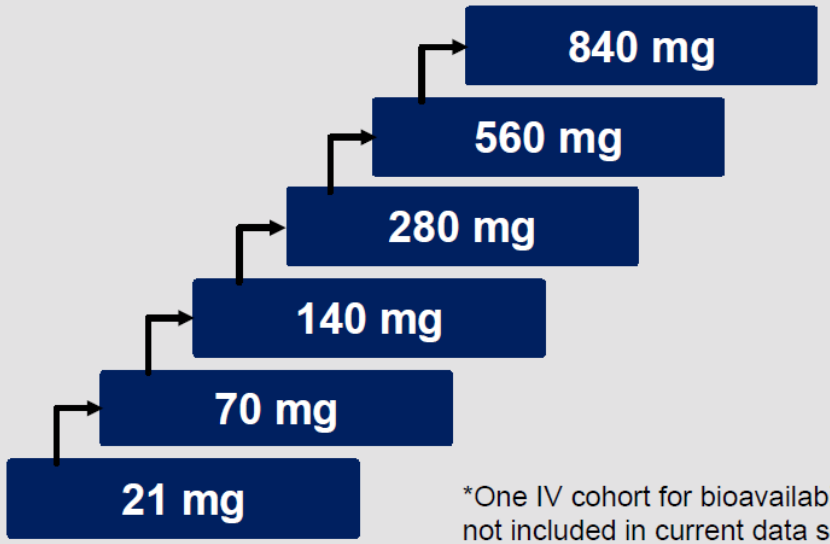
12

Note that two subjects dropped out of the Phase 1b at the high dose. This discontinuation rate is not unusual for the GLP-1 class, however.

AMG133 Was Dosed Q4W – Once Monthly

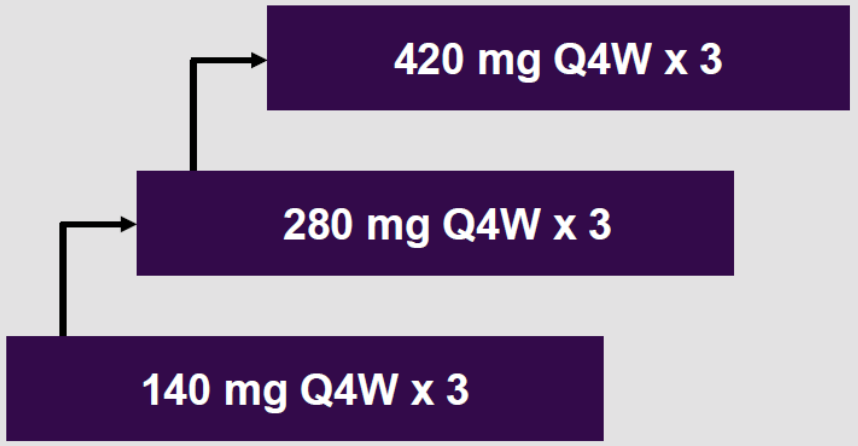
STUDY SCHEMA

Single Ascending Dose Cohorts*
AMG 133:Placebo (6:2) SC x 1



*One IV cohort for bioavailability not included in current data set

Multiple Ascending Dose Cohorts**
AMG 133:Placebo (6:2) SC Q4W × 3



**3 cohorts not included due to ongoing trial/analysis; 1 with digital tools and 2 with 2- or 4-week dose escalation strategies

SC, subcutaneous; IV, intravenous; mg = milligram; Q4W, every 4 weeks.

Understanding GIP: Insulin Signaling is Essential to Life. Without Insulin We Can't Store Energy. Without Energy We Starve.

Type 1 Diabetes Induces Starvation Because Patients Can't Make Insulin Needed to Convert Glucose to Fat. Similarly, by reducing insulin production by roughly 60% to 70% a perfect GIP inhibitor can induce the effect of partial starvation despite eating a normal amount of food.

Before and after pictures of child treated with insulin in the 1920s. Lilly got insulin to this child just in time.

Patient JL, 15 pounds December 15, 1922

Patient JL, 29 pounds February 15, 1923

Type I diabetes has been described as 'starvation in the midst of plenty.' Despite hyperphagia and high levels of circulating fuels, insulin deficiency prevents effective use of fuels by many tissues, hence 'starving' them of nutrition."*

Prior to the invention of insulin, children with Type 1 diabetes starved to death. To the left is a remarkable photo of a child who was fortunate to get access to Lilly's insulin before death by starvation.

* *Endocr Rev*, Volume 40, Issue 1, February 2019, Pages 1–16

Understanding GIP: When Glucose Goes Through the Gut Something Happens: GIPr is Agonized

A landmark study performed in humans was published in 1964 in *Lancet*.[1]

The study showed that blood insulin levels were about three times greater after humans consumed glucose compared to when it was given intravenously (IV), while blood glucose levels were similar.

Thus, something in the intestine was responsible for 2/3 of the effect; a yet to be identified incretin hormone.

The principal incretin hormone proved to be gastric inhibitory polypeptide (GIP).[2]

Explanation: IV glucose bypasses the gut which avoids agonism of GIP, in turn resulting in less insulin signaling.

insight review articles

Insulin signalling and the regulation of glucose and lipid metabolism

Alan R. Saltiel* & C. Ronald Kahn†

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†Joslin Diabetes Centre, Harvard Medical School, Boston, Massachusetts 02215, USA (e-mail: c.ronald.kahn@joslin.harvard.edu)

The epidemic of type 2 diabetes and impaired glucose tolerance is one of the main causes of morbidity and mortality worldwide. In both disorders, tissues such as muscle, fat and liver become less responsive or resistant to insulin. This state is also linked to other common health problems, such as obesity, polycystic ovarian disease, hyperlipidaemia, hypertension and atherosclerosis. The pathophysiology of insulin resistance involves a complex network of signalling pathways, activated by the insulin receptor, which regulates intermediary metabolism and its organization in cells. But recent studies have shown that numerous other hormones and signalling events attenuate insulin action, and are important in type 2 diabetes.

Despite periods of feeding and fasting, plasma glucose remains in a narrow range between 4 and 7 mM in normal individuals. This tight control is governed by the balance between glucose absorption from the intestine, production by the liver and uptake and metabolism by peripheral tissues. Insulin increases glucose uptake in muscle and fat (see Box 1), and inhibits hepatic glucose production, thus serving as the primary regulator of blood glucose concentration. Insulin also stimulates cell growth and differentiation, and promotes the storage of substrates in fat, liver and muscle by stimulating lipogenesis, glycogen and protein synthesis, and inhibiting lipolysis, glycogenolysis and protein breakdown (Fig. 1). Insulin resistance or deficiency results in profound dysregulation of these processes, and produces elevations in fasting and postprandial glucose and lipid levels.

Insulin increases glucose uptake in cells by stimulating the translocation of the glucose transporter GLUT4 from intracellular sites to the cell surface (see Box 1). Up to 75% of insulin-dependent glucose disposal occurs in skeletal muscle, whereas adipose tissue accounts for only a small fraction[1]. Despite this, mice with a knockout of the insulin receptor in muscle have normal glucose tolerance[2], whereas those with a knockout of the insulin-sensitive glucose transporter in fat have impaired glucose tolerance, apparently owing to insulin resistance being induced in muscle and liver[3]. Both obesity and lipoatrophy also cause insulin resistance and predisposition to type 2 diabetes, demonstrating that adipose tissue is crucial in regulating metabolism beyond its ability to take up glucose[4]. Although insulin does not stimulate glucose uptake in liver, it blocks glycogenolysis and gluconeogenesis, and stimulates glycogen synthesis, thus regulating fasting glucose levels. Insulin action in tissues not normally considered insulin sensitive, including brain and pancreatic β-cell, may also be important in glucose homeostasis[5,6] (see below).

Proximal insulin-signalling pathways

The insulin receptor

The insulin receptor belongs to a subfamily of receptor tyrosine kinases that includes the insulin-like growth factor (IGF)-1 receptor and the insulin receptor-related receptor (IRR)[7]. These receptors are tetrameric proteins consisting of two α- and two β-subunits that function as allosteric enzymes in which the α-subunit inhibits the tyrosine kinase activity of the β-subunit. Insulin binding to the α-subunit leads to derepression of the kinase activity in the β-subunit followed by transphosphorylation of the β-subunits and a conformational change that further increases kinase activity[8]. Insulin, IGF-1 and the IRR receptors can form functional hybrids; thus, an inhibitory mutation in one receptor can inhibit the activity of the others[9].

Homologues of the insulin/IGF-1 receptor have been identified in *Drosophila*, *Caenorhabditis elegans* and metazoan marine sponges[9]. These lower organisms use some of the same downstream signals critical to the regulation of mammalian cells, including phosphatidylinositol-3-OH kinase (PI(3)K), Akt and forkhead transcription factors. Inhibitory mutants of the insulin/IGF system in *C. elegans* live longer than normal animals, raising a number of interesting questions about the association of hyperinsulinaemia/insulin resistance with conditions that shorten life span, such as obesity, diabetes and accelerated atherosclerosis.

Insulin-receptor substrates

At least nine intracellular substrates of the insulin/IGF-1 receptor kinases have been identified (Fig. 2). Four of these belong to the family of insulin-receptor substrate (IRS) proteins[8]. Other substrates include Gab-1, p60[dok], Cbl, APS and isoforms of Shc[10]. The phosphorylated tyrosines in these substrates act as 'docking sites' for proteins that contain SH2 (Src-homology-2) domains. Many of these SH2 proteins are adaptor molecules, such as the p85 regulatory subunit of PI(3)K and Grb2, or CrkII, which activate small G proteins by binding to nucleotide exchange factors. Others are themselves enzymes, including the phosphotyrosine phosphatase SHP2 and the cytoplasmic tyrosine kinase Fyn. Substrate binding to these SH2 proteins can regulate their activities, or in some cases their subcellular location.

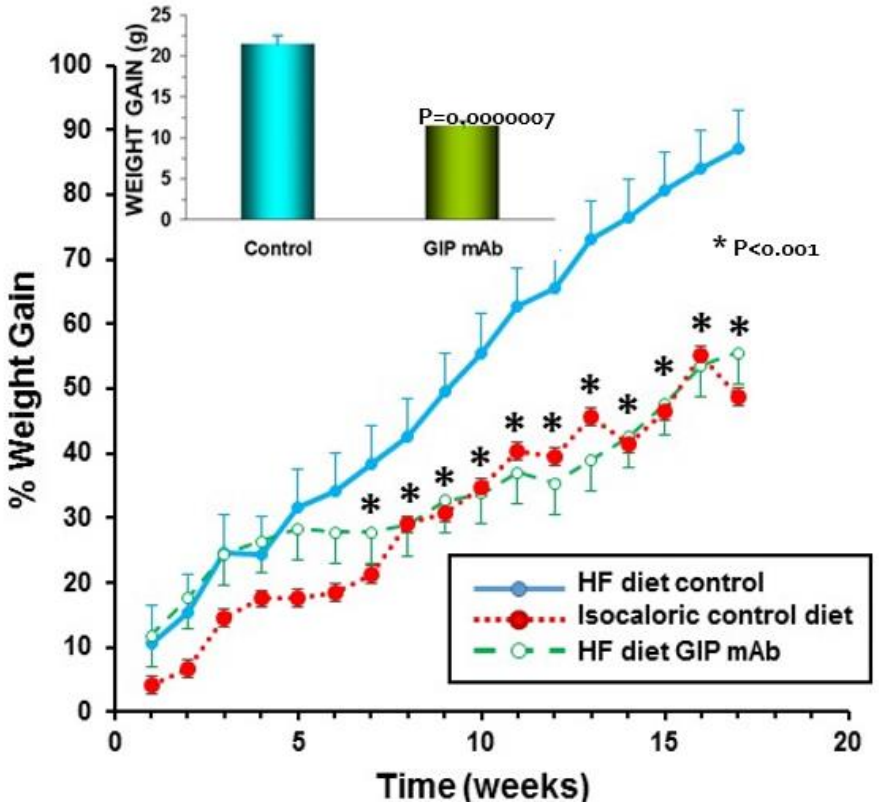
Although the IRS proteins are highly homologous, recent studies in knockout mice and cell lines suggest that they serve complementary, rather than redundant, roles in insulin/IGF-1 signalling. IRS-1-knockout mice exhibit generalized pre- and post-natal growth retardation, as well as insulin resistance in peripheral tissues and impaired glucose tolerance[11,12]. IRS-2-knockout mice also exhibit insulin

NATURE | VOL 414 | 13 DECEMBER 2001 | www.nature.com © 2001 Macmillan Magazines Ltd 799

Saltiel and Kahn identified GIP as the main explanation of why insulin production largely requires that glucose pass through the gut.

[1] McIntyre N et al. *Lancet* 1964; 2:20-21
[2] Saltiel AR and Kahn CR. *Nature* 2001; 414:799-806

Boylan and Wolfe: GIP Blockade = Big Effect on Weight



Source: Boylan MO et al. Am J Physiol 2015; 309:E1008-E1018.

- Mike Wolfe and Mike Boylan conducted a series of pathbreaking experiments at Case Western in which they explored whether GIP blockade might be a good strategy for weight loss.
- This work was independent of Amgen's genetic work but led to very similar insights.
- In this seminal study done in C57BL/6 mice, a GIP antibody attenuated the insulin response to oral glucose by 2/3 (similar to the 1964 human study in *Lancet*) and eliminated the insulin response to co-administered intraperitoneal glucose.
- The effect of the anti-GIP mAb on weight was dramatic; weight gain *decreased by 46.5%* and was equivalent to the low-fat diet control mice.
- There were *no differences* in the amount of food consumed among the treatment groups.
- An intriguing possibility with GIP blockage is that the nausea and potential muscle loss side effects of GLP-1's could be avoided. You eat the same amount of food but just fail to store it as fat because you are making less insulin.

Amgen Scientists Replicate Boylan and Wolfe Findings with GIPr Antagonist and Dual GIP and GLP1 Modulator

Killion *et al.*, *Science Translational Medicine, 2018*

METABOLISM

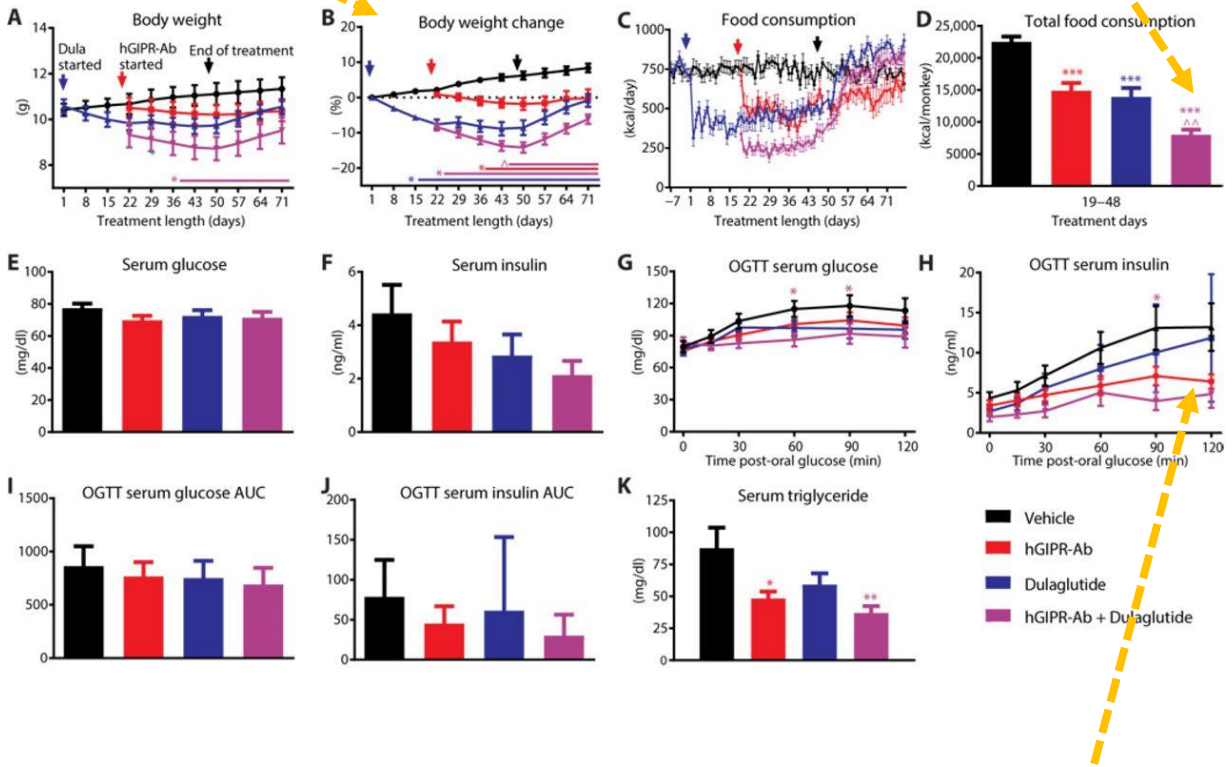
Anti-obesity effects of GIPR antagonists alone and in combination with GLP-1R agonists in preclinical models

Elizabeth A. Killion[1]*, Jinghong Wang[2]*, Junming Yie[1]*†, Stone D.-H. Shi[3], Darren Bates[3], Xiaoshan Min[4], Renee Komorowski[1], Todd Hager[5], Liying Deng[1], Larissa Atangan[1], Shu-Chen Lu[1], Robert J. M. Kurzeja[1], Glenn Sivits[1], Joanne Lin[3], Qing Chen[3], Zhulun Wang[4], Stephen A. Thibault[4], Christina M. Abbott[3], Tina Meng[3], Brandon Clavette[6], Christopher M. Murawsky[6], Ian N. Foltz[6], James B. Rottman[7], Clarence Hale[1], Murielle M. Véniant[1], David J. Lloyd[1]‡

Glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) has been identified in multiple genome-wide association studies (GWAS) as a contributor to obesity, and GIPR knockout mice are protected against diet-induced obesity (DIO). On the basis of this genetic evidence, we developed anti-GIPR antagonistic antibodies as a potential therapeutic strategy for the treatment of obesity and observed that a mouse anti-murine GIPR antibody (muGIPR-Ab) protected against body weight gain, improved multiple metabolic parameters, and was associated with reduced food intake and resting respiratory exchange ratio (RER) in DIO mice. We replicated these results in obese nonhuman primates (NHPs) using an anti-human GIPR antibody (hGIPR-Ab) and found that weight loss was more pronounced than in mice. In addition, we observed enhanced weight loss in DIO mice and NHPs when anti-GIPR antibodies were codosed with glucagon-like peptide-1 receptor (GLP-1R) agonists. Mechanistic and crystallographic studies demonstrated that hGIPR-Ab displaced GIP and bound to GIPR using the same conserved hydrophobic residues as GIP. Further, using a conditional knockout mouse model, we excluded the role of GIPR in pancreatic β-cells in the regulation of body weight and response to GIPR antagonism. In conclusion, these data provide preclinical validation of a therapeutic approach to treat obesity with anti-GIPR antibodies.

Weight changes in monkeys similar to those seen in humans with AMG133. Adding the GIPr antagonist makes a big difference.

Food consumption down around a third with mono GIPr or GLP-1 and down 70%+ with dual GIPr and GLP-1.



Mono GIPr inhibition reduces NHP insulin by around 65% when monkeys were subject to a glucose challenge.

Source: https://www.science.org/doi/10.1126/scitranslmed.aat3392

Other GIP Antagonists in Development

We are aware of at least three companies working on various strategies to block GIP. Each has its pro's and con's.

9METERS BIOPHARMA

NM-136 is an antibody that blocks glucose-dependent insulinotropic polypeptide (GIP), a hormone found in the upper small intestine that is released into circulation after food is ingested. NM-136 has been shown to prevent GIP from binding to its receptor, which in preclinical obesity models has been shown to significantly decrease weight and abdominal fat by reducing nutrient absorption from the intestine. 9 Meters indicates that it may be in Phase 1 with this compound by 2024.

ANTAG THERAPEUTICS

The research teams of professors Mette M. Rosenkilde and Jens J. Holst have discovered naturally occurring therapeutic peptides that are being investigated in several human studies.

Antag is pursuing a peptide approach to antagonizing GIP and is currently in the process of completing preclinical studies.

The company expects to be in the clinic in 2024.

GMAXBio

GMAX is a Chinese biotech that was established by Amgen alums. Their GMA 106 is rationally designed using GMAX's GPCR and M-Body technologies. Like AMG133, this M-body is composed of an anti-GIPR anti-body fused with a GLP1 peptide. It can simultaneously interact with GLP-1R and GIPR and regulate both signaling pathways to synergistically suppress appetite, reduce blood glucose and fat accumulation, and improve insulin resistance. This drug is well into Phase 1 studies at present.

Paradox: How Can AMG133 (Which Antagonizes GIP) and Tirzepatide (Which Agonizes GIP) Both Be So Effective?

GIP as a Therapeutic Target in Diabetes and Obesity: Insight From Incretin Co-agonists

Jens Juul Holst[1,2] and Mette Marie Rosenkilde[1]

[1]Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark; and [2]NNF Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

J Clin Endocrinol Metab. 2020 Aug 1;105(8):e2710–6.

Another important difference is that GLP-1 inhibits appetite and food intake (5), resulting in weight loss upon chronic administration, whereas GIP generally is thought to have no effects on food intake (6). Despite this, some researchers have kept working with GIP and have developed analogs, modified to have activity also on other receptors including the GLP-1 receptor. Application of these in clinical trials has been surprisingly successful. Most recently, the pharmaceutical company, Eli Lilly, presented impressive Phase 2 results in overweight patients with T2DM treated with tirzepatide, a mono-molecular, long-acting (weekly) GIP-GLP-1 co-agonist (7). A 6-month treatment with this compound resulted in near-normalization of glycated hemoglobin levels and weight losses reaching 2-digit percentages, with both effects exceeding what was obtained in the same study with a long-acting GLP-1 receptor agonist, dulaglutide. Increasing the confusion even further, another company, Amgen, presented preclinical data from nonhuman primates showing that a GIP receptor antagonist (a monoclonal antibody), both alone and in combination with GLP-1, effectively reduced the normal increase in body weight in obese animals (8). In addition, upon comparison of results from animal studies, it appears that almost identical results can be obtained with certain proven GIP agonists and GIP antagonists, at least with respect to their effects on body weight (8-10). **In other words, both GIP agonism (normally thought to be inactive) and GIP antagonism appear to be effective in T2DM and obesity.**

Source: https://academic.oup.com/jcem/article/105/8/e2710/5847843

Paradox Addressed: Tirzepatide's GLP-1 Signalling Likely Enhanced by GIP Co-Agonism

GIP as a Therapeutic Target in Diabetes and Obesity: Insight From Incretin Co-agonists

Jens Juul Holst[1,2] and Mette Marie Rosenkilde[1]

[1]Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark; and [2]NNF Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

J Clin Endocrinol Metab. 2020 Aug 1;105(8):e2710–6.

Nevertheless, it was recently shown that N-terminal modifications of exendin-4 (a strong GLP-1 receptor agonist) will turn it into a biased agonist with a lower tendency to arrestin recruitment and/or receptor internalization and therefore with potentially greater efficacy and tolerability as a therapeutic (58). A similar alteration in GLP-1 receptor signaling profile was recently established for a dual acting GIP-GLP-1 peptide (59). It is thus possible that the observed beneficial effects in vivo of dual GIP-GLP-1 agonists—at least partly—rely on altered signaling of the molecule toward a biased signaling profile for one, or both, of the components. If both mechanisms apply to the GIP- GLP-1 co-agonists, the effect might be even greater. It is still unclear how the GIP part of the co-agonist would lead to weight loss, but **if the incorporation of GIP activity in the co-agonist changes the GLP-1 signaling, then it would make sense that even the GIP part of the molecule might contribute to an enhanced weight-losing effect**. It should be possible with careful molecular pharmacological experimentation to determine whether it is the influence of one part of the co-agonist (GIP) on the signaling pathways of the other part that makes a co-agonist like tirzepatide so effective, despite the overwhelming evidence that GIP, investigated in isolation, does not possess these activities. Such experiments are ongoing, and we will probably soon have at least some answers to this **mind-boggling paradox**.

Source: https://academic.oup.com/jcem/article/105/8/e2710/5847843

Unmet Needs in the Obesity Drug Landscape

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

Significant Room for Players to Compete by Feature Differentiation

Allison Gatlin, Investors Business Daily, Dec 8, 2022

“But Narimon Honarpour, Amgen's vice president of general medicines, says there's room for multiple medications in the obesity treatment market. More than 600 million people have obesity, including 40% of the U.S. population. Not all patients respond well to one drug, he said.

‘Unraveling which patient segment benefits the most from which therapy, having a consistent response to therapy from patients is very important," he told *Investor's Business Daily*. "What I think we can conclude — though I can't give you a firm number on what the market size and opportunity would be — is that it's going to be, and is currently, a very large market.’”

Source: https://www.investors.com/news/technology/amgen-stock-here-is-what-we-know-about-its-belated-obesity-treatment/. Photo from Getty Images.

Key Unmet Needs in Obesity Drug 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:

1. Avoidance of Nausea Side Effect
2. Avoidance of the "Rebound Effect"
3. Reduction in Drug Cost
4. Oral Delivery
5. Avoidance of Muscle Loss
6. Less Frequent Dosing
7. Drugs That Can be Safely Provided Direct to the Patient

#1: Nausea is an Issue with GLP-1 Agonists

Optum Pharmacy Care Services, 2023

Since GLP-1 agonists impact many physiological processes, side effects are not uncommon. Some that are common to all GLP-1 agonists include nausea, vomiting and diarrhea. Other possible side effects for GLP-1 agonists include pancreatitis, increased risk of low blood sugar, kidney problems and changes in vision.

Injected weekly, Wegovy is essentially a higher dosage of semaglutide. While Ozempic is injected at a dosage of 0.5 mg or 1 mg for type 2 diabetes, the dose for Wegovy is 2.4 mg. To reduce the potential for side effects, the dose of Wegovy is gradually increased over 16 to 20 weeks.

In addition to these common side effects, Wegovy contains a boxed warning about the potential risk of thyroid C-cell tumors.

A key priority is to design out the nausea side effect associated with the current generation of GLP-1 drugs.

Source: https://www.optum.com/business/insights/pharmacy-care-services/page.hub.diabetes-drugs-obesity.html

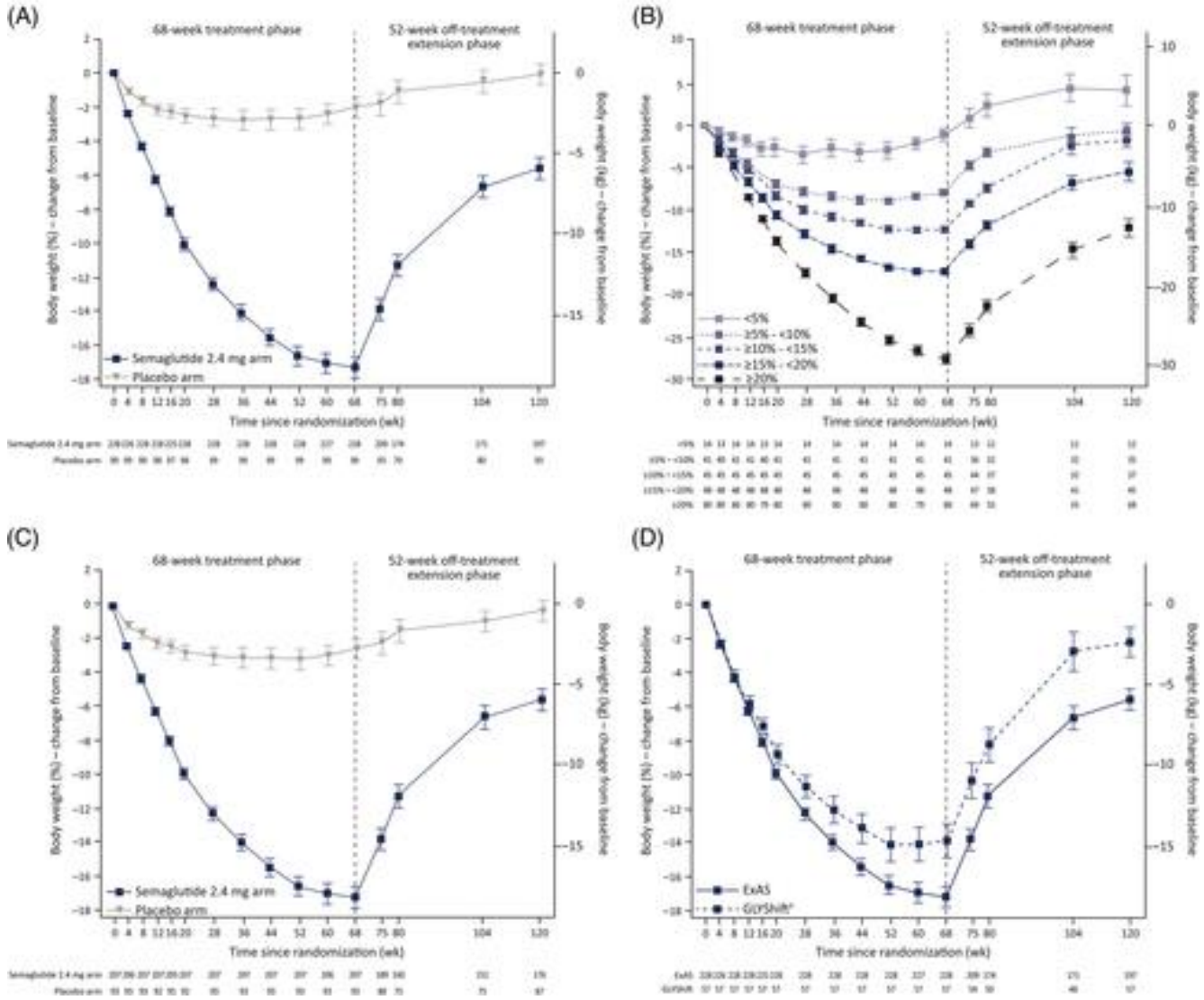
#2: The Rebound Effect

Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension

John P. H. Wilding D.M, Rachel L. Batterham MBBS, Melanie Davies M.D, Luc F. Van Gaal M.D, Kristian Kandler M.D, Katerina Konakli PhD, Ildiko Lingvay M.D ... See all authors

Diabetes, Obesity and Metabolism, April 2022

"One year after withdrawal of once-weekly subcutaneous semaglutide 2.4 mg and lifestyle intervention, **participants regained two-thirds of their prior weight loss**, with similar changes in cardiometabolic variables. Findings confirm the chronicity of obesity and suggest ongoing treatment is required to maintain improvements in weight and health."



Source: https://dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.14725

The Rebound Effect: Is it a Bug or a Feature?

People who overeat appear to put their weight back on when they go off GLP-1's.

From a pharma perspective this is a **desirable feature**. Patients will need to be on their obesity drugs forever basically or will regain weight.

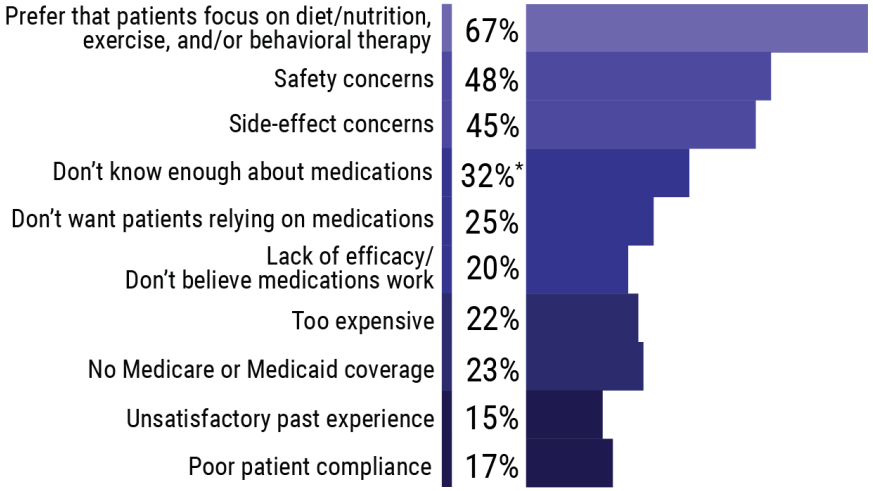
Each patient becomes quite valuable. If you could get paid $1,000 a month forever, the NPV would work out to $120,000 if you had a 10% discount rate (model for value of a perpetuity). To be clear, other CVM drugs for blood pressure and lipids also require long-term administration. It's not as if obesity drugs are uniquely burdensome in this regard.

From a **payor / societal perspective**, this is quite challenging. If you must cover a million persons at $120k / each, you would be on the hook for $120 billion in expense. But there are over 50 million obese persons in the U.S. The cost is very high.

Physicians are also concerned. We have spoken to several who worry about putting their patients on GLP-1's forever. The data suggest that long-term administration of GLP-1's is not associated with safety issues and patients continue to benefit (see, for example, Courtney et.al. (2017) for seven-year data).* As shown in the chart at right, many physicians prefer to avoid weight loss drugs. In one recent survey, physicians indicated that they see 136 obese patients a month; these physicians planned to keep only a third of their GLP-1 patients on the drugs indefinitely. Physicians are conservative when it comes to new drugs.

A particular physician concern expressed at ADA with rebound is that patients may lose muscle on the way down and then replace it with fat on the way up.

Why do nonprescribers avoid weight loss drugs?



* 47% for OB/GYNs

"Ninety-four surveys were analyzed. Seventy-six percent of all PCPs did not prescribe weight loss medications for long-term weight loss and 58% of PCPs had negative perceptions of pharmacotherapy. Differences existed between prescribing patterns and attitudes of advanced practice clinicians and physicians. Safety concerns were the greatest barrier. Having 2+ comorbidities and severe obesity were facilitators for prescribing weight loss medications."

Source: https://onlinelibrary.wiley.com/doi/abs/10.1002/2327-6924.12481

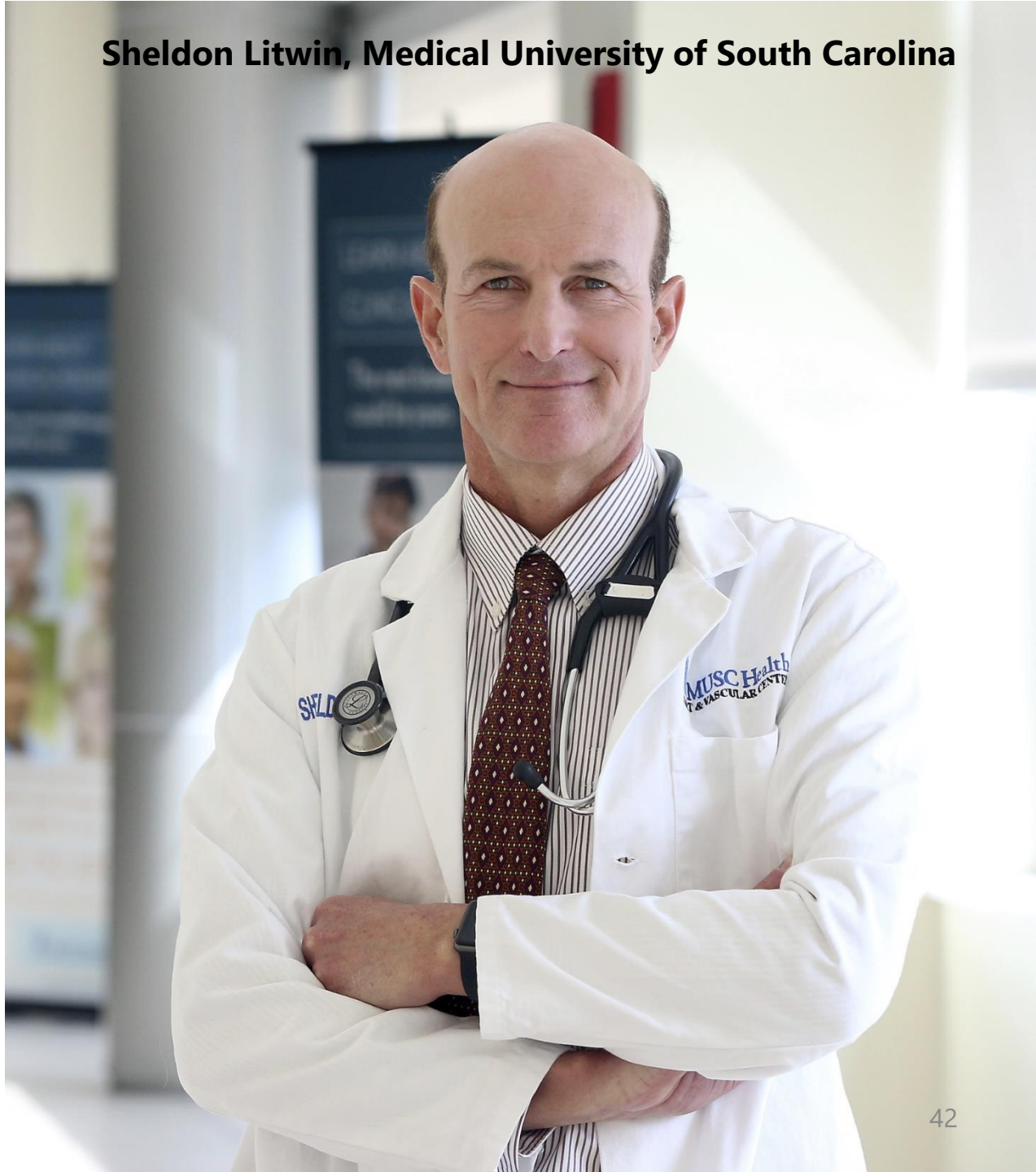
* Note: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5357070/

#3: Cost is a Major Issue

Sheldon Litwin, MD, a cardiologist at the Medical University of South Carolina, *Pharmacy Times*, Mar 8, 2023

"The other big issue with the new drugs is the cost. And they're very, very expensive drugs. I don't know if they have to be or not, but they are. And when we're prescribing them for diabetes, they're usually covered by insurance, although there may be a higher copay. But if we're giving them just for weight loss in patients that don't have diabetes, at this point in time, most insurance plans and most federal plans like Medicare are not covering the cost of the medicines. And they're retailing for about $1,300 a month or $16,000 a year, which is not affordable for most of my patients. So, access is still a big issue."

Source: https://www.pharmacytimes.com/view/expert-following-decades-of-challenges-anti-obesity-drugs-have-leapt-forward-in-recent-years



ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Medications for Obesity Management: Effectiveness and Value

Evidence Report

August 31, 2022

Table ES1. Evidence Ratings for Treatment of Adults with Obesity

Treatment	Comparator	Evidence Rating
Semaglutide	Lifestyle modification	B+
Liraglutide	Lifestyle modification	B
Phentermine/Topiramate	Lifestyle modification	C++
Bupropion/Naltrexone	Lifestyle modification	C+
Semaglutide	Liraglutide	C+
	Phentermine/topiramate	C+
	Bupropion/naltrexone	C++

Information about ICER's Evidence Rating Matrix may be found here.

At current prices and with commonly accepted cost-effectiveness benchmarks, results suggest that phentermine/topiramate in addition to lifestyle modification is cost effective compared with lifestyle modification alone. The cost effectiveness of treatment of obesity with semaglutide or liraglutide in patients without diabetes mellitus exceeds commonly used thresholds. Bupropion/naltrexone is cost effective only at higher thresholds (see Table 4.5).

The health-benefit price benchmark for semaglutide is $7,500 to $9,800 per year; this would require a discount from the wholesale acquisition cost of 44-57%.

Source: https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Evidence_Report_083122.pdf

ICER's view expressed here is that as currently priced the GLP-1's are too expensive to justify reimbursement.

Both Lilly and Novo are running studies today to disprove this type of analysis by showing the societal savings from using obesity drugs.

But clearly an unmet need in the market is to deliver strong weight loss at a lower price.

#4: Oral Options Desirable

Michael Erman, Reuters, “Novo Nordisk rivals see room to compete in $100 billion weight-loss drug market,” May 8, 2023

“Pfizer believes an oral therapy will appeal to people who want to avoid injections. The company plans to enroll some patients in its late-stage trial who have already used Wegovy or Mounjaro to show they can effectively switch to the Pfizer alternative.

Eli Lilly is working on an oral GLP-1. Novo Nordisk already offers Rybelsus, an oral version of the same compound (semaglutide) in Wegovy for diabetes, although its success has been limited.

"More treatment options to help improve the lives of those living with obesity are good advancements for patients and a testament to the significant unmet need of addressing obesity," a Novo spokesperson said.

Dr. Jamie Kane, chief of obesity medicine at New York's Northwell Health, called the new weight-loss drugs ‘very promising.’”

Many patients prefer an oral option.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisk-rivals-see-room-compete-100-bln-weight-loss-drug-market-2023-05-04/. Photo from Getty Images.

Selected GLP-1 Oral Drug Candidates in Development

Orforglipron

Saima Sidik, "Beyond Ozempic: brand-new obesity drugs will be cheaper and more effective," *Nature*, June 26, 2023

"Both Wegovy and Mounjaro require weekly injections, which many people find unpleasant. What's more, the drugs both belong to a group of molecules called peptides, which are expensive and labour-intensive to produce. The list prices for Wegovy and Mounjaro are more than US$1,000 per month, and supply shortages have sometimes made the drugs hard to find. Orforglipron, however, is a non-peptide molecule that's easy to produce and package into a pill. The drug's price has not yet been set, but it will probably be much cheaper than existing weight-management drugs, says internal-medicine physician Sean Wharton at McMaster University in Hamilton, Canada. "I see it as a game changer, myself," says Wharton, who co-authored the orforglipron study."

Danuglipron

Pfizer, Press Release, June 26, 2023

Pfizer Inc. (NYSE: PFE) today announced its decision to continue to progress one oral late-stage glucagon-like peptide-1 receptor agonist (GLP-1-RA) candidate toward further clinical development for the potential treatment of adults with obesity and Type 2 diabetes mellitus (T2DM). Results previously published in the Journal of the American Medical Association Network Open from the Phase 2 study (NCT03985293) of danuglipron in T2DM showed dose-dependent placebo-adjusted reductions (doses ranging from 2.5 mg through 120 mg for 16 weeks) in HbA1c of up to -1.16%; fasting plasma glucose of -33.24 mg/dL; and body weight of -4.17 kg over 16 weeks. The most common adverse events were nausea, vomiting and diarrhea. The Phase 2b study of danuglipron in non-diabetic obesity participants is currently ongoing (doses ranging from 40 mg through 200 mg for up to 32 weeks) and expected to complete by end of year.

Structure Therapeutics completed a Phase 1 study of GSBR-1290, an orally available small molecule GLP-1 receptor agonist being developed for the treatment of patients with type 2 diabetes mellitus and obesity. The Company completed its Phase 1 single ascending dose (SAD) study in September 2022. GSBR-1290 was generally well tolerated and demonstrated dose-dependent pharmacokinetic (PK) and pharmacodynamic (PD) activity in 48 healthy volunteers. The Company has completed dosing of its Phase 1b multiple ascending dose (MAD) study focused on safety, PK and tolerability in 24 healthy volunteers, and has initiated a Phase 2a study in T2DM and obesity. Topline data from the Phase 1b MAD study and the Phase 2a study are expected to be announced in the latter half of the fourth quarter of 2023.

Sources: (1) Lilly: https://www.nature.com/articles/d41586-023-02092-9, (2) Pfizer: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-provides-update-glp-1-ra-clinical-development

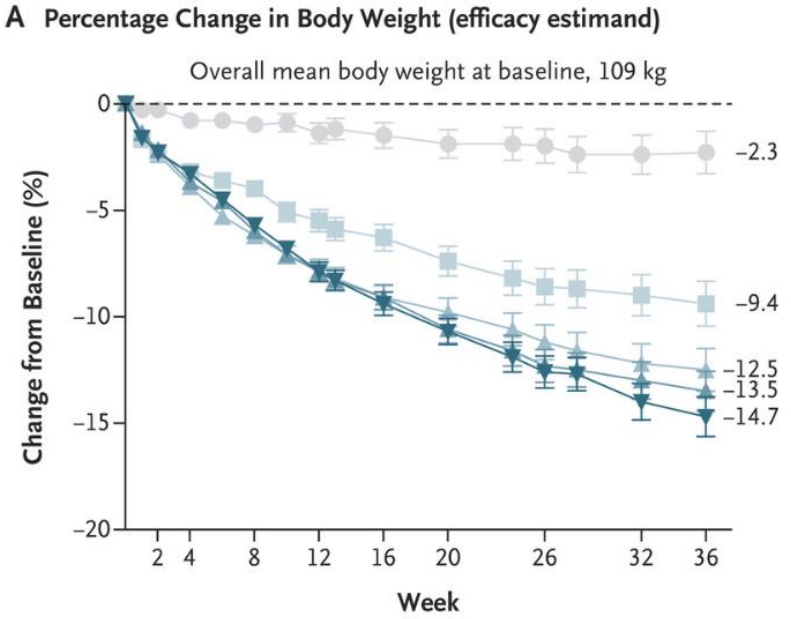
Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., et al., for the GZGI Investigators*

***New England Journal of Medicine*, June 23, 2023**

In this phase 2, randomized, double-blind trial, we enrolled adults with obesity, or with overweight plus at least one weight-related coexisting condition, and without diabetes. Participants were randomly assigned to receive orforglipron at one of four doses (12, 24, 36, or 45 mg) or placebo once daily for 36 weeks. The percentage change from baseline in body weight was assessed at week 26 (primary end point) and at week 36 (secondary end point).

A total of 272 participants underwent randomization. At baseline, the mean body weight was 108.7 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 37.9. At week 26, the mean change from baseline in body weight ranged from −8.6% to −12.6% across the orforglipron dose cohorts and was −2.0% in the placebo group. At week 36, the mean change ranged from −9.4% to −14.7% with orforglipron and was −2.3% with placebo. A weight reduction of at least 10% by week 36 occurred in 46 to 75% of the participants who received orforglipron, as compared with 9% who received placebo. The use of orforglipron led to improvement in all prespecified weight-related and cardiometabolic measures. The most common adverse events reported with orforglipron were gastrointestinal events, which were mild to moderate, occurred primarily during dose escalation, and led to discontinuation of orforglipron in 10 to 17% of participants across dose cohorts. The safety profile of orforglipron was consistent with that of the GLP-1 receptor agonist class.



Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2304286

Emerging Opportunity for Oral Polypills

In the same sense that we are seeing incretin protein companies developing duals and triple combos, it should be possible to combine multiple active agents to create a particularly effective oral anti-obesity medication.

For example, both Vivus' Qsymia® and Currax's Contrave® combine known active agents.

The four companies shown at right have particularly promising oral options for the treatment of obesity.

It strikes us that one might be able to combine these approaches to develop a highly effective polypill.

AstraZeneca

REGENERON

Regeneron and AZ are in a collaboration to target GPR75 for obesity. This is based on REGN's finding that mutations in the GPR75 gene associated with protection against obesity.

glaceum

Vutiglabridin is an orally available modulator of mitochondrial paraoxonase-2 (PON2). It has completed its phase 1 studies with optimal safety profile and target exposure, and its phase 2a study for the treatment of obesity is near completion.

inversago PHARMA

Inversago had impressive Phase 1 obesity data with a CB1 inverse agonist at ADA. Now going into other indications in Phase 2 studies. MOA same as rimonabant but company has engineered out toxicity issues. Private Canadian biotech company.

KALLYOPE

Kallyope is testing two compounds in Phase 1b trials in 2023. They expect to be producing data in obesity as the year unfolds in both obese subjects and in persons with Type 2 diabetes.

GWAS Study by Regeneron Discovers GPR75 Target

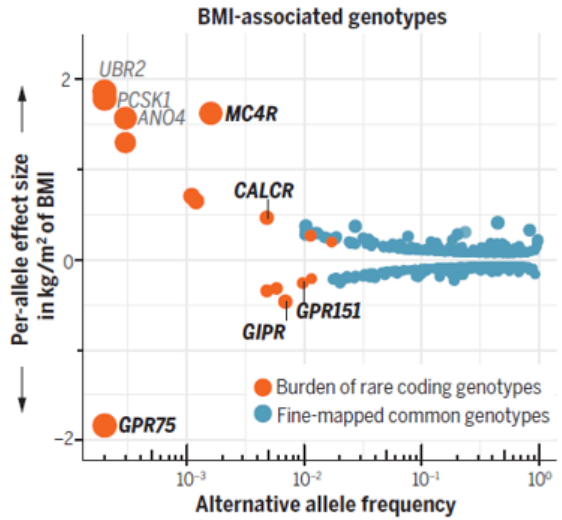
Akbari *et al.*, *Science* **373**, 73 (2021) 2 July 2021

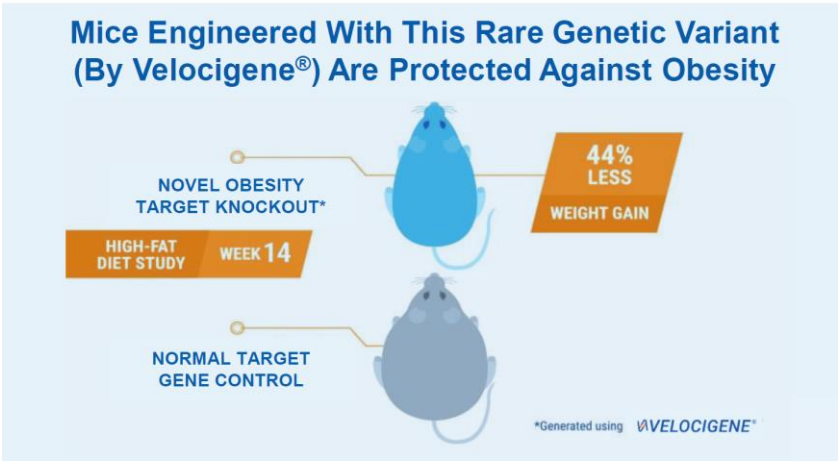
RESEARCH ARTICLE SUMMARY

HUMAN GENOMICS

Sequencing of 640,000 exomes identifies *GPR75* variants associated with protection from obesity

Parsa Akbari†, Ankit Gilani†, Olukayode Sosina†, Jack A. Kosmicki, Lori Khrimian, Yi-Ya Fang, Trikaldarshi Persaud, Victor Garcia, Dylan Sun, Alexander Li, Joelle Mbatchou, Adam E. Locke, Christian Benner, Niek Verweij, Nan Lin, Sakib Hossain, Kevin Agostinucci, Jonathan V. Pascale, Ercument Dirice, Michael Dunn, Regeneron Genetics Center, DiscovEHR Collaboration, William E. Kraus, Svati H. Shah, Yii-Der I. Chen, Jerome I. Rotter, Daniel J. Rader, Olle Melander, Christopher D. Still, Tooraj Mirshahi, David J. Carey, Jaime Berumen-Campos, Pablo Kuri-Morales, Jesus Alegre-Díaz, Jason M. Torres, Jonathan R. Emberson, Rory Collins, Suganthi Balasubramanian, Alicia Hawes, Marcus Jones, Brian Zambrowicz, Andrew J. Murphy, Charles Paulding, Giovanni Coppola, John D. Overton, Jeffrey G. Reid, Alan R. Shuldiner, Michael Cantor, Hyun M. Kang, Goncalo R. Abecasis, Katia Karalis, Aris N. Economides, Jonathan Marchini, George D. Yancopoulos, Mark W. Sleeman, Judith Altarejos, Giusy Della Gatta, Roberto Tapia-Conyer‡, Michal L. Schwartzman‡, Aris Baras‡*, Manuel A. R. Ferreira‡, Luca A. Lotta‡*





Murtaza et.al., Biochimie, April 2022:

The metabolic syndrome is a plethora of related disorders that are frequently associated with morbidity and mortality in addition to economic burden. While various treatment options are available, the need to understand the pathology and find new targets still remains.

Recent data have suggested GPR75 as one such exciting target that has shown to a highly druggable potential. In this review, we have discussed the recent findings on GPR75 in terms of its expression and signaling and the way it could be a novel target in diseases associated with metabolic syndrome including obesity, dyslipidemia, diabetes, cardiovascular disease, and cerebrovascular disease. In addition, the opportunities and challenges related with the druggable potential of GPR75 have also been highlighted in this review.

Sources: https://www.science.org/doi/10.1126/science.abf8683, https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-genetics-center-discovers-gpr75-gene-mutations-protect, https://www.sciencedirect.com/science/article/abs/pii/S0300908422000141

Kallyope Pursuing Orals Involving Gut-Brain Axis

KALLYOPE

Led by Jay Galeota and Nancy Thornberry, Kallyope harnesses multiple incretins to induce a weight loss effect and can design therapeutics that turn on or turn off specific incretins.

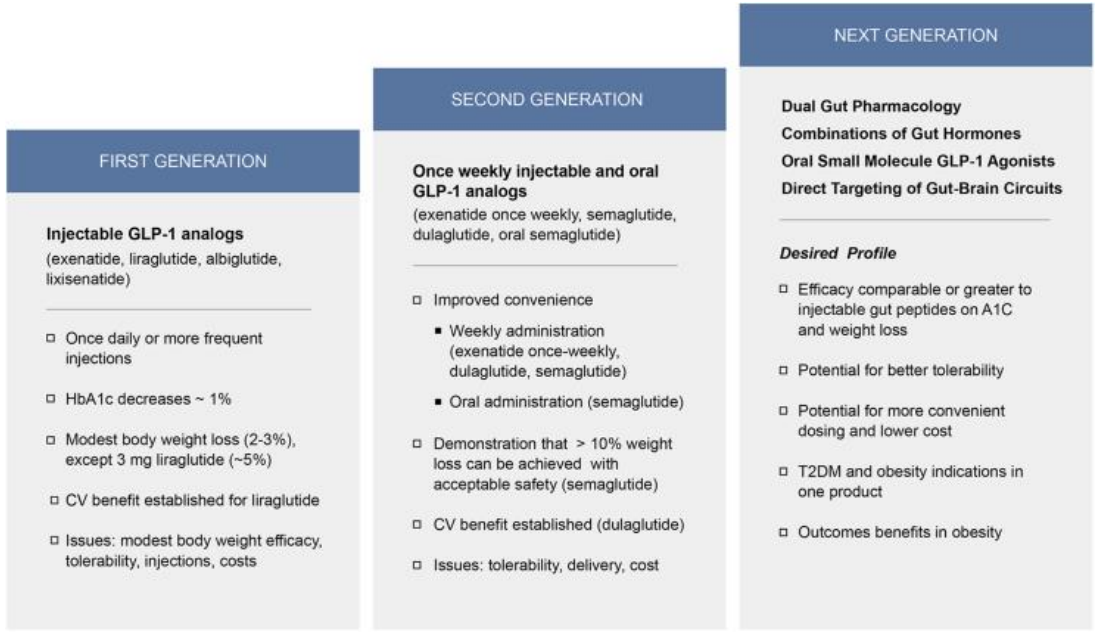
The company is focused on direct targeting of gut-brain circuits using a next generation approach highlighted at right.

Kallyope is testing two compounds in Phase 1b trials in 2023. They expect to be producing data in obesity as the year unfolds in both obese subjects and in persons with Type 2 diabetes.

While the MOA has not been specifically released, Kallyope has a published patent which described four potential targets for its drugs and can deliver these targets solo or in combination.

The article cited at right lays out the approach described in the patent. Key targets include GPR40, AMPK, GPR119 and SSTR5.

Richards P, Thornberry NA, Pinto S. The gut-brain axis: Identifying new therapeutic approaches for type 2 diabetes, obesity, and related disorders. *Mol Metab*. 2021 Apr;46:101175.



"The role of the gut-brain axis has been particularly well established in regulating appetite and metabolism. Indeed, gut hormones, most notably GLP-1, have been pursued as therapeutics in multiple drug discovery programs for diabetes and obesity over the past two decades. While some of the beneficial effects of GLP-1 and other gut hormones, most notably glucose control, may not involve gut-brain circuitry, the importance of this system in the regulation of feeding has been clearly established."

"As nutrients and bile acids pass through the duodenum and into the jejunum, multiple EECs containing GLP-1, PYY, and NTS as well as CCK, GIP, and SCT are activated. All of the receptors for these peptides, with the exception of GIP, are expressed by vagal afferents. GLP, PYY, and CCK receptors have been detected in the ENS. GLP-1, GIP, PYY, and NTS receptors are expressed in central feeding centers. How these hormones signal to the brain alone and in combination after a meal has yet to be fully determined, but when co-infused, they produce strong satiety effects."

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8085592/

Inversago Pharma's INV-202, a Peripheral Cannabinoid Receptor 1Blocker for Metabolic Syndrome, is Highly Promising

June 23, 2023 - MONTREAL & SAN DIEGO--(BUSINESS WIRE)--Inversago Pharma Inc. ("Inversago"), a leader in the development of peripherally-acting CB1 receptor (CB1r) blockers to address complications associated with metabolic and fibrotic diseases, today announced data from its Phase 1b trial for INV-202 to be presented in a poster session at the 83rd American Diabetes Association Scientific Sessions (ADA) in San Diego. INV-202 is a potential first-in-class, peripherally-acting CB1r blocker, being developed to treat metabolic syndrome and associated complications. The Phase 1b study was a randomized, double-blind clinical trial conducted in 37 adult subjects (46% female; mean age, 55 years) with features of metabolic syndrome to evaluate the PK/PD relationship and other biomarkers of 25 mg of INV-202 administered orally, once daily, over 28 days. Metabolic syndrome was defined by hypertriglyceridemia, abdominal obesity, and impaired glucose tolerance. At 25 mg, INV-202 was well-tolerated with no serious adverse events (SAEs) reported during the treatment period. Observed adverse events (AE) were predominately GI related.

In the post-hoc analysis, over the 28-day treatment period, clinically significant and progressive weight loss of an average decline of 3.50 kg (7.7 lb) for the INV-202-treated subjects was shown. This compared with a gain of 0.55 kg (1.2 lb) on average for subjects on placebo ($p<0.01$). Weight loss for subjects treated with INV-202 averaged a 3.3% decline versus a 0.5% gain for subjects on placebo ($p<0.01$). Average waist circumference was reduced by -1.91 cm (-3/4 in) for treated subjects compared to an increase of +0.02 cm (+1/64 in) for subjects on placebo ($p=0.03$).

INV-202-treated subjects also reported average decline in hemoglobin A1C (HgbA1C) of -0.005% over the treatment period versus an increase of +0.065% for subjects on placebo ($p=0.08$).

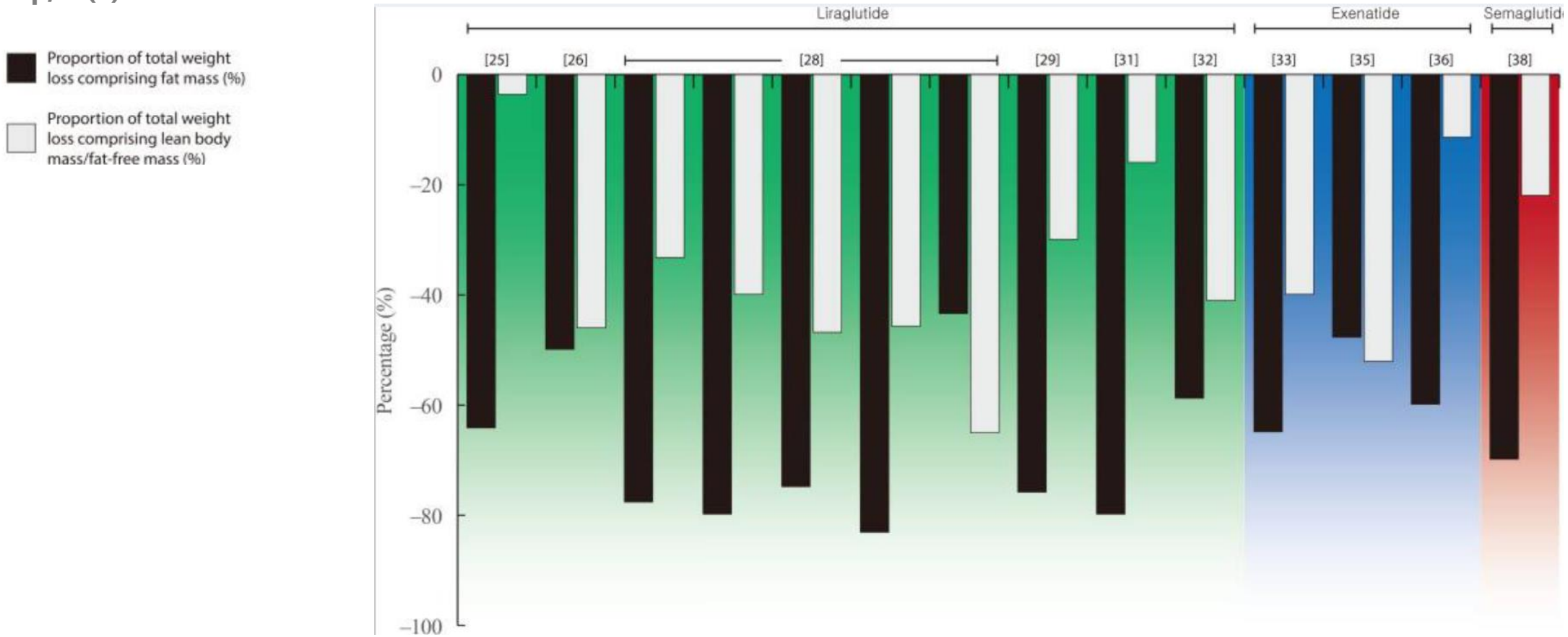
Inversago popped up at ADA with striking data for a CB1r blocker showing 3.8% placebo-adjusted weight loss in patients with metabolic syndrome at four weeks. These data are similar in magnitude to what has been seen with other oral agents including Orforglipron and are stronger than what has been seen with Pfizer's oral GLP-1. What is interesting here is that the CB1r MOA is orthogonal to what others are doing and could make for good combo therapy approaches.

Source: https://www.businesswire.com/news/home/20230623384277/en/Inversago-Pharma-Presents-Data-from-Phase-1b-Trial-of-INV-202-a-Peripheral-CB1r-Blocker-for-Metabolic-Syndrome-at-the-83rd-American-Diabetes-Association-Scientific-Sessions

#5: Avoidance of Muscle Loss a Priority

The median percent of weight lost in past GLP-1 agonist studies due to loss of lean mass is in the low 40's.

Sargeant JA, Henson J, King JA, Yates T, Khunti K, Davies MJ. A Review of the Effects of Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors on Lean Body Mass in Humans. Endocrinol Metab (Seoul). 2019 Sep;34(3):247-262



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6769337/

Muscle Mass Loss is Typical in Obesity Management

Advisory Board, "Another semaglutide side effect: Loss of muscle mass?," March 23, 2023

"Endocrinologists and obesity medicine specialists said that while muscle mass loss can be a side effect of semaglutide, it is not unique to the drug or the GLP-1 agonist drug class.

"Muscle mass loss is part-and-parcel to losing weight," said Amy Rothberg of the **University of Michigan**, who is also a spokesperson for the **Endocrine Society**. "So in the context that semaglutide helps people lose weight, they are going to lose muscle mass."

"But you lose muscle mass irrespective of the modality, whether that's diet and exercise, bariatric surgery, or medications," she said.

Karl Nadolsky, an endocrinologist and obesity medicine specialist at **Holland Hospital**, noted that "all weight-loss interventions result in some lean mass loss." According to Nadolsky, lean mass loss involves both muscle loss and things like fluid loss. Nadolsky highlighted subgroup data from the STEP 1 Study — semaglutide's primary clinical trial — which looked at 95 people who were on the drug and 45 people who received a placebo. The researchers conducted scans on all participants to monitor their body mass.

Participants who received the drug lost an average of 10.4% of their fat mass and 6.9% of their lean body mass, and participants who received a placebo lost an average of 1.2% of their fat mass and 1.5% of their lean body mass. "The placebo group lost almost 50% more lean mass than fat mass," Nadolsky said. While the data indicate that the drug caused lean mass loss, "the percentage of fat mass loss to lean mass loss is favorable." According to Rothberg, people generally lose fat mass to lean mass at a ratio of 2:1. While this varies by age, gender, and physical conditioning, Rothberg noted that the STEP 1 data appear to fall within those parameters."

Source: https://www.advisory.com/daily-briefing/2023/03/22/wegovy-muscle-mass

Tirzepatide Associated with Much More Fat Mass Loss than Lean Mass Loss

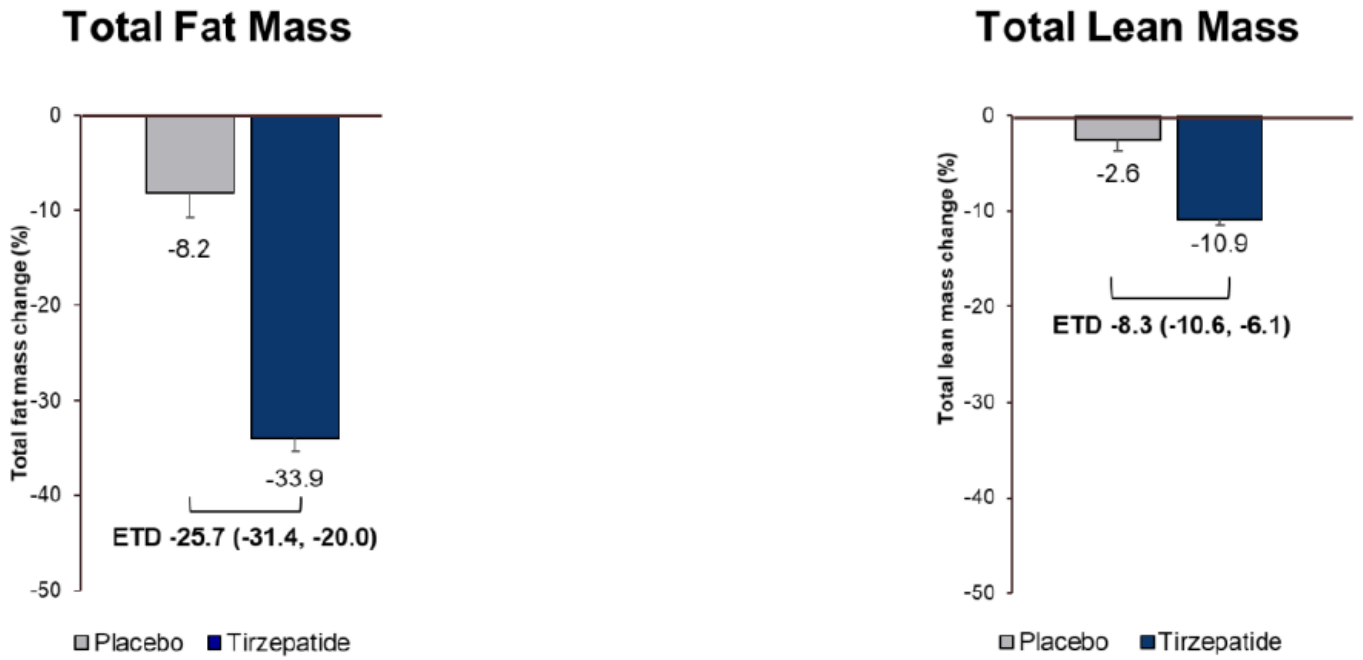


Figure S8. Change in body composition. Data are least squares means and 95% confidence interval. Data are shown for placebo and pooled tirzepatide 5 mg, 10 mg, and 15 mg groups. Enrolled n=255; completers with both baseline and week 72 DXA n=160. Abbreviations include ETD, estimated treatment difference.

Source: https://www.nejm.org/doi/full/10.1056/NEJMoa2206038

Muscle Loss is of Particular Concern with Older Patients

Andrea Petersen, "Ozempic Can Make You Thin, Not Necessarily Healthy," *WSJ*, June 28, 2023

"When people lose weight, particularly when they lose a lot of weight quickly as can happen with Ozempic and other GLP-1 medications, they lose not only fat but also lean muscle mass. Lean muscle is important for strength and metabolism (since muscle burns more calories than fat) and high-protein foods like chicken, fish, eggs and tofu contain the amino acids that are building blocks of muscle, says Dr. Amanda Velazquez, director of obesity medicine at Cedars-Sinai in Los Angeles.

Gudzune is particularly concerned about the loss of muscle mass with her patients ages 70 and older who are on GLP-1 drugs. Muscle loss can lead to falls and difficulty doing daily movements that are important for remaining independent, such as getting up and down from a chair, she notes. Gudzune says she starts her older patients taking GLP-1 medications on a strength-training routine with a resistance band."

Source: https://www.wsj.com/articles/ozempic-diet-exercise-healthy-43eee86c

Drug Development Candidates that Are Promising for Selectively Targeted Fat Over Muscle Mass

There are a number of approaches that are being explored to selectively reduce fat mass rather than muscle mass.

We have already highlighted Amgen's GIP antagonism approach – which does not necessarily induce appetite suppression but instead inhibits the storage of glucose in adipocytes by reducing insulin levels.

Rivus is focused on increasing the inefficiency of cellular metabolism, thereby causing more fat to be burned.

Versanis is blocking an adipocyte receptor whose signalling is required to store fat.

Rivus PHARMACEUTICALS

Rivus is in Phase 2 studies for obesity and other CV indications with drugs that we believe are mitochondrial uncouplers. Company raised a $132mm Series B financing in 2022 led by RA Capital. The company reported Phase 2a data at AASLD in Nov 2022 that its drug was highly selective for reduction of fat over muscle mass. The company's approach is based on an idea dating back to the 1930s and has very high market potential if its can demonstrated an acceptable safety profile. Currently, the lead study underway is for heart failure management in persons with obesity. This is protected by a newly filed patent.

Versanis

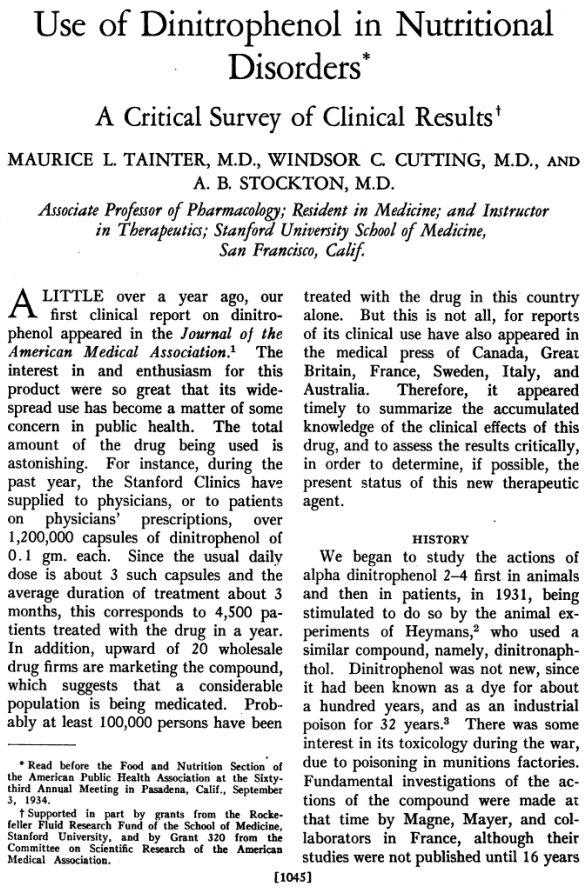
Versanis is developing Bimagrumab and is in Phase 2b studies with this long-acting drug. Bimagrumab is a monoclonal antibody that blocks ActRII signaling in adipose cells, mobilizing and metabolizing fat.
Activin signaling via ActRII receptors directly promotes lipid storage, acting as a key driver of visceral fat accumulation and obesity. Bimagrumab decreases body fat, especially abdominal visceral fat, while at the same time increasing muscle mass. Since initial development, bimagrumab has been administered to more than 1,000 patients for up to 18 months across more than 20 clinical studies.

Rivus is Pursing the "Original Idea" in Weight Management: Mitocondrial Uncoupling

Tainter, Stockton & Cutting, JAMA, 1933

"We have recently suggested that alpha-dinitrophenol (1-2-4) might have therapeutic value in conditions in which an increased metabolic rate would be beneficial. Study of its pharmacologic properties shows that it has the power to increase metabolism to very high levels without causing important damage to vital organs and functions. Serious harm is apparently only caused by the drug in large doses which produce too great metabolic stimulation, with resulting fever. In low, or therapeutic, doses, the metabolism may be increased 50 per cent or more over considerable periods of time without unpleasant symptoms or toxicity. Such an action is useful in treating obesity, since the increased metabolism results in loss of weight, just as it does with thyroid medication. This paper is in the nature of a progress report on results obtained to date of treating 113 consecutive cases of obesity observed in clinic and private practice."

American Journal of Public Health, 1934



Use of Dinitrophenol in Nutritional Disorders*

A Critical Survey of Clinical Results†

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A LITTLE over a year ago, our first clinical report on dinitrophenol appeared in the *Journal of the American Medical Association*.[1] The interest in and enthusiasm for this product were so great that its widespread use has become a matter of some concern in public health. The total amount of the drug being used is astonishing. For instance, during the past year, the Stanford Clinics have supplied to physicians, or to patients on physicians' prescriptions, over 1,200,000 capsules of dinitrophenol of 0.1 gm. each. Since the usual daily dose is about 3 such capsules and the average duration of treatment about 3 months, this corresponds to 4,500 patients treated with the drug in a year. In addition, upward of 20 wholesale drug firms are marketing the compound, which suggests that a considerable population is being medicated. Probably at least 100,000 persons have been treated with the drug in this country alone. But this is not all, for reports of its clinical use have also appeared in the medical press of Canada, Great Britain, France, Sweden, Italy, and Australia. Therefore, it appeared timely to summarize the accumulated knowledge of the clinical effects of this drug, and to assess the results critically, in order to determine, if possible, the present status of this new therapeutic agent.

HISTORY

We began to study the actions of alpha dinitrophenol 2–4 first in animals and then in patients, in 1931, being stimulated to do so by the animal experiments of Heymans,[2] who used a similar compound, namely, dinitronaphthol. Dinitrophenol was not new, since it had been known as a dye for about a hundred years, and as an industrial poison for 32 years.[3] There was some interest in its toxicology during the war, due to poisoning in munitions factories. Fundamental investigations of the actions of the compound were made at that time by Magne, Mayer, and collaborators in France, although their studies were not published until 16 years

* Read before the Food and Nutrition Section of the American Public Health Association at the Sixty-third Annual Meeting in Pasadena, Calif., September 3, 1934.

† Supported in part by grants from the Rockefeller Fluid Research Fund of the School of Medicine, Stanford University, and by Grant 320 from the Committee on Scientific Research of the American Medical Association.

[1045]

In 1918 an industrial worker exposed to a dye called dinitrophenol passed away after experiencing severe weight loss.[1] Researchers at Stanford led by Professor Tainter sought to understand how this dye caused such dramatic weight loss and published the papers shown at left. This was the original approach to obesity therapeutics – coming far earlier than the notions pursued today.

Ultimately, dinitrophenol was determined to be unsafe but was briefly used with great effect to treat obesity at a Stanford clinic. These drugs have the function of increasing the speed of mitochondrial energy consumption through what is known as mitochondrial uncoupling.

This led Allen Cunningham and colleagues to form a company called Gencia in 2002 which focused on developing safer mitochondrial uncouplers, eventually leading to a collaboration with Takeda.[2]

When Takeda exited cardiometabolic disease, Rivus was formed and is now in Phase 2b with a study in obese individuals with heart failure.[3]

Sources: https://jamanetwork.com/journals/jama/article-abstract/245872, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1558869/

1. Warthin, A. S. "A fatal case of toxic jaundice caused by dinitrophenol." *Bull Int Assoc Med Mus* 7 (1918): 123-126. 2 https://www.fiercebiotech.com/partnering/takeda-bets-500m-on-a-freshly-unstealthed-biotech, 3 https://biobuzz.io/rivus-pharma-obesity-therapy/

Rivus Approach: Promising Data

Rivus PHARMACEUTICALS

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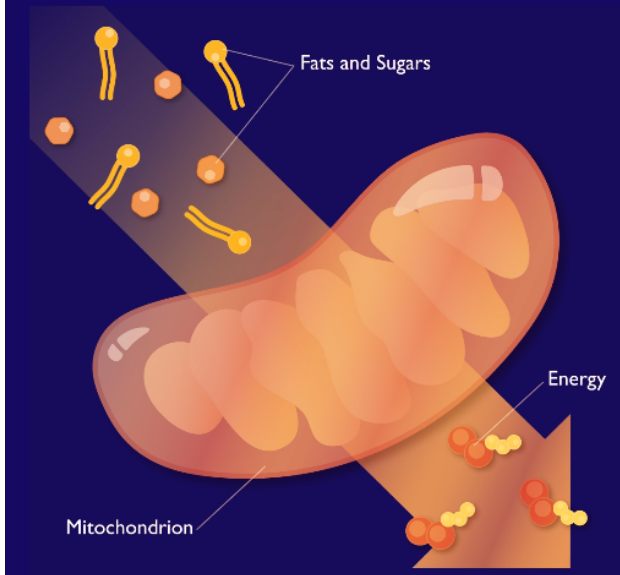
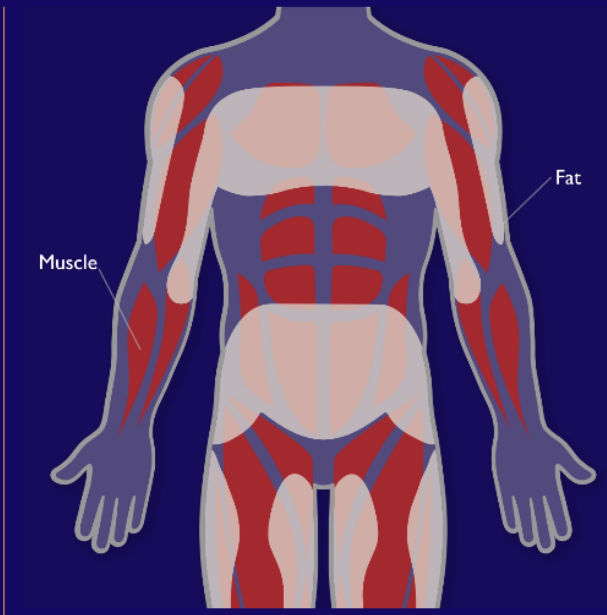
Leveraging the powerhouse of the cell to achieve better health

By harnessing the natural mechanism of mitochondrial uncoupling, Rivus' therapies accelerate metabolism with the aim of enabling healthy lives for millions.



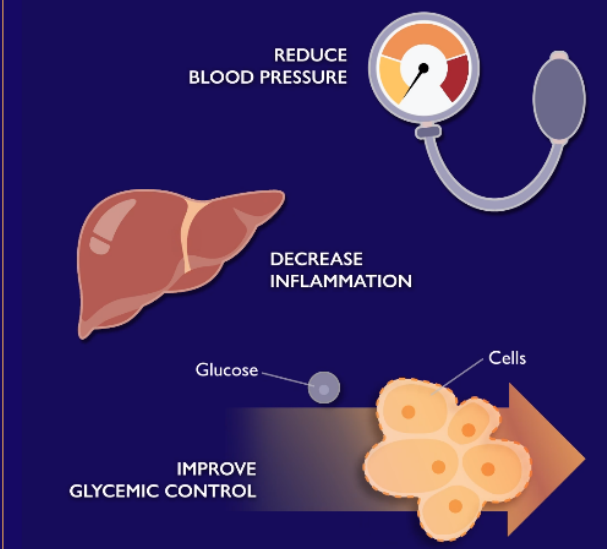
IMPROVE CELLULAR METABOLISM

Controlled metabolic accelerators (CMAs) like HU6 are oral, small molecule therapies designed to improve cellular metabolism. CMAs harness a natural metabolic process in mitochondria, the powerhouse of cells, to increase the breakdown of fats and sugars and increase resting energy expenditure.



REDUCE FAT, PRESERVE MUSCLE

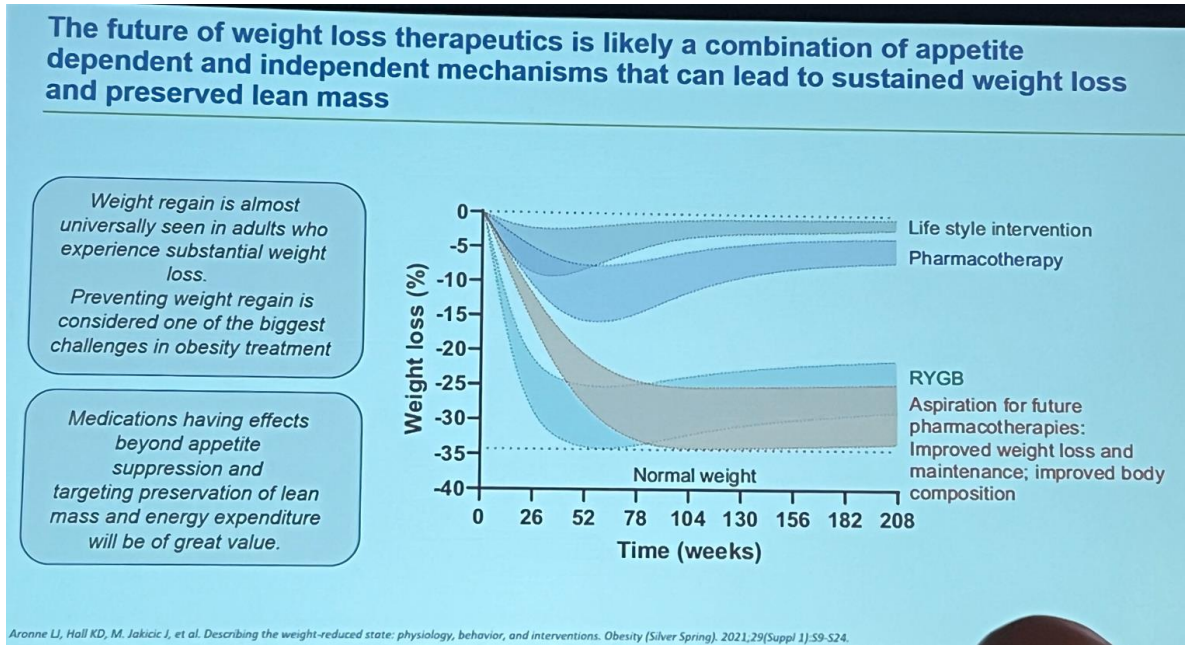
By increasing energy expenditure, CMAs decrease fat throughout the body while maintaining skeletal muscle mass. Muscle retention is critical to minimize fat regain and reduce cardio-metabolic risk.

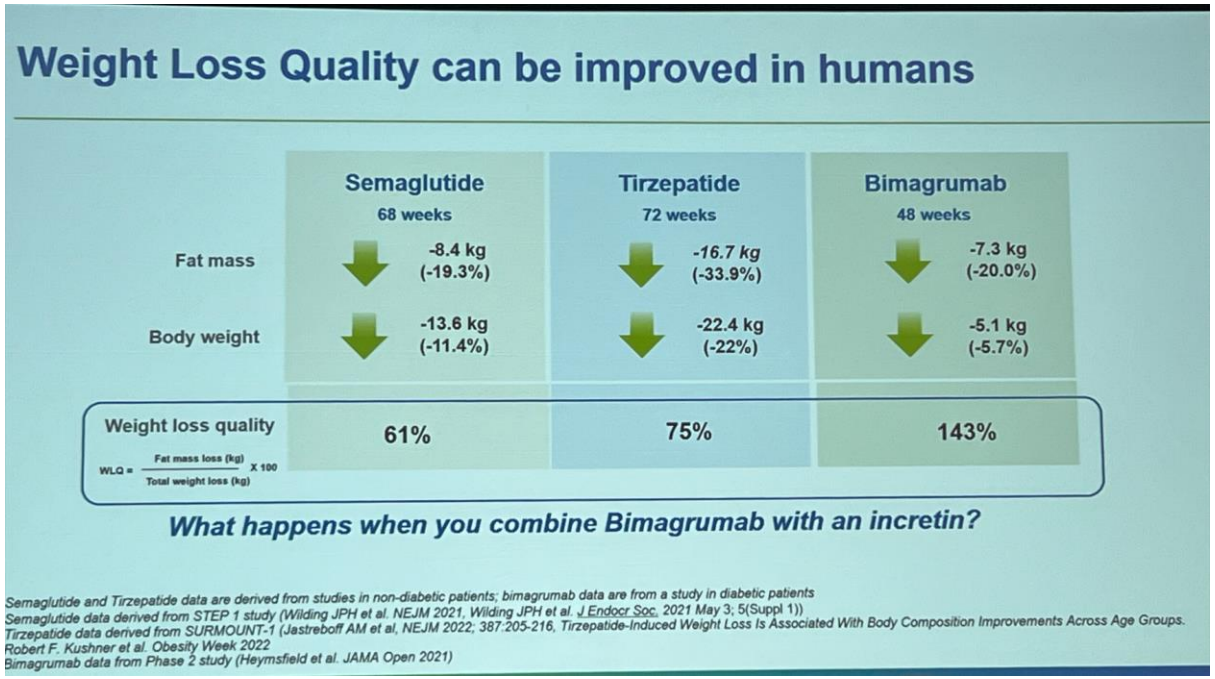


CLINICAL OPPORTUNITY

In a Phase 2 clinical trial, HU6, a first-in-class CMA, was shown to improve disease markers of blood pressure, inflammation and glycemic control. CMAs are now being studied to treat obesity, a common driver of cardio-metabolic diseases, with the aim of improving the health of millions.

Versanis Slides at ADA





As one might expect Versanis emphasized the importance of combining appetite suppression medications with other approaches in its presentation at ADA. They introduced the idea of weight loss quality by comparing fat mass loss to total body weight loss from various studies.

Source: Presentation slides from the 83rd Scientific Sessions of the American Diabetes Association, June 2023.

#6: Longer Acting Therapies Desirable

Global Data, "Unmet needs in the obesity market," April 13, 2023

One such need in the obesity space is for longer-acting therapies. Despite the anticipated arrival of novel therapies to treat obesity in the next ten years, GlobalData forecasts that major opportunities will remain for pharmaceutical companies to develop drugs for obesity that are longer acting. KOLs interviewed by GlobalData highlighted the need to develop therapies with lower frequencies of administration, as therapies with the lowest frequency of administration in the obesity space still require administration on a weekly basis. Furthermore, GlobalData's primary research revealed that many people are not keen on or will not be able to tolerate receiving a weekly injection.

A key priority is to create options that require less frequent administration – particularly for injectable drugs.

We are aware of two promising long-acting agents: Amgen's AMG133 involves monthly dosing and Versanis' Bimagrumab involves quarterly dosing.

Source: https://www.pharmaceutical-technology.com/comment/unmet-needs-obesity-market/

#7: Drugs that Do Not Need Specialists

Global Data, "Unmet needs in the obesity market," April 13, 2023

"Another significant unmet need in the obesity market is the availability and accessibility of specialists. This is an important obstacle that needs to be overcome to optimise coverage for obesity. Factors that can negatively influence access to specialists include the lack of access to and fragmentation of weight management services, associated costs, lack of time, and the stigma that surrounds obesity. KOLs highlighted that health inequality has a massive impact on obesity and that clinical trials, therefore, do not accurately reflect the obese population, particularly patients who are more socially deprived or patients from different socioeconomic backgrounds."

There is a substantial lack of medical infrastructure to treat the obese population in the United States. This is particularly true because obesity is endemic in less well-off populations.

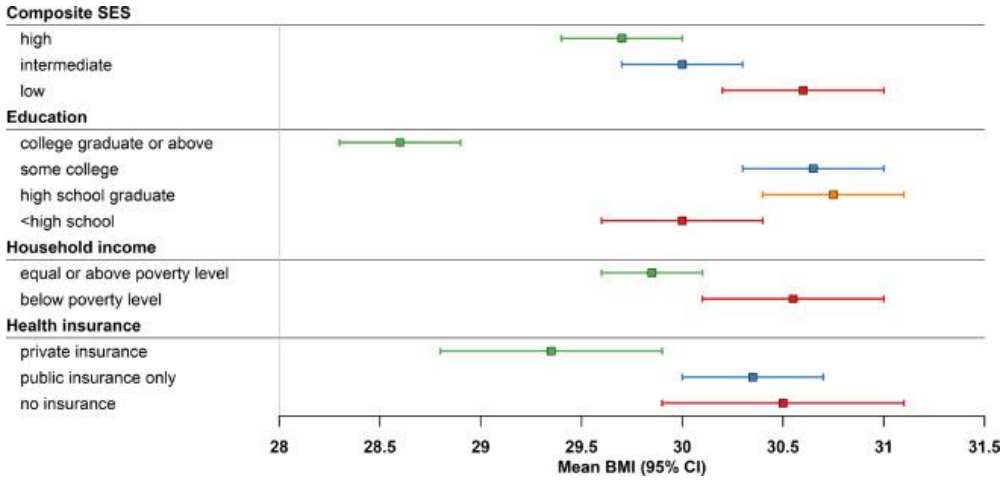
Opportunities to reach populations out of reach of specialists include distribution via the OTC channel and the e-Prescribing channel.

Source: https://www.pharmaceutical-technology.com/comment/unmet-needs-obesity-market/

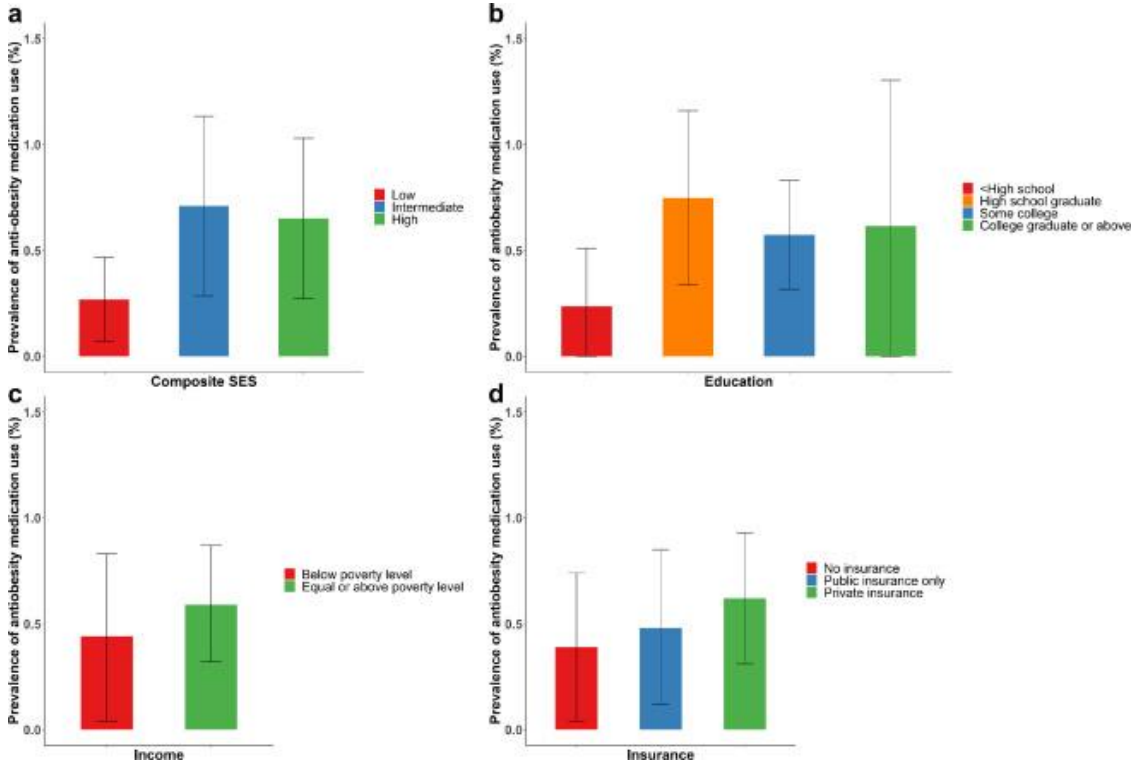
Big Unmet Need for Obesity Drugs Among Poor and Those with Less Education

Lyu B, Chang AR, Inker LA, Selvin E, Grams ME, Shin JI. Socioeconomic status and use of obesogenic and anti-obesity medications in the United States: A population-based study. *Lancet Reg Health Am.* 2022 Jul;11:100249.

Obesity Most Prevalent in Lower Social Economic Status (SES) Populations…



… Yet those populations are least likely to use anti-obesity medications.



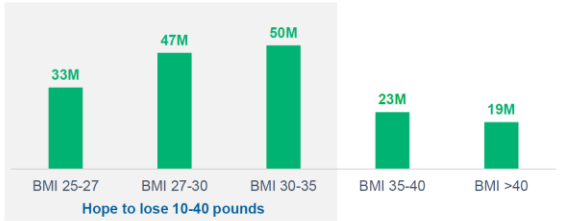
Source: https://pubmed.ncbi.nlm.nih.gov/35928911/

An Interesting Affordable Option: Plenity®

Majority of Americans Want to Lose <40 Pounds[1]

Most of Them Don't Want / Qualify for & Can't Afford Rx Drugs

US Population[2]



Plenity Label Covers >150M Americans of which 61million interested in losing 10+ pounds

~$75B[3] opportunity in weight loss and weight management

Diet & exercise **don't work** for the majority of people

1. Based on Qualtrics survey assessing consumer weight loss goals for people with a BMI between 25-40
2. Based on 2013-2014 cycle of NHANES data
3. MarketResearch.com: "U.S. Weight Loss Market Shrinks by 25% in 2020 with Pandemic, but Rebounds in 2021" by John LaRosa, on March 10, 2022

GELESIS

Meet Plenity: FDA Cleared, Clinically Proven & Well Tolerated

Designed to make you Feel Fuller, Eat Less, and Lose Weight

1. Safety & Ease

Safety: Unprecedented safety profile as demonstrated in our clinical trials and our real-world data

Ease: Three pills, twice daily

2. Effective & Proven

Effectiveness: 6 out of 10 people in our FDA clinical trials lost an average of 22 lbs and 3.5 inches in only 24 weeks

Proven: Strong sales growth with high consumer satisfaction

3. Affordable & Accessible

Affordable: Costs $1.75 per dose and can be purchased easily online

Accessible: With broad online distribution **without an Rx** (coming soon[1])

New Therapies Have Ignited the Category, but They Have Limitations

	GLP-1 Limitations	Plenity
Access & Affordability:	"can cost $1,400 a month..." "we'd bankrupt the health system." — AXIOS	• **Affordable** & easily **accessible** as OTC • Could eventually be a step through therapy for GLP1s
Safety & Tolerability:	"There are worse things than being fat... [like] wanting to barf all the time." — New York	• **Widest label** of any Rx therapy • **Unparalleled safety** profile in 200,000 patients
Chronic Use / Rebound:	"Patients don't want to be on an injectable forever..." "I was insatiable…hungry all the time. It shocked me how fast it happened." — The New York Times	• **Orally administered**, with no limits on duration of treatment • Potential upside as an **"off ramp"** for patients cycling off GLP-1s

Effective & Proven

Robust Efficacy and Safety in Clinical Trials and the Real World

Responders

Adults **achieving 5% or greater** weight loss in only 24 weeks

6 out of **10**

These responders lost on average 10% of their weight (22 lbs) and ~3.5 inches from their waist

Plenity doubled the odds of achieving 5% or greater weight loss compared with placebo

Super Responders

Adults **achieving 10% or greater** weight loss in only 24 weeks

26% were "super-responders" to Plenity, **losing on average 14% of their weight (30 lbs)**

Safety / Side Effects / Tolerability

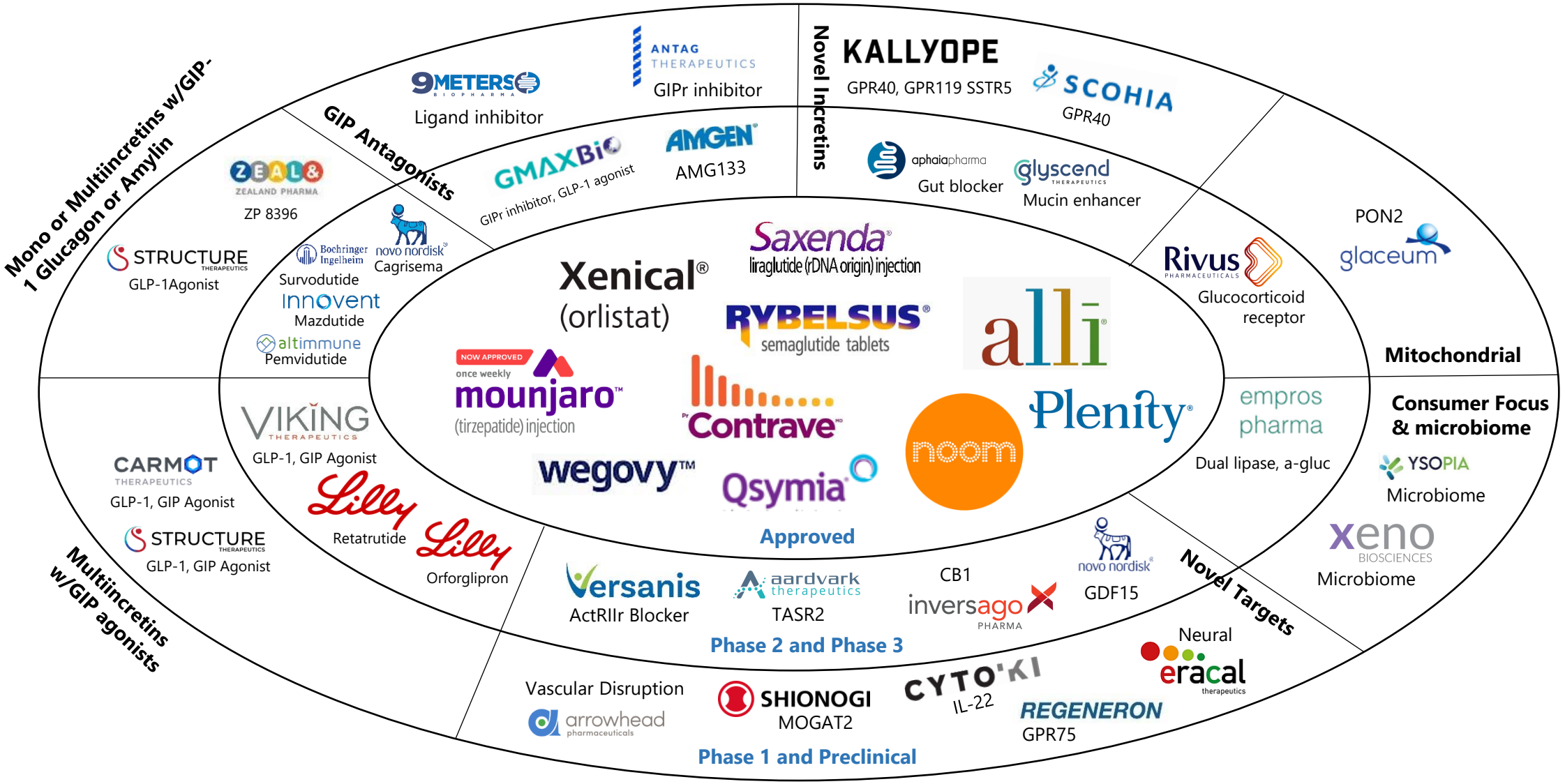
Plenity had a side effect profile equal to placebo, and no serious adverse events

Source: https://ir.gelesis.com/

Obesity Drug Pipeline: Other Biotech Companies to Watch

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

Obesity Drug Pipeline



Emerging Gut Restricted Approaches

We are aware of at least three companies that use gut-restricted approaches to manage obesity.

Aardvark's drug stimulates release of a number of gut peptides.

Aphaia is trying to accelerate the release of "good" hormones from enteric cells by bathing them in local glucose.

In contrast, Glyscend uses a barrier approach which attempts to shield food from the gut's incretin receptors. The goal is to mimic the beneficial effect of Roux-en-Y gastric surgery using a pill.

aardvark therapeutics

ARD-101 is a gut restricted drug that conveys systemic effects via activation of gut peptide hormone secretion, including GLP-1, GLP-2, and cholecystokinin (CCK). CCK has long been recognized as an interesting pharmaceutical target because its release is triggered with food and helps suppress feelings of hunger. ARD-101 stimulates the release of the body's natural CCK, but primarily targets vagal nerve afferents located near the gut - in turn induces positive effects on hunger, metabolism, and inflammation through gut-brain signaling. Has Phase 1b data.

aphaiapharma

APH-012 is a bead formulation of glucose that releases glucose in the gut. This induces the release of the full spectrum of enteral hormones that control appetite, hunger, satiety, glucose metabolism, and other homeostatic functions. Aphaia showed this in a Phase 1 study. In Q1 2024, Aphaia will have weight loss data that will allow one to evaluate whether this approach is competitive in the emerging market. One major benefit of the approach may be less nausea side effects associated with other approaches.

glyscend THERAPEUTICS

Glyscend attempts to block the activity of incretins from the gut in order to impact obesity. The company's Mucus Complexing Polymer (MCP) platform invented through research originating at Johns Hopkins University. Glyscend is ingeniously targeting mechanisms inside the GI tract to treat a variety of metabolic and chronic conditions. Glyscend presented data at ADA showing that its drug was successful in reducing body weight and postprandial glucose.* These data were from a 14-day study, so it is hard yet to interpret and compare to other agents.

* See https://www.businesswire.com/news/home/20230531005626/en/Glyscend-Therapeutics-Announces-Positive-Topline-Phase-2a-Clinical-Results-and-Progress-with-GLY-200-a-First-in-Class-Treatment-for-Type-2-Diabetes-and-Obesity

Other Emerging Approaches to Watch

We are struck by the richness, diversity and ingenuity of the current obesity pipeline. We believe that there will be a range of exciting options for managing excess weight in the decade ahead.

arrowhead pharmaceuticals

Arrowhead is in Phase 1 with Adipotide®, a peptide that targets a protein on the surface of blood vessels supporting white adipose tissue. The effect is to eliminate cells by disrupting blood supply. Treatment with adipotide induced targeted apoptosis within blood vessels of white adipose tissue and resulted in rapid weight loss and improved insulin resistance in obese monkeys.

empros pharma

EMP16 combines acarbose, a carbohydrate metabolizer with orlistat, a well-known lipase inhibitor. EMP16 has shown promising efficacy in a 6-month clinical trial and has a fully enrolled Phase 3 study underway. This drug may be a candidate for direct-to-consumer and/or OTC models given the known safety of its elements.

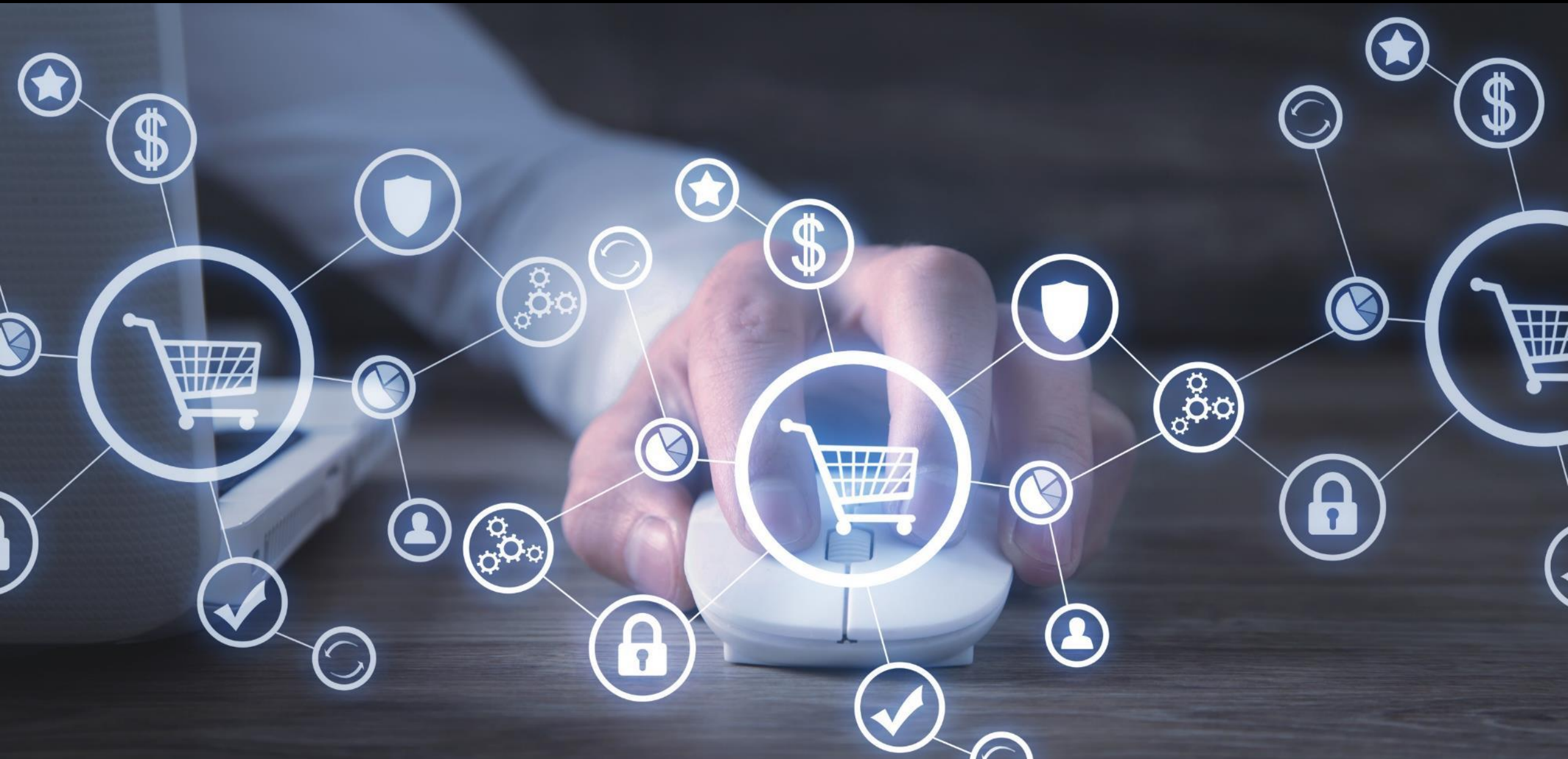
eracal therapeutics

Eracal studied targets that impact weight in Zebrafish. They are in preclinical studies of a program called ERA-379 based on this work that works by disrupting neural circuits for hunger. MOA not disclosed. Eracal has recently entered into a collaboration with Nestlé Health Science.

xeno BIOSCIENCES

XEN-101 is a microbiome treatment for obesity planned to be evaluated in a Phase I clinical trial. XEN-101 is a first-in-class oral formulation, engineered to produce weight loss by mimicking the microbiome changes induced by gastric bypass surgery. XEN-101 has demonstrated profound weight loss effects in animal models and humans with limited side effects.

The Consumerization of Obesity Treatments



A New Class of ‘Game-Changer’ Weight-Loss Drugs Exploded in Popularity in 2022

Gabby Landsverk, *Business Insider*, November 25, 2022

“A new category of weight loss medications, repurposed from diabetes treatment, are seriously changing how we think about and approach weight management.

In 2021 the medication semaglutide, called a "game changer" in the industry, officially got the FDA's approval to be prescribed for weight loss. In 2022, it has soared in popularity, becoming more widely used and spurring more research. In the past year, another promising drug has also been eyed for approval as a weight loss treatment.”

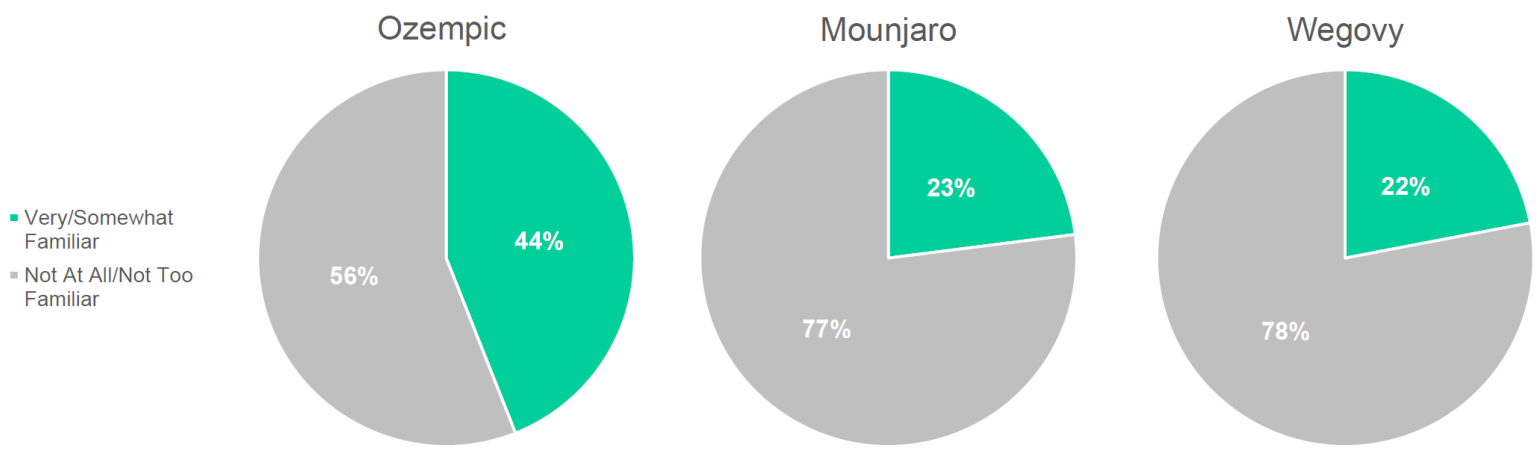
Source: https://money.yahoo.com/class-game-changer-weight-loss-170000151.html

Recent Harris/Stat Poll Shows Broad Familiarity with GLP-1 Drugs

STAT-HARRIS POLL: OBESITY AND WEIGHT LOSS MEDS.

45% Of Americans Familiar; Younger, More Urban, Non-White More Familiar

How familiar are you with the following weight-loss medicines?



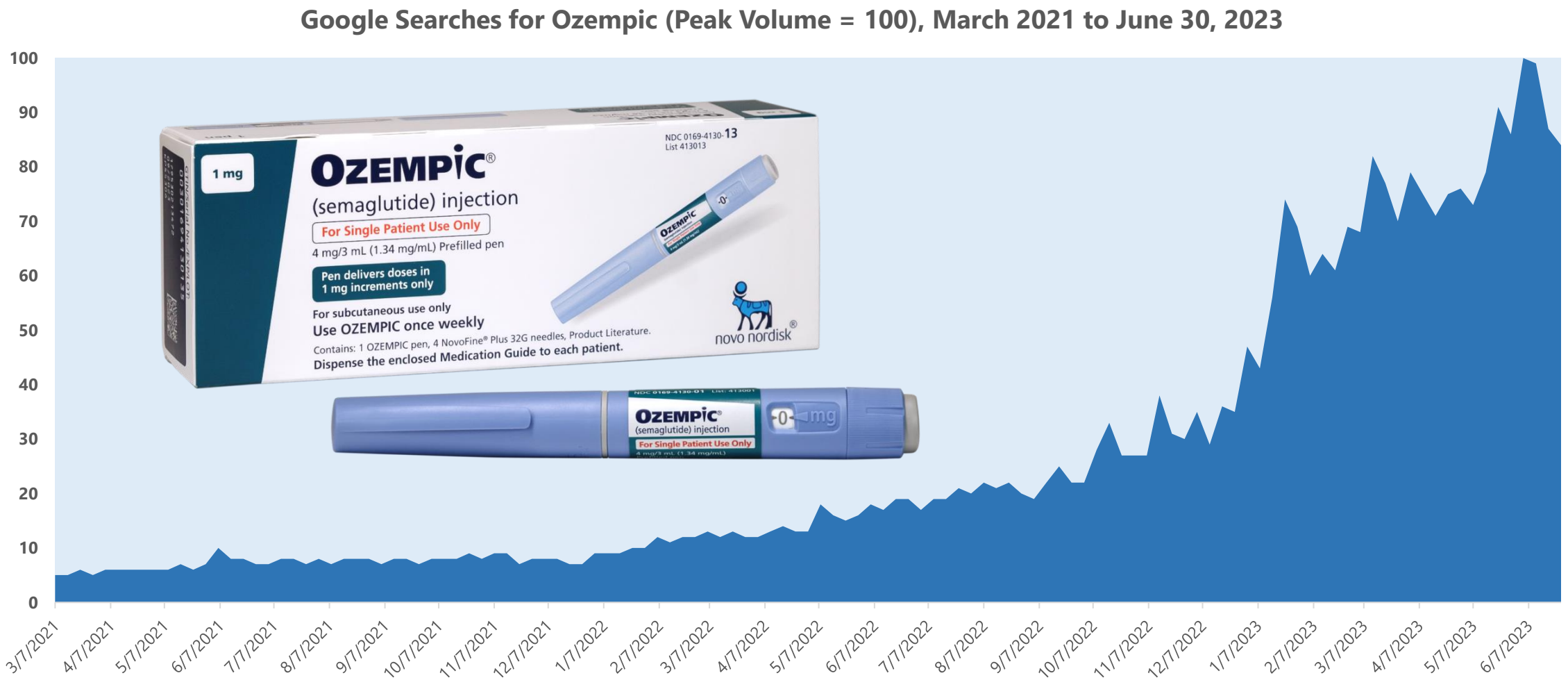
Source: STAT-Harris Poll (n=2,046 US Adults 18+, Fielded June 2-4, 2023)

5

Nearly half of Americans are aware of the new generation of weight loss drugs and are interested in using them. Interest in these products is off the charts.

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

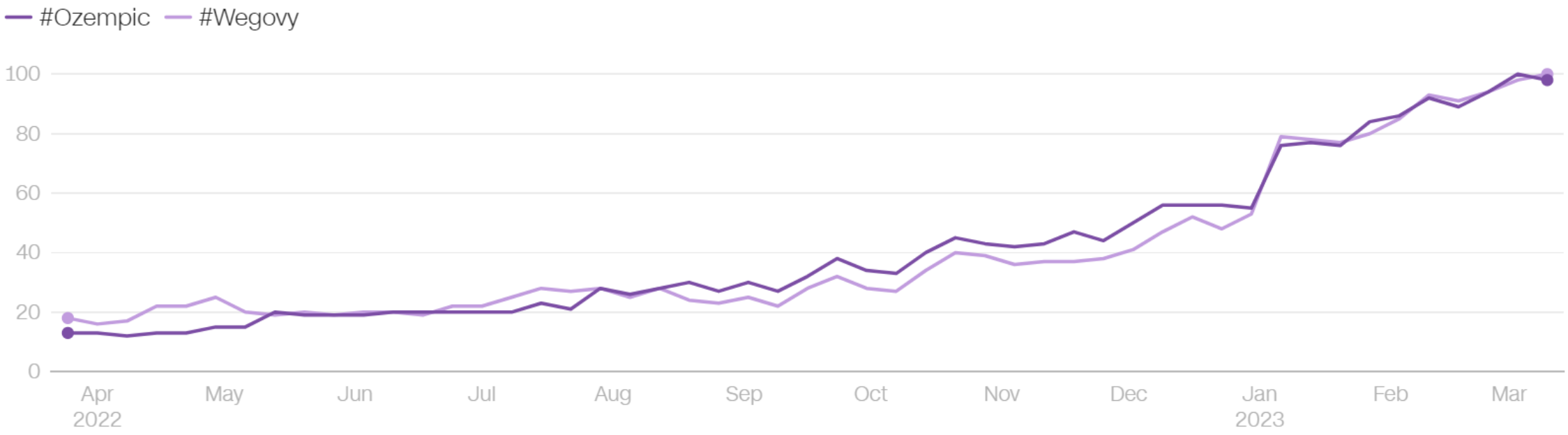
Google Search Volume for Ozempic Up 20X in Two Years (3X in the Last Six Months)



Same Phenomenon Underway on TikTok

#Ozempic and #Wegovy more popular than ever on TikTok

This chart shows the relative volume of posts and views of #Ozempic and #Wegovy against peak volume (a value of 100). Both hashtags reached their peak volumes in early-March.



Source: https://www.cnn.com/2023/03/17/health/ozempic-shortage-tiktok-telehealth/index.html

Focus: Obesity drug Wegovy's popularity has US employers rethinking insurance coverage

Patrick Wingrove, Reuters, June 27, 2023

"Until late last year when Wegovy prescriptions began to rise, weight-loss coverage represented a marginal expense for employers because the available branded drugs were ineffective and little used, or readily substituted by cheaper generics, the healthcare consultants said.

Employers also were supportive of treatments that could help reduce the risk of diseases that are exacerbated by excess weight including heart conditions and diabetes.

The arrival to market of Wegovy in 2021 and in 2022 Mounjaro, a similar diabetes treatment from Eli Lilly that is being prescribed off-label but is not yet approved for weight loss, have changed that dynamic."

Most American's get health insurance through employers. Most employers self-insure.

As noted at left, employers are struggling with the cost of the high volume of prescriptions for Wegovy® and Mounjaro® coming through in 2023.

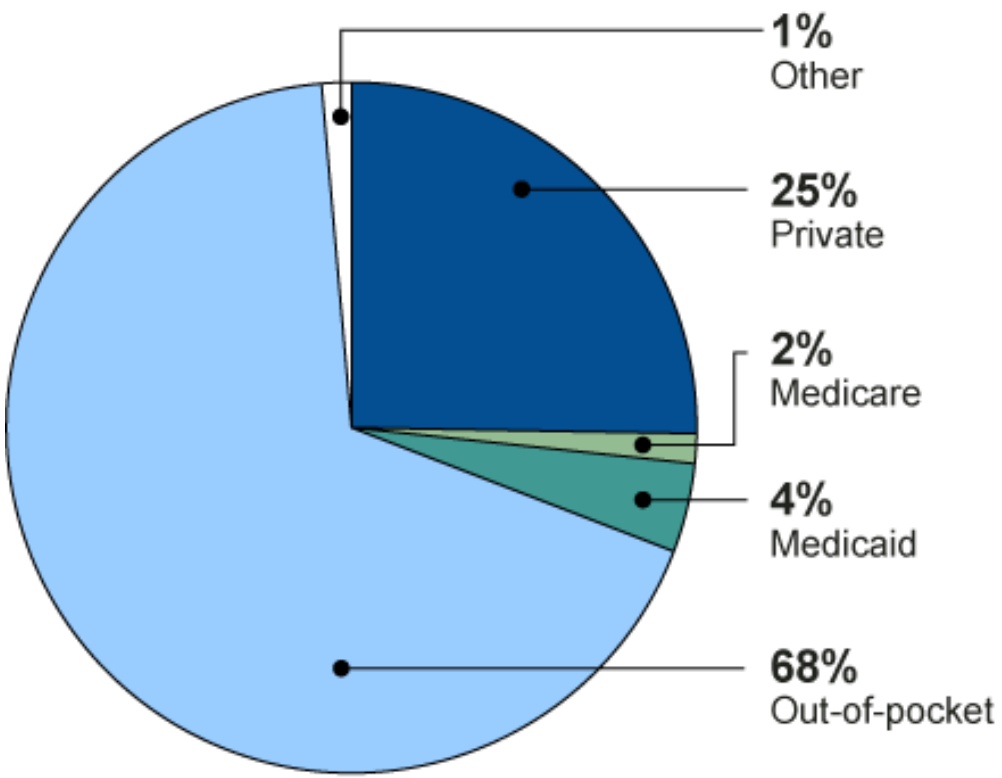
Source: https://www.reuters.com/business/healthcare-pharmaceuticals/obesity-drug-wegovys-popularity-has-us-employers-rethinking-insurance-coverage-2023-06-27/

The Patient Isn't Waiting for Health Plans and Medicare to Cover their Obesity Drugs

Due to a lack of long-term data on outcomes, many plans exclude weight loss medicines from coverage or relegate them to higher tiers on formularies.

According to AHRQ, 68% of U.S. expenditures for weight loss medicines are out-of-pocket.

These are relatively old data.



Source: Agency for Healthcare Research and Quality's (AHRQ) estimates from the Medical Expenditure Panel Survey, 2012-2016. | GAO-19-577

Other payments include payments made by federal government sources such as the Veterans Administration.
For figure notes, see figure 2 in the report.

Source: https://www.gao.gov/products/gao-19-577

Onilne Advertising for GLP-1 Medications Ozempic® and Wegovy® Online Far Outpaces Viagra®

NBC News, "More than 4,000 ads for Ozempic-style drugs found running on Instagram and Facebook," June 15, 2023

Online pharmacies, medical spas and diet clinics are running thousands of weight-loss ads on social media for the drugs Ozempic and Wegovy or for their active ingredient, capitalizing on a surge of interest in the medications but also angering some consumers who say they're being inundated with ads suggesting they could benefit from the drug.

On Facebook and Instagram alone, there were more than 4,000 active ad campaigns in the U.S. mentioning semaglutide, the drugs' active ingredient, according to multiple searches over several days on the ad library of the apps' parent company, Meta.

By that measure, semaglutide is more heavily marketed on social media than even the erectile-dysfunction drug Viagra, which was mentioned in 800 active ad campaigns on Instagram and 930 campaigns on Facebook as of Monday and has long been known to be a favorite subject of online marketers. Meta does not provide spending amounts for such ad campaigns.

The current interest in obesity drugs is very high.

There is five times more advertising for Semaglutide today than for Viagra®.

Source: https://www.nbcnews.com/tech/internet/ozempic-weight-loss-drug-ads-instagram-wegovy-semaglutide-rcna88602

Obesity Drugs Consumerization Trend

Overwhelmingly, news stories about the popularity of Ozempic®, Wegovy® and Mounjaro® have highlighted the risks of direct consumer access.

A number of groups have noted that current shortages of Semaglutide mean that those with the highest need, diabetics, may be getting crowded out by image conscious consumers who do not have the same medical need. There is particular concern with the shift of consumers to online web sites where product can be dispensed rapidly using e-prescribing.

We wish to note that even if prescribed online, a physician is still involved. Further, online sites are giving a much broader part of the U.S. population access to these drugs as a very large percent of the population does not regularly see doctors.

Further, while both the FDA and Novo Nordisk have been talking about the risks associated with online access of compounded Semaglutide we are not aware of negative health reports of such access. Compounded product is available at much lower prices (but only while the product is on the FDA shortage list) and is allowing a much broader part of the U.S. population access to GLP-1 agonists. Compounding is a routine part of our system. We do not doubt, of course, that there are some abuses and risks. A thin person who uses Ozempic® to get even thinner. Not unlike the 22-year-old man who gets Viagra®.

A vendor or two who sells an unsafe compounded product. But it's also worth noting that both Meta and Google police advertisers on their sites heavily.

If 2021 was the year in which the world began to use telehealth, 2023 is the year when American's are learning to use e-Prescribing. It's no longer about ED drugs or baldness medications. Ozempic® is a valuable drug to forestall chronic disease.

The widespread use of e-Prescribing websites to access obesity medications is a **major phenomenon** and, if appropriately leveraged, a very positive one for the pharma industry. More Americans can gain access to needed drugs. More Americans are taking charge of their health online. And there is an opportunity for pharma to reach the patient directly.

If you will, we think a long-term trend is well underway: the consumerization of access to pharmaceutical products. It's important as well because private pay drugs accessed online are often less expensive for the consumer than the co-pay on drugs paid for by insurance.

When we look back in a decade, we believe that the early 2020's will have proven to be a watershed moment when patients learned to take real action that could forestall chronic disease by going online. Far from a problem, we see a major opportunity for pharma.

How Big is the Obesity Market?

Today's Estimates of Market Size Likely Underestimate the Ultimate Spend on Obesity Drugs

Private research firm and brokerage house consensus peak sales for the GLP-1 class is around $30 billion but there are estimates that run as high as $100 billion.

In this section we ask "what is a reasonable estimate of peak sales given the enormous unmet need and consumer interest in these products?"

Allison Gatlin, *Investors Business Daily*, Dec 8, 2022

"Market researchers with Reports and Data estimate the market was worth $8.39 billion in 2020 and will grow to $28.1 billion by 2028. Grand View Research expects the market to hit $15.6 billion by 2024. Yet another analysis group, Research and Markets, pegs the obesity treatment market at $25.3 billion by 2027."

For those hoping to find an official Stifel estimate of peak sales for obesity drugs in this section, you will be disappointed. We are not prepared to make such a forecast.

But we wish to make several points:

1. It is very difficult to predict the total market size because we not yet seen long-term outcomes data yet from companies like Novo for Semaglutide or Lilly for Tirzepatide.
2. Further, there are so many new agents in development that have potential to satisfy unmet needs in the market that it is quite challenging to predict how the market might evolve. It is particularly striking to us to review market forecasts from, say 2019, and to see how wrong they were. The market changed radically afterwards.
3. The U.S. insured market potential is very likelyi *in excess of the $100 billion* that has been described in some brokerage reports.
4. The consumer end market demand is similarly large. That is, if insurers (ultimately, governments and employers) don't want to pay for the demand, consumers are willing to pay themselves.

Source: https://www.investors.com/news/technology/amgen-stock-here-is-what-we-know-about-its-belated-obesity-treatment/

Why is the Market Opportunity So Large?

1. **Chronic treatment.** Obesity drugs will be needed over a long period of time. We have reviewed approved drugs and those in the pipeline. Except for bariatric surgery, there are no solutions available to patients that do not involve long-term administration of products. Perhaps one day, such a drug will be developed but today we do not see one in the pipeline.

2. **Pays for Payors.** Payors will ultimately make money by covering obesity drugs. It appears highly likely that the data will show massive reductions in chronic disease outcomes from patients who stay on incretin-based drugs over the long run. Because obesity-linked chronic diseases are the #1 source of cost in the U.S. healthcare system, it is likely that a long-term study will show the benefit to payors for covering the drugs.

3. **Aesthetic Driver Powerful.** The societal demand for obesity reduction is driven by a desire to look thin. Forty percent of American's are obese and almost all of them would pay money to look thinner. This source of demand is driving the market to a private pay approach.

4. **Obesity Not Going Away.** Regrettably, the harmful "Western Diet" is spreading. KFC is branching across China and McDonald's is well on its way to full globalization.

5. **Multiple Needs / Niches in the Market.** The market will have a diverse set of players offering products with different labels and price points. Some drugs will be for the "post-GLP-1 period" to avoid rebound and will be inexpensive, reasonably effective and safe.* Other drugs could be a bit less safe and will be available to those who medically need to drop substantial weight. Other drugs will have labels that encompass chronic conditions like NASH or heart failure. Even addiction or Alzheimer's might be possible indications.

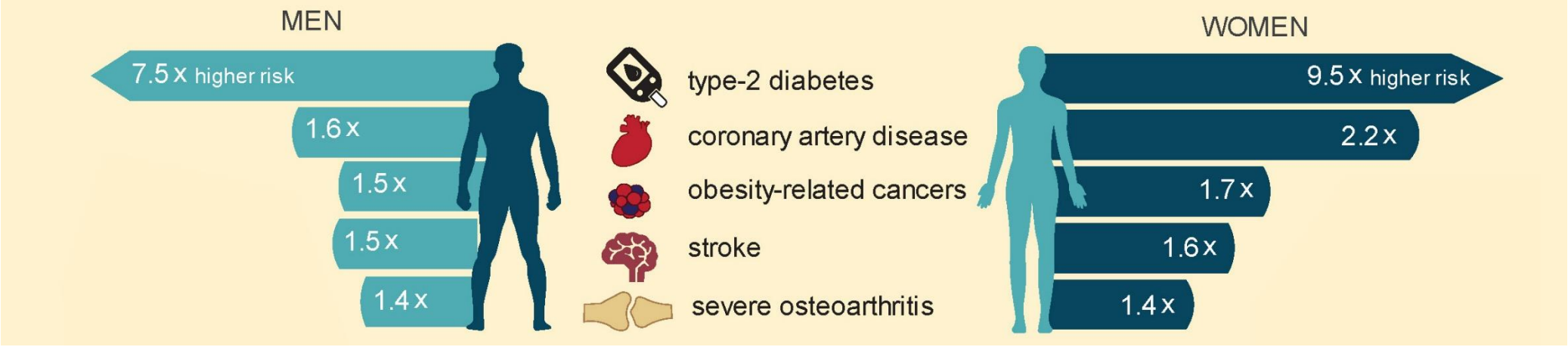
6. **Definition of "Obesity" Will Broaden.** The relevant market will grow. For example, we are shifting from notions of avoidance of too high cholesterol today to managing patients to "optimal cholesterol." The same can be true with weight. There are also subpopulations of persons with normal BMI who have heightened cardiometabolic risk – the so-called "skinny fat." (see, for example, https://jcto.weill.cornell.edu/news/skinny-fat).

* Gelesis' Plenity product comes to mind. It fills your stomach with cellulose, is inexpensive, can be OTC and is reasonably effective.

Why The U.S. Government and Insurers Will Ultimately Agree to Cover Obesity Drugs: Obesity Costs are a Huge Societal Burden

STOP OBESITY ALLIANCE
STRATEGIES TO OVERCOME & PREVENT

"Approximately 1 in 4 women and 1 in 8 men gain 44 pounds or more between the ages of 18 and 55 years. New research suggests that preventing excessive weight gain during this period may be a promising target for intervention. Weight gain ≥ 44 pounds during early to middle adulthood significantly increases chronic disease risk"



Source: https://stop.publichealth.gwu.edu/fast-facts/obesity-related-chronic-disease

Novo Nordisk Chart on Obesity Comorbidities

Obesity is associated with multiple comorbidities, which may be improved with weight management

Life expectancy decreases as BMI increases[1]

Normal BMI
Almost 80% chance of reaching age 70

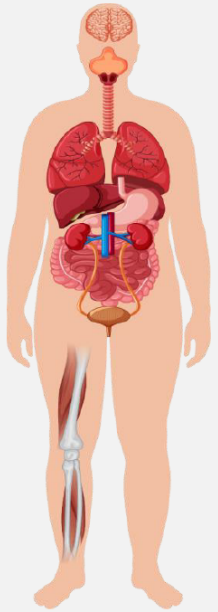
BMI 35–40 kg/m²
~60% chance of reaching age 70

BMI 40–50 kg/m²
~50% chance of reaching age 70

Obesity related comorbidities[2]

Mental
- Depression
- Anxiety

Mechanical
- Asthma
- GERD
- Physical functioning
- Incontinence
- Knee osteoarthritis
- Sleep apnea
- Chronic back pain



Metabolic
- NAFLD
- Gallstones
- Infertility
- Type 2 diabetes
- Prediabetes
- Thrombosis
- Gout
- Cancers*
- CVD:
  - Stroke
  - Dyslipidemia
  - Hypertension
  - Coronary artery disease
  - HFpEF

*Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate
1 Prospective Studies Collaboration. Lancet. 2009;373:1083–96. 2 Adapted from Sharma AM. Obes Rev 2010;11:808–9; Guh DP et al. BMC Public Health 2009;9:88; Luppino FS et al. Arch Gen Psychiatry 2010;67:220–9; Simon GE et al. Arch Gen Psychiatry 2006;63:824–30; Church TS et al. Gastroenterology 2006;130:2023–30; Li C et al. Prev Med 2010;51:18–23; Hosler AS. Prev Chronic Dis 2009;6:A48.
BMI: Body mass index; GERD: gastro-oesophageal reflux disease; HFpEF: heart failure with preserved ejection fraction; NAFLD: non-alcoholic fatty liver disease; CVD: Cardiovascular disease; HFpEF: Heart failure with preserved ejection fraction

Source: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/pdfs/ada/ada-investor-presentation-2023.pdf

A Quantitative Look at Payor Cost Savings

Assumed Payor Cost of Ozempic® with Rebates/Discounts/Coupons:	**$6,000**
AAF Annual Direct Costs of Chronic Disease in the U.S.:	**$904,800,000,000**
AAF Annual Total Costs of Chronic Disease in the U.S.:	**$3,700,000,000,000**
AAF Annual Total Per Person with Chronic Disease:	**$28,030**
What Percent of Chronic Disease Costs Would Need to be Avoided to Break Even on Paying for "GLP-1's for Life" for Persons at Risk of Chronic Disease Due to Obesity?	**21.4%**

Assuming a $6000 a year cost and the above estimates of the costs of chronic disease, a payor who bears those costs such as the U.S. government would want to see evidence that the use of GLP-1's for life would reduce chronic diseases costs by 21.4% to break even.

Source: https://www.americanactionforum.org/research/chronic-disease-in-the-united-states-a-worsening-health-and-economic-crisis/

Lilly Q1 2023 Investor Presentation: Ongoing Marketing Studies of Tirzepatide

Study	Indication*	Title	Phase	Patients	Primary Outcome**	Primary Completion	Completion
NCT04184622	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1)	3	2539	Percent Change from Baseline in Body Weight	Apr 2022	May 2024
NCT04657016	Obesity	A Study of Tirzepatide (LY3298176) In Participants After A Lifestyle Weight Loss Program (SURMOUNT-3)	3	806	Percent Change from Randomization in Body Weight	Apr 2023	May 2023
NCT04660643	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight for the Maintenance of Weight Loss (SURMOUNT-4)	3	783	Percent Change from Randomization (Week 36) in Body Weight	Apr 2023	May 2023
NCT04844918	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity Disease (SURMOUNT-J)	3	261	Percentage of Participants who Achieve ≥5% Body Weight Reduction	Jun 2023	Jun 2023
NCT05822830	Obesity	A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight With Weight Related Comorbidities (SURMOUNT-5)	3	700	Percent Change from Baseline in Body Weight	Feb 2025	Mar 2025
NCT05556512	Obesity	A Study of Tirzepatide (LY3298176) on the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO)	3	15000	Time to First Occurrence of Any Component Event of Composite (All-Cause Death, Nonfatal Myocardial Infarction (MI), Nonfatal Stroke, Coronary Revascularization, or Heart Failure Events)	Oct 2027	Oct 2027

Study	Indication*	Title	Phase	Patients	Primary Outcome**	Primary Completion	Completion
NCT04255433	Type 2 Diabetes	A Study of Tirzepatide (LY3298176) Compared With Dulaglutide on Major Cardiovascular Events in Participants With Type 2 Diabetes (SURPASS-CVOT)	3	13299	Time to First Occurrence of Death from Cardiovascular (CV) Causes, Myocardial Infarction (MI), or Stroke (MACE-3)	Oct 2024	Oct 2024
NCT05260021	Type 2 Diabetes	A Study to Evaluate Tirzepatide (LY3298176) in Pediatric and Adolescent Participants With Type 2 Diabetes Mellitus Inadequately Controlled With Metformin or Basal Insulin or Both (SURPASS-PEDS)	3	90	Change From Baseline in Hemoglobin A1c (HbA1c)	Nov 2027	Dec 2027
NCT04166773	Nonalcoholic Steatohepatitis	A Study of Tirzepatide (LY3298176) in Participants With Nonalcoholic Steatohepatitis (SYNERGY-NASH)	2	196	Percentage of Participants with Absence of NASH with no Worsening of Fibrosis on Liver Histology	Jan 2024	Feb 2024
NCT05412004	Sleep Apnea	Obstructive Sleep Apnea Master Protocol GPIF: A Study of Tirzepatide (LY3298176) in Participants With Obstructive Sleep Apnea (SURMOUNT-OSA)	3	469	Percent Change from Baseline in Apnea-Hypopnea Index (AHI)	Mar 2024	Mar 2024
NCT04847557	HFpEF	A Study of Tirzepatide (LY3298176) in Participants With Heart Failure With Preserved Ejection Fraction and Obesity (SUMMIT)	3	700	A Hierarchical Composite of All-Cause Mortality, Heart Failure Events, 6-minute Walk Test Distance (6MWD) and Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS) Category	Jun 2024	Jul 2024
NCT05536804	CKD	A Study of Tirzepatide (LY3298176) in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes (TREASURE-CKD)	2	140	Change from Baseline in Kidney Oxygenation in Participants With or Without T2D [Time Frame: Baseline, Week 52]; Blood oxygenation-level dependent magnetic resonance imaging (BOLD MRI)	Oct 2025	Nov 2025

These two giant studies are the right ones for Lilly to run. By showing the effect of Tirzepatide use on mortality and chronic health cost outcomes in persons with both obesity and Type 2 diabetes, Lilly should be able to remove any doubt that GLP-1 agonists are highly beneficial for society from both an outcomes and costs perspective. Importantly, the second study will be completed by the end of 2024 which means broad reimbursement for Tirzepatide could be in place by 2025.

Source: https://investor.lilly.com/static-files/76c6788c-ea65-4c9f-9a57-e8bceb2fa290

Novo Nordisk Outcomes Trials for CagriSema

Phase 3 trial programme in type 2 diabetes, REIMAGINE, expected to initiate in second half of 2023

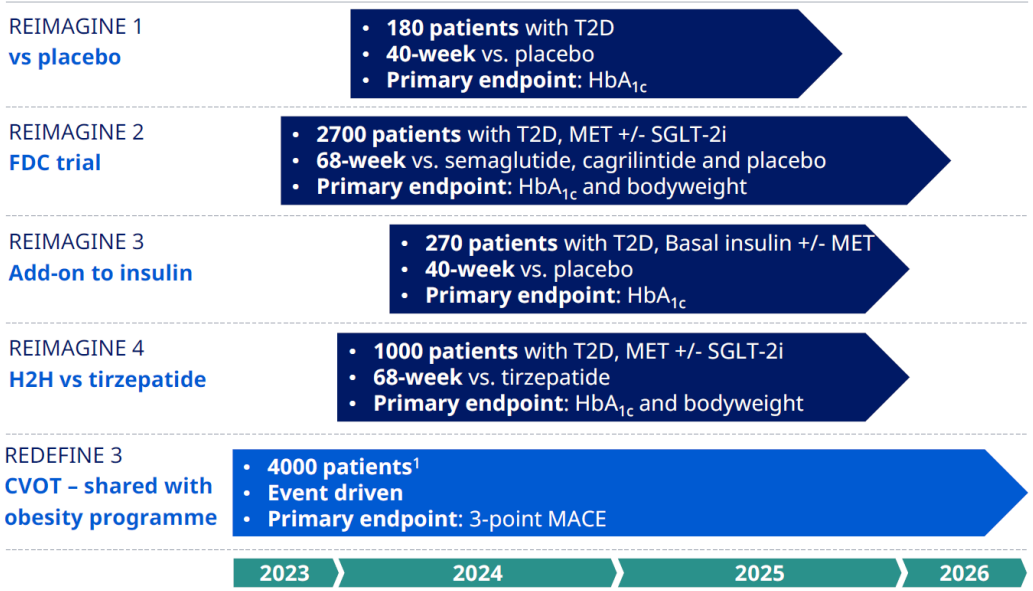
CagriSema characteristics

CagriSema is a fixed dose combination of injectable cagrilintide 2.4 mg and semaglutide 2.4 mg

Phase 3a programme with CagriSema in T2D:

- Aims to confirm efficacy and safety across four global trials
- Expected completion during 2025/2026

Global phase 3 trial programme



1 65% of patients with T2D, 35% without T2D
FDC: Fixed dose combination; T2D: Type 2 Diabetes; H2H: Head-to-head; CVOT: Cardiovascular outcomes trial; 3P: Three point; MACE: Major adverse cardiovascular event; MET: Metformin; SGLT-2i: sodium-glucose co-transporter-2 inhibitor
Note: CagriSema is a fixed dose combination of injectable cagrilintide 2.4 mg and injectable semaglutide 2.4 mg

Source: https://www.novonordisk.com/content/dam/nncorp/global/en/investors/pdfs/ada/ada-investor-presentation-2023.pdf

Novo's strategy is a little different than Lilly's. They are running a smaller outcomes trial (4,000 subjects vs. 28,000) that will be event driven. Their study will have 65% T2D patients. They are also running a head-to-head study of Cagri against tirzepatide.

It's interesting to see that Novo is doing their big trial with CagriSema® rather than Semaglutide.

We are struck by the comparison of Merck and BMS in the checkpoint field. Merck, in part, ended up with higher share, by outspending BMS on clinical studies – building a broader label. Depending on how these studies pan out, Lilly may do something similar.

The need for these large outcome studies is going to be important for emerging contestants such as Amgen, Carmot, Viking and Sun.

So Just How Big is the Potential Insured Market?

It's possible to defend insured market size estimates of $50 billion to $200 billion. It all depends on how many individuals go on the drugs. The history of statin usage would support numbers at the high end of this range.

Prevalence of Obesity in the United States: **41.9%** (CDC).

Number of persons in the U.S.: **332 million** (US Census)

Number of obese persons in the U.S.: **139 million**

Market Sizing:

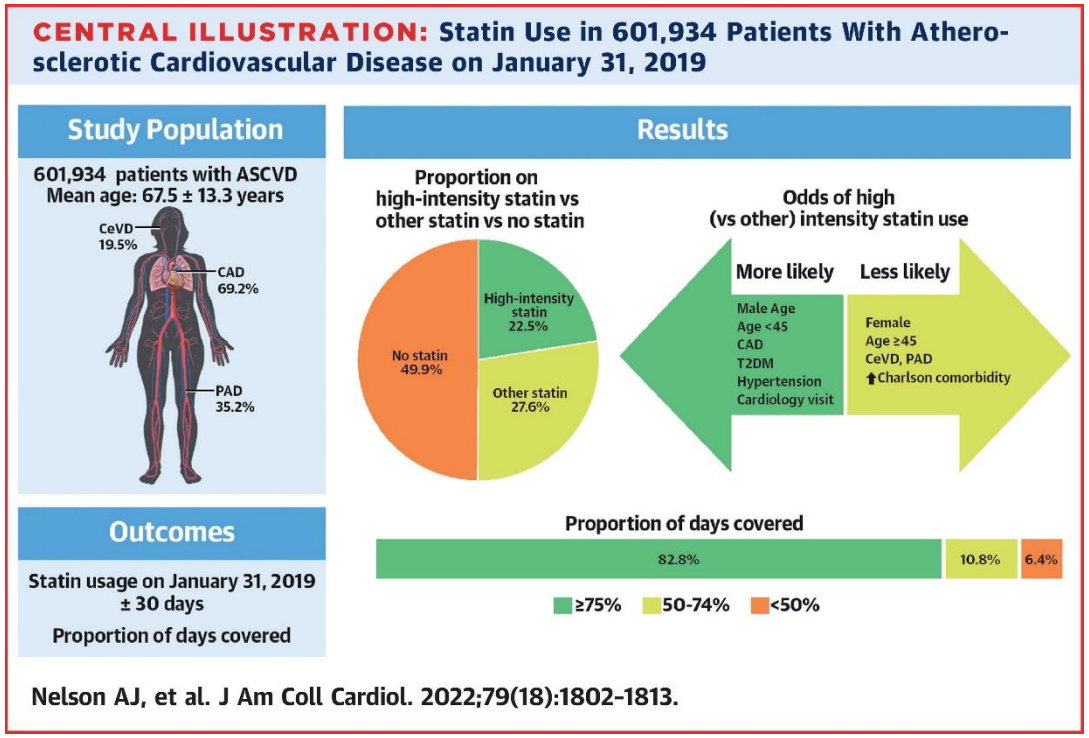
10% of U.S. obese persons (4% of population) on GLP-1s @$5000 a year: **$69.5 billion**

20% of U.S. obese persons (8% of population) on GLP-1s @$5000 a year: **$139 billion**

30% of U.S. obese persons (12% of population) on GLP-1s @$5000 a year: **$208.5 billion**

The actual total addressable market (TAM) for a U.S. obesity drug at $5k/year in the U.S. is a mind-boggling $695 billion. That's close to the entire Medicare budget.

Comparison Point: Fewer Americans have high cholesterol than obesity (around 30%). Approximately 39 million Americans use statins (over 18% of the total adult population). Roughly 50% of Americans with atherosclerosis take a statin every day.



Nelson AJ, et al. J Am Coll Cardiol. 2022;79(18):1802-1813.

Sources: https://www.cdc.gov/obesity/data/prevalence-maps.html, https://www.cdc.gov/nchs/products/databriefs/db177.htm, https://www.uspharmacist.com/article/hypercholesterolemia-trends

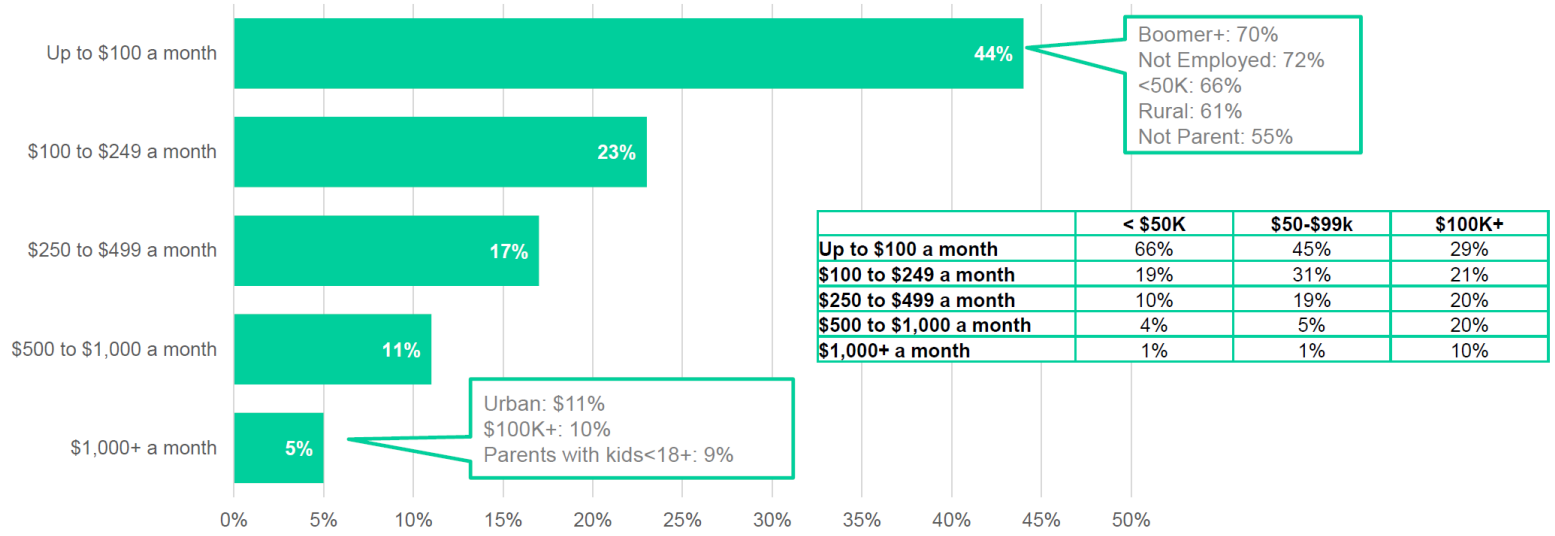
But the Real Argument for Market Size is the Consumer

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.

STAT-HARRIS POLL: OBESITY AND WEIGHT LOSS MEDS.

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

Without insurance, the cost of popular weight-loss medicines (e.g., Ozempic, Wegovy, Mounjaro, etc.) can cost close to $1,000 a month. How much would you be willing to spend out-of-pocket each month on weight-loss medicines?
(Base: Those who are interested in weight loss meds, n=1,017)



	< $50K	$50-$99k	$100K+
Up to $100 a month	66%	45%	29%
$100 to $249 a month	19%	31%	21%
$250 to $499 a month	10%	19%	20%
$500 to $1,000 a month	4%	5%	20%
$1,000+ a month	1%	1%	10%

Source: STAT-Harris Poll (n=2,046 US Adults 18+, Fielded June 2-4, 2023)

8

Americans are willing to spend a fair bit on obesity drugs out of their own pocket.

The survey at left reported by *Stat*+ on June 21 shows the percent that would be willing to spend money on GLP-1's without insurance coverage.

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

So Just How Big is the Potential Private Pay Market?

It's possible to defend private pay U.S. market size estimates of $70 billion to $200 billion. This is quite unusual as most private pay markets for "consumer-friendly" type drugs such as Viagra® are much smaller.

Prevalence of Obesity in the United States: **41.9%** (CDC).

Number of adults in the U.S.: **258 million** (US Census)

Number of obese adults in the U.S.: **108 million**

Total Market Sizing:

Monthly Price Point of $1000: 5% of 108mm people @$12,000 annually = **$154.8 billion**

Monthly Price Point of $500: 11% of 108mm people @$9000 annually = **$170.3 billion**

Monthly Price Point of $375: 17% of 108mm people @$4500 annually = **$197.4 billion**

Monthly Price Point of $175: 23% of 108mm people @$2100 annually = **$124.6 billion**

Monthly Price Point of $50: 44% of 108mm people @$600 annually = **$68.1 billion**

We use the price range midpoints from the Stat/Harris poll in the analysis at left and estimate the implied market size from the number of persons interested in obesity drugs at each price point.

Importantly, the consumer market is less dependent on outcomes data and more dependent on strength of the drug and perceived safety and ease of use.

Consumers obviously would prefer orals and a lower price point, if possible.

A large fraction of Americans already spend over $1,000 a year on iPhones. Perhaps they would do the same to stay slim.

Sources: https://www.cdc.gov/obesity/data/prevalence-maps.html, https://www.cdc.gov/nchs/products/databriefs/db177.htm, https://www.uspharmacist.com/article/hypercholesterolemia-trends

The iPhone Market Analogue

Is it possible to have a $100 billion+ consumer product? Consumers must really want a product and be willing to pay for it. Worldwide iPhone sales last year were $205 billion (about 40% was the U.S.). Given the consumer mania for obesity drugs we see no particular reason why drug revenue with this order of magnitude is unachievable.

Apple Inc.

CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS (Unaudited)
(In millions, except number of shares which are reflected in thousands and per share amounts)

	Three Months Ended		Twelve Months Ended	
	September 24, 2022	September 25, 2021	September 24, 2022	September 25, 2021
Net sales:				
Products	$ 70,958	$ 65,083	$ 316,199	$ 297,392
Services	19,188	18,277	78,129	68,425
Total net sales [1]	90,146	83,360	394,328	365,817
Cost of sales:				
Products	46,387	42,790	201,471	192,266
Services	5,664	5,396	22,075	20,715
Total cost of sales	52,051	48,186	223,546	212,981
Gross margin	38,095	35,174	170,782	152,836
Operating expenses:				
Research and development	6,761	5,772	26,251	21,914
Selling, general and administrative	6,440	5,616	25,094	21,973
Total operating expenses	13,201	11,388	51,345	43,887
Operating income	24,894	23,786	119,437	108,949
Other income/(expense), net	(237)	(538)	(334)	258
Income before provision for income taxes	24,657	23,248	119,103	109,207
Provision for income taxes	3,936	2,697	19,300	14,527
Net income	$ 20,721	$ 20,551	$ 99,803	$ 94,680
Earnings per share:				
Basic	$ 1.29	$ 1.25	$ 6.15	$ 5.67
Diluted	$ 1.29	$ 1.24	$ 6.11	$ 5.61
Shares used in computing earnings per share:				
Basic	16,030,382	16,487,121	16,215,963	16,701,272
Diluted	16,118,465	16,635,097	16,325,819	16,864,919
[1] Net sales by reportable segment:				
Americas	$ 39,808	$ 36,820	$ 169,658	$ 153,306
Europe	22,795	20,794	95,118	89,307
Greater China	15,470	14,563	74,200	68,366
Japan	5,700	5,991	25,977	28,482
Rest of Asia Pacific	6,373	5,192	29,375	26,356
Total net sales	$ 90,146	$ 83,360	$ 394,328	$ 365,817
[1] Net sales by category:				
iPhone	$ 42,626	$ 38,868	$ 205,489	$ 191,973
Mac	11,508	9,178	40,177	35,190
iPad	7,174	8,252	29,292	31,862
Wearables, Home and Accessories	9,650	8,785	41,241	38,367
Services	19,188	18,277	78,129	68,425
Total net sales	$ 90,146	$ 83,360	$ 394,328	$ 365,817

Source: Apple earnings report, 2022, https://www.apple.com/newsroom/2022/10/apple-reports-fourth-quarter-results/ Photo from Apple web site.

Disclosure

STIFEL | Healthcare

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