

BARON INSIGHTS FEATURE

A Multi-Billion-Dollar Drug Market



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Key Takeaways

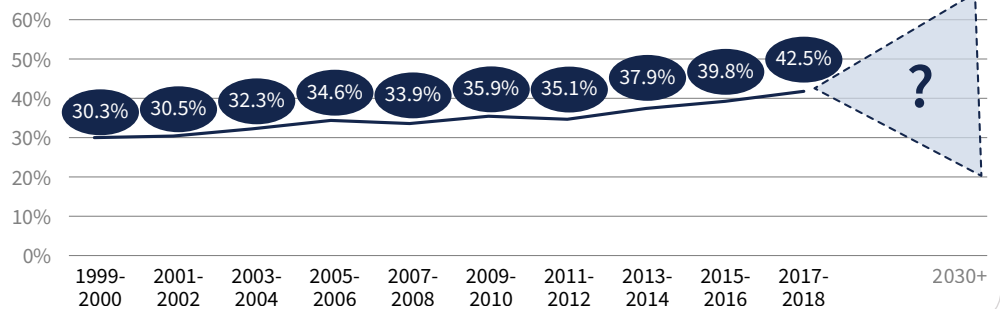
- The new obesity drugs have the potential to be the largest drug class in the history of health care.
- We estimate a \$150 billion opportunity in the U.S. alone.
- Eli Lilly and Novo Nordisk dominate the space, but we see room for multiple players to win.

Without question, the biggest development in health care in 2023 was the exploding popularity of a new class of weight loss drugs. With the potential to slow down, stop, or even reverse an obesity crisis that has been spiraling out of control – particularly in the United States but more and more abroad as well – these drugs have generated excitement on both Wall Street and Main Street.

It is hard to underestimate how big the market for these drugs could be. Globally, an estimated one billion people are obese,¹ meaning that they have a BMI (body mass index) of 30 or more.² In the U.S. alone, 42.5%, or more than two out of five, adults are classified as obese.³ This percentage has been increasing at an alarming rate; in 1980, it was just 13%.⁴ Some experts believe that, at the current rate, by 2030, the percentage of obese adults in the U.S. could reach 50%.⁵

Given this vast patient population, weight loss drugs potentially could be the largest drug class in the history of health care, representing a \$150 billion opportunity in the U.S. alone. In this piece we describe the origin of and science behind these drugs, the

Prevalence of Obesity in the U.S. Population



potential impact they could have on a wide array of obesity-related diseases, and where we are seeing investment opportunities.

A brief history of GLP-1s

First for diabetes

The new weight loss drugs – known as GLP-1s – were originally developed to treat Type 2 diabetes. These drugs act like the natural hormone GLP-1 or “glucagon-like peptide 1”, which stimulates the production of insulin, which helps diabetics control their blood sugar. However, the natural GLP-1 hormone is very short-lived, disappearing within minutes, so scientists developed longer lasting drugs that mimic the GLP-1 action.

¹ World Health Organization. World Obesity Federation.

² BMI is calculated by dividing a person’s weight in kilograms by the square of height in meters.

³ Center for Disease Control. National Health and Nutrition Examination Survey.

⁴ National Health and Nutrition Examination Survey II.

⁵ Ward 2019. <https://www.nejm.org/doi/full/10.1056/NEJMsa1909301>

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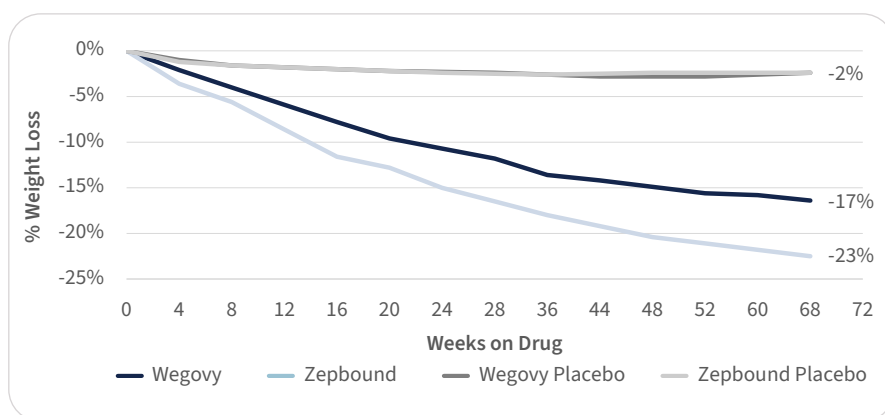
Since the first GLP-1 drug was approved to treat diabetes in 2005, there have been several generations of these drugs, each more convenient and more effective in controlling blood sugar than its predecessor. When GLP-1 drugs were first launched, doctors reserved them for use in hard-to-treat cases. But with growing familiarity and newer versions, doctors are increasingly prescribing GLP-1s earlier in a patients' course of diabetes. By 2018, we estimate roughly 4% of Type 2 diabetics in the U.S. were on a GLP-1.⁶

Earlier generations of GLP-1 drugs had only a limited impact on weight loss. Over time, scientists realized that the GLP-1 drugs had important effects on the brain that regulate appetite and refined the drugs to be more effective on those mechanisms. The newest generation of GLP-1 drugs – Novo Nordisk A/S's Ozempic and Eli Lilly and Company's Mounjaro⁷– cause significant weight loss and have driven an acceleration in adoption by diabetics. We estimate that at the end of 2023, nearly five million patients, or roughly 15% of Type 2 diabetics, were on GLP-1 drugs, representing a 50% increase from 2022.⁸ We think GLP-1s should be considered the standard of care in Type 2 diabetes and that, over time, a majority of diabetes patients should be on GLP-1 drugs.

Now for obesity

Given the impressive weight loss that these newest GLP-1 drugs produced in diabetics, scientists studied the drugs in non-diabetic obese patients, where they drove even more impressive weight loss – on the order of 15% to 20% of a patient's starting weight. Ozempic, rebranded as Wegovy, and Mounjaro, rebranded as Zepbound, were approved specifically for obesity in 2021 and 2023, respectively.

Obesity is a chronic disease that has broad implications for a person's health. Excess weight is closely related to metabolic syndrome and cardiovascular disease.



Evidence is accumulating that using GLP-1 drugs to treat obesity can help save lives. In a clinical trial, Wegovy reduced an obese person's risk of heart attack, stroke, or death by 20%. In the same patient population, the risk of death fell by 19%, heart attacks fell by 28%, and hospitalization due to heart failure by 18%.

So far, there have been no major safety concerns seen with GLP-1s in the 18 years they have been on the market.⁹ The main side effects are nausea, vomiting, and other gastrointestinal issues, which are typically mild and tend to go away after the initial dose titration period. The effects relate to how the drug works through the brain receptors and the slowdown in gastric emptying. To avoid or mitigate these effects, it is important that patients take the drug under the supervision of a medical professional.

We are still in the very early innings of using GLP-1s to treat obesity. We estimate that at the end of 2023, one million people in the U.S. were on GLP-1 drugs for weight loss (and not for diabetes), which represents only 1% of the eligible population.

A massive market opportunity

We estimate more than half of the U.S. adult population, or 137 million people, are eligible for GLP-1s per the FDA approved label. This number includes 32 million with diabetes, 87 million who are obese, and 18 million who are overweight with comorbidities such as high blood pressure or cholesterol.

Although it can take decades to reach peak penetration for some medications, we think obesity treatments will scale more rapidly because obesity is not asymptomatic, patients are eager to get treatment, and awareness is high.

The list price for Wegovy and Zepbound is \$12,000 to \$16,000/year. Insurance companies pay around \$6,000/year after negotiated discounts and rebates. Eli Lilly is also offering a cash pay discount price of \$6,600/year for patients without coverage.¹⁰

While the current supply-constrained market provides little incentive for companies to lower prices, we expect the net price of these drugs to come down over time as access grows, as has been the case with previous mass market primary care drugs. Although health economists have suggested GLP-1s are cost-effective at current prices,¹¹ we would not be surprised to see net pricing in the \$3,000/year range in the future.

⁶ Baron Capital analysis of Symphony Health Prescription Data.

⁷ Mounjaro and other drugs in the pipeline work through other pathways as well. For example, Mounjaro is also a GIP-receptor agonist, which has additional weight loss and metabolic benefits.

⁸ Baron Capital analysis of Symphony Health Prescription Data.

⁹ Like almost any drug, there is a small risk of serious side effects. Please consult your doctor.

¹⁰ First Data Bank. Symphony Health. Eli Lilly Company Website. NovoNordiskCompany Website. Baron Capital Analysis.

¹¹ Institute for Clinical and Economic Review (ICER). https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Final_Evidence_Report_and_Meeting_Summary_122223.pdf Olivieri 2024. <https://www.nature.com/articles/s41366-024-01467-w#MOESM1>

Today

List "sticker" price	\$12k-\$16k/year
What manufacturer receives	~\$6k/year
Patient co-pay with insurance	~\$25/Rx
Patient whose insurance doesn't cover the medication	\$6.6k/year (discounted cash price)

In the future?

As low as \$2k-\$3k/year as supply and access grows?

In summary, we estimate a \$100 billion to \$150 billion/year opportunity in the U.S. alone, assuming that, in 10 to 15 years, 60% of diabetics and 30% of other eligible obese patients are paying \$2,000 to \$3,000/year for a GLP-1. The overseas market offers even more opportunity.

At the same time, we believe that, for several reasons, many investors underestimate the sheer size of the long-term opportunity.

- **Near-termism:** Most investors are focused on the very near term, and not three or more years down the road, let alone 10 to 15.
- **Size of launch:** This is the biggest primary care launch since statins and blood pressure medications came to market in the 1980s and 1990s. For reference, immunology drugs represent \$77 billion/year and diabetes drugs \$74 billion/year in the U.S. despite treating far fewer patients.
- **Newness of disease:** Obesity as a disease is relatively new. In 1980, just 13% of Americans were obese, and excess weight was viewed as a lifestyle choice, not a disease.
- **History of failure:** The track record of failed prior weight loss drugs has raised the question whether GLP-1s will ultimately fail as well.

Obviously, we feel differently. While these drugs have boosted the share price of Eli Lilly and Novo Nordisk along with several smaller rivals, we see plenty of runway for future growth. We think there is compelling evidence to support our view that the new obesity drugs have the potential to be the largest drug class in the history of health care.

What's next?

Given the enormous potential, competitors of Novo Nordisk and Eli Lilly are scrambling to get into the space. We are currently tracking more than 50 weight loss drugs in development. In the meantime, both Eli Lilly and Novo Nordisk have next-generation versions in Phase 3 trials that drive even greater weight loss and further generations in earlier stages of development. Eli Lilly also has a once-daily pill developed for less severe patients in late-stage trials. Companies are also looking at developing drugs with additional mechanisms to drive even greater weight loss or provide other benefits, such as treating fatty liver disease.

Ultimately, incumbency and first-to-market status will matter unless a new drug is meaningfully better. However, we see room for multiple players to win.

Stocks to watch

Eli Lilly and Novo Nordisk are the undisputed leaders in the GLP-1 space, and we think the market will remain a duopoly at least until 2027 or 2028.

We have been investing in this space primarily through ownership of Eli Lilly. In addition to Zepbound, the company has a pipeline of next generation GLP-1s, including a triple hormone receptor agonist, which

has shown even greater weight loss in clinical trials, and a daily oral GLP-1, which should expand market access because it is cheaper and easier to manufacture and offers the convenience of a daily pill.

Eli Lilly is also a leader in treatments for Alzheimer's disease, oncology, and immunology. It has been expanding its internal pipeline with early-stage external assets that could contribute to growth in the out years.

While its shares trade at a high valuation on near-term estimates, we think Eli Lilly's longer-term prospects make this stock worth holding. We view Eli Lilly as a unique company with a compelling growth profile, strong competitive advantages, and a top-rated management team. Its R&D productivity is well above the industry average, and it has first mover advantage, clinical expertise, manufacturing capabilities, and payer relationship advantages in the diabetes and obesity markets.

We estimate sales will triple and earnings will quadruple by 2030. We also think Eli Lilly can continue to grow its top line above peers beyond 2030, which supports a multiple higher than where mature pharmaceutical companies typically trade.

In addition to Eli Lilly, we have shares in two pick-and-shovel companies that manufacture products for injectable medicines. West Pharmaceutical Services, Inc. makes auto-injectors and syringe plungers. We think GLP-1s could add a couple of points of

Stocks to watch



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annual revenue growth to its 7% to 9% long-term target. Stevanato Group S.p.A. makes glass syringes and cartridges and will soon start manufacturing auto-injectors as well. As with West, we believe GLP-1s could add another 2% to its current targeted low-teens annual growth.

Novo Nordisk is following up on the success of Wegovy with another injectable called CagriSema that combines the active ingredients in Wegovy with another target. Trial data suggests that it may be even more effective in driving weight loss.

Eli Lilly and Novo Nordisk have set high bars in terms of efficacy, safety, convenience, but we are following a number of other pipeline drugs. We believe that, in the future, rather than a “one size fits all” solution for obesity, there will be different treatments available to treat different endpoints, whether it is pure obesity, diabetes, heart failure, fatty liver, or something else.

A small biotech company called Viking Therapeutics, Inc. has a competitor akin to Zepbound. Its share price has more than doubled on news of positive results from its Phase 2 trial in late February. Amgen Inc. has a Phase 2-ready product called MariTide that adds a different mechanism. Roche Holding AG, a large pharmaceutical, recently acquired a company with a Phase 2-ready injectable asset similar to Zepbound. Another large pharmaceutical, Pfizer Inc., has been working on developing an obesity drug, but it recently stumbled with two assets that do not appear to be competitive.

A changing obesity-related landscape

Obesity drugs could potentially have a negative impact on other types of treatments related to obesity. In fact, the market reacted quickly to news demonstrating these drugs’ ability to help people shed pounds by punishing companies that develop products or treatments for obesity-related issues. While we suspect the market may have overreacted, we do see GLP-1s reshaping aspects of the health care landscape in certain respects over the long term. In the meantime, several of these suddenly disfavored stocks are now trading at what we think are attractive valuations.

The most direct impact, in our view, will be on bariatric surgeries. We would expect many candidates for bariatric surgery to try a GLP-1 first, even if some ultimately opt for surgery. This could be relevant to medical device companies like Intuitive Surgical, Inc., which makes the da Vinci surgical robot. While Intuitive has commented that it is seeing a slowdown in bariatric surgeries using its robot, this surgery represents less than 5% of its business, and the company has many other growth drivers.

Type 2 diabetes is another area of possible impact. GLP-1s are very effective for diabetics and can help patients delay or even prevent the need to start insulin treatments. We can imagine that, in 10 or 20 years, there will be fewer insulin-dependent diabetics.

This development could impact a company like DexCom, Inc., which makes continuous glucose monitors (CGMs) linked to a patient’s or caregiver’s smart phone or smart watch through the cloud. However, we think CGMs will remain a key tool for diabetics, including non-insulin-dependent diabetics. This latter group represents a very large addressable market -- five times the number of insulin-dependent patients -- few of which currently use CGMs.

GLP-1s could also affect treatments for sleep apnea, a potentially serious disorder in which breathing repeatedly stops and starts. Obese people are prone to sleep apnea because extra neck fat can cause the airway to collapse. We think GLP-1s will be effective for these patients.

However, we know that, even with significant weight loss, many patients will still have sleep apnea, because weight loss does not help with cases where the tongue blocks the airway. We like Inspire Medical Systems, Inc., which makes a device that stimulates the hypoglossal nerve, causing the tongue to move forward and open the airway. We estimate only 5% of eligible patients are getting treated with Inspire therapy today.

Conclusion

Obesity is a serious health crisis that continues to escalate. It is associated with many serious health consequences, including heart disease, stroke, diabetes, osteoarthritis, and cancer. According to the World Health Organization, 44% of diabetes, 23% of ischemic heart disease, and as much as 41% of certain cancers can be attributed to being overweight or obese. Obesity can have unexpected negative impacts as well. While just over 2% of U.S. adults who contracted COVID-19 were hospitalized, more than 30% of those hospitalizations were attributed to obesity.¹²

In addition, obesity and its related complications are major drivers of rising health care costs, diminished health-related quality of life, and the recent decline in U.S. life expectancy. In 2016, the aggregate medical cost due to obesity and its associated chronic diseases was estimated to be \$480 billion, with indirect costs totaling \$1.24 trillion once work loss costs are factored in.¹³

The new weight loss drugs have the potential to have a significant impact on this crisis. They have been shown to reduce weight by 15% to 20%, with few major side effects or safety concerns. We think people will be motivated to try GLP-1s for health, lifestyle, and aesthetic reasons. Over time, we expect this space could represent the largest growth opportunity in the history of health care, one in which multiple players can win.

¹² Sources: National Library of Medicine – National Center for Biotechnology Information; Center for Disease Control

¹³ Milken Institute.

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Portfolio holdings as a percentage of net assets as of 12/31/2023 for securities mentioned are as follows: Eli Lilly and Company – 9.6%; West Pharmaceuticals, Inc. – 1.9%; Stevanato Group, S.p.A. – 1.1%.

The Fund did not have a position in the following companies as of 12/31/2023: Novo Nordisk, Inc., Amgen Inc., Roche Holding AG, Viking Therapeutics, Inc., Pfizer Inc. Baron Health Care Fund top 10 holdings as of 12/31/2023: Eli Lilly and Company – 9.6%, UnitedHealth Group Incorporated – 9.4%, Intuitive Surgical, Inc. – 4.8%, Merck & Co., Inc. – 4.5%, Thermo Fisher Scientific Inc. – 4.5%, Vertex Pharmaceutical Incorporated – 4.4%, Boston Scientific Corporation – 4.0%, Rocket Pharmaceuticals, Inc. – 3.7%, argenx SE – 3.6%, Zoetis Inc. – 3.0%.

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