

Sector Insights

What investors should know about GLP-1 drugs

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Summary

In Health Care, a sector otherwise lacking in excitement, GLP-1s have captured investor attention in a major way. Given that over 40% of the U.S. population has obesity and over 70% is considered overweight, the interest in GLP-1s is understandable. While the drugs are expensive, the costs associated with obesity and obesity-related health conditions are especially significant. Looking forward, the market for weight-loss drugs should continue expanding rapidly as various factors will likely make them more accessible to patients. Meanwhile, a growing list of other potential indications for GLP-1s could further expand the ultimate market opportunity.

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Why have GLP-1 drugs garnered so much attention?

GLP-1 drugs, or glucagon-like peptide 1 agonists, have enjoyed considerable success for the treatment of obesity and have been the obvious bright spot in the Health Care sector over the past two years. Were it not for the overwhelming interest and excitement surrounding artificial intelligence (AI), we believe the hysteria over GLP-1s would have been even more significant. GLP-1 drugs have actually been around for nearly 20 years for use against diabetes but have gained prominence in the past year or so due to their effectiveness against obesity.

Importantly, unlike some so-called “miracle weight-loss drugs” of the past, the clinical data for GLP-1s has generally remained favorable to date, and the body of data continues to build and expand into other possible indications. The success of effective drugs for obesity clearly has far-reaching implications for health-care systems and patient health. Longer term, the rapidly expanded use of GLP-1s could have significant near-term implications for the federal budget in the U.S., while a favorable impact on the obesity epidemic could have important longer-term implications on the health system. More on this later.

While clinical data can be fickle and change quickly, the nature of GLP-1 drugs and their lengthy history would appear to limit (but not eliminate) the risk of unexpected, adverse clinical outcomes. The potential market opportunity for GLP-1s is tremendously fluid, with additional clinical data for obesity and several other indications emerging. Recently, favorable clinical data on GLP-1s for both sleep apnea and dementia has emerged, providing another potential boost to their long-term market opportunity. But given that over 70% of adults in the U.S. are considered overweight or obese, the market opportunity for obesity alone is tremendous.

The obesity epidemic

Obesity is a significant issue in the U.S. and globally, as are the health-care costs associated with obesity and obesity-related conditions. Many estimates suggest the annual health-care costs associated with obesity run in excess of \$200 billion in the U.S., though a Milken Institute study put the total annual costs, direct and indirect, of chronic diseases caused by obesity and excess weight at \$1.72 trillion in the U.S. To make that even more concerning, that study used health-care costs from 2016 — eight years ago — to arrive at this estimate.

While it is exceedingly difficult to arrive at a consensus for the costs of obesity, the numbers are daunting. According to the Centers for Disease Control (CDC), approximately 74% of adults are considered to be either overweight or have obesity in the U.S., of which approximately 42% have obesity. Not surprisingly, these numbers have trended higher over time. Globally, 39% of the population has obesity, a number that is expected to increase to 51% by 2035.¹ From an insurance perspective, whether commercial or government (that is, Medicare and Medicaid), these alarming numbers and trends present quite the conundrum. While the potential cost savings of lower rates of obesity would benefit insurance companies from a longer-term perspective — the chart below shows the cost differential for enrollees with or without an obesity diagnosis — coverage remains unavailable for a large number of GLP-1 users and potential users as many insurance companies remain in the process of determining their coverage approach. As of October 2023, a survey of 205 companies showed that 76% covered GLP-1 drugs for diabetes, but only 27% covered GLP-1 drugs for weight loss. Another 13% were considering covering GLP-1 drugs for weight loss.² Going forward, we expect coverage to continue to expand with the growing evidence of effectiveness for other conditions and comorbidities.

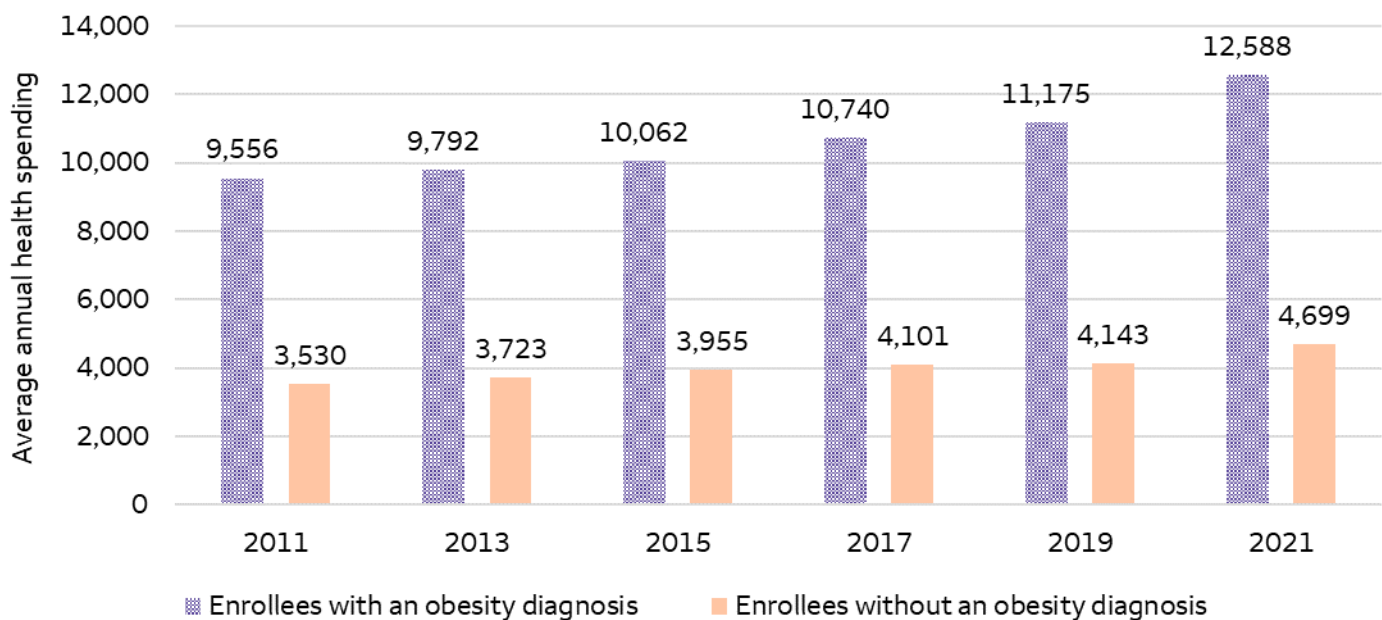
1. Jeffrey Kluger, “More Than Half of the World Will Be Obese By 2035, Report Says,” Time, March 21, 2023.

2. Cheryl Winokur Munk, “Most employer health plans don’t cover new blockbuster weight loss drugs, but that’s going to change,” CNBC, February 16, 2024.

Facts and figures associated with obesity

- Nearly 90% of U.S. adults diagnosed with diabetes were considered overweight or obese according to the CDC. Roughly 28% were considered overweight, 46% were considered obese, and 16% suffered from extreme obesity.
- According to the American Heart Association, obesity-related cardiovascular deaths tripled between 1999 and 2020, and nearly 130 million adults suffer from cardiovascular disease.
- Two-thirds of adults diagnosed with arthritis in the U.S. are overweight or suffer from obesity according to the CDC.
- Obesity is also closely associated with several other conditions, including sleep apnea and kidney disease. Not surprisingly, obesity is also associated with higher health-care costs, as shown in the figure below.

Average annual health spending of enrollees with or without an obesity diagnosis



Source: Peterson-KFF Health System Tracker. Data as of July 29, 2024. Includes enrollees with insurance plans from large employers who have a diagnosis of overweight or obesity.

Evaluating the current market landscape

GLP-1 medications have existed since 2005 and were originally approved for the treatment of type 2 diabetes. A growing body of anecdotal data made it clear that GLP-1s also provided a weight loss benefit, however, and Novo Nordisk A/S's (or Novo's) Wegovy was first approved as a treatment for obesity in the summer of 2021. Wegovy is essentially a higher-dose version of Novo's Ozempic diabetes drug, with both drugs featuring semaglutide as the active ingredient. Next, Eli Lilly and Company (Eli Lilly or Lilly) officially entered the GLP-1 market with Zepbound, or tirzepatide, which gained Food and Drug Administration (FDA) approval in November 2023. Zepbound is Lilly's obesity version of Mounjaro, which is specifically approved for type 2 diabetes.

Enthusiasm for GLP-1s has been driven by their effectiveness for weight loss. For example, clinical trials showed users of Wegovy losing an average of 15% of their body weight and users of Zepbound losing an average of 20%. The combination of semaglutide and lifestyle changes led to about 33.7 pounds of weight loss, and users have reported relatively mild side

effects for the most part (more on this later). Still, not all patients benefit from GLP-1s (10% – 15% experience little weight loss), and side effects and cost have led to a rather high dropout rate for patients. In addition, many patients gain weight back when discontinuing GLP-1 usage. Nonetheless, the success of GLP-1s has been unprecedented to date.

While competition is on the way, we expect Novo Nordisk (Wegovy) and Eli Lilly (Zepbound) to remain the dominant players in the GLP-1 market for the foreseeable future — this has to do with their currently approved products as well as their efforts to rapidly develop follow-on products. Given the rapid growth of the GLP-1 market, however, it certainly is no surprise that many other companies are working to develop similar compounds. Several compounds are either in or entering Phase 3 trials in the near future, though regulatory and manufacturing hurdles should prevent any near-term competition. In addition, a clinical bar has been set that new entrants to the market must meet or exceed. Amgen Inc. (Amgen), for example, is developing MariTide, which is intended to have longer-lasting effects with less-frequent dosing. We believe MariTide is unlikely to gain FDA clearance until late 2026 or early 2027, and as a result, Lilly and Novo Nordisk retain a meaningful window of expected market dominance. According to forecasts from Bloomberg, Eli Lilly and Novo Nordisk are expected to dominate the GLP-1 anti-obesity market for the foreseeable future.

Key takeaways

Enthusiasm for GLP-1s has been driven by their effectiveness for weight loss, with clinical trials showing users losing 15% – 20% of their body weight.

While significant, unexpected side effects could derail the GLP-1 market, we think their lengthy history and the fact that their method of action is well understood mitigates that risk.

What could change? Well, the emergence of significant, unexpected side effects for GLP-1s could derail the market. But given the lengthy history of these drugs for type 2 diabetes, we believe the chances of that occurring continue to diminish. Side effects are certainly an issue and have led to a fairly meaningful dropout rate for individuals taking GLP-1s, so we certainly do not dismiss this risk. But the method of action of this category of drugs is well understood, and thus the risk of surprises continues to ease. As next-generation compounds emerge, however, the side-effect risk will be at least somewhat renewed and will remain an area worthy of continued observation.

Estimated size of the GLP-1 market

Estimates regarding the size of the potential market for GLP-1 drugs have been extremely fluid. Over the past 18 months, market projections have been increased repeatedly and significantly, reflecting growing public awareness, strong clinical data, and the potential for other uses of GLP-1 drugs going forward.

Looking at current estimates of the GLP-1 market, we note that in just a few short months, third-party estimates have increased significantly — most now suggest a market opportunity well in excess of \$100 billion, with some expectations as high as \$150 billion by the early 2030s according to a recent Reuters story.³ As mentioned above, market-size estimates and expectations have continued to move higher over the past year, driven by growing consumer awareness; favorable clinical data, especially Novo Nordisk's SELECT Trial in August 2023; and increasing manufacturing capacity and supply. Expanding reimbursement should also drive market growth. In one example, Medicare and Medicaid have historically not covered anti-obesity medications, but a March 8, 2024 news release announced coverage of Wegovy for adults with diagnoses of overweight or obese along with cardiovascular disease. This change in policy should drive increased GLP-1 usage among individuals on Medicaid and Medicaid, a group that represented roughly 38% of the U.S. as of 2022.⁴ Going forward, acceptance of GLP-1s for indications other than obesity or in conjunction with obesity should allow for more widespread coverage and expanded usage.

3. Hollie Adams and Brendan McDermid, "Weight-loss drug developers line up to tap market worth \$150 billion," Reuters, July 17, 2024.

4. Katherine Keisler-Starkey, Lisa N. Bunch, and Rachel A. Lindstrom, "Health Insurance Coverage in the United States: 2022," United States Census Bureau, September 12, 2023.

Understanding GLP-1 drugs — Mechanisms and next-generation variants

As mentioned, GLP-1 drugs have been available and prescribed for nearly 20 years in the management of type 2 diabetes. The primary use of these drugs started to transition toward obesity within the past few years, however, and given the demonstrated success for that indication, manufacturers have had trouble keeping up with demand in recent quarters. But how do these drugs work as it relates to obesity?

How GLP-1 drugs work

In reasonably simple terms, GLP-1 receptor agonists increase the secretion of insulin, which in turn helps lower blood-sugar levels. In addition, GLP-1s help limit the release of glucagon, a hormone that increases blood-glucose levels. Essentially, insulin lowers blood sugar levels while glucagon raises them, and GLP-1 drugs act on both hormones. In addition, GLP-1s have been shown to reduce or slow the rate at which food leaves a patient's stomach (known as gastric emptying). This results in an extended feeling of fullness following meals and thus helps reduce a patient's appetite, which is similar to the method of action for gastric bypass surgery (that is, reducing the size of a patient's stomach).

Next-generation obesity drugs

Next-generation obesity drugs will look to provide superior outcomes, including weight loss, while reducing side effects. There are multiple ongoing development programs across the pharmaceutical and biotech industries looking at combination products, new delivery methods, and entirely different compounds. With the majority of GLP-1s currently taking the form of injections, the near-term focus for many companies is to develop an oral obesity medication, the proverbial diet pill. Other alternative delivery methods are also being studied, including micro-needle patches and implantable delivery devices.

With respect to combination therapies, compounds that combine both GLP-1s and GIPs (glucose-dependent insulintropic polypeptides) are already on the market (Mounjaro and Zepbound), with several other variations of agonists being studied. Novo Nordisk's CagriSema is one of the combination compounds furthest along. CagriSema is a combination of semaglutide and amylin analogue cagrilintide, and the product is currently in Phase 3 trials for both obesity and type 2 diabetes. Based on previously reported Phase 2 data, the product could deliver both glycemic control and weight loss that would be superior to semaglutide and as good as or better than Lilly's tirsepatide (Mounjaro and Zepbound).

Meanwhile, Amgen's MariTide is similar to Lilly's Zepbound as they both influence appetite and insulin secretion by focusing on the receptors for the hormones GLP-1 and GIP. While both of these drugs are similar to Novo's Wegovy drug, MariTide and Zepbound take a different approach to GIP. Zepbound is a dual agonist of both GLP-1 and GIP, increasing their activity, while MariTide is a monoclonal antibody that activates GLP-1 but suppresses the GIP receptor. Amgen's initial commentary regarding Phase 2 results suggest strong data and a differentiated product. In earlier studies, MariTide data suggested possible advantages including once-per-month dosing (instead of weekly) and more durable weight loss when trial participants stopped taking the drug. Amgen is expected to report detailed Phase 2 data in late 2024.

Again, the goal of next-generation products will be to deliver superior results while lessening side effects. But products that offer additional benefits beyond weight loss will be in a particularly strong position to gain market share and, importantly, to garner reimbursement. We are seeing growing evidence that GLP-1s can address multiple conditions or provide multiple benefits (for example, weight loss and reduced cardiovascular risks), which significantly strengthens the case for both usage and reimbursement. We believe companies will actively seek to expand on this theme going forward as new compounds and formulations emerge.

Potential applications beyond obesity

While the use of GLP-1 drugs has dramatically increased due to their success for obesity, the eventual market opportunity for GLP-1s could benefit significantly from expansion into several other significant indications. The effectiveness for other indications should also have favorable implications for reimbursement, as we have already seen with the FDA's recent approval of Wegovy for to help reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease and either obesity or overweight.⁵

Potential indications being evaluated include significant opportunities such as alcoholism, sleep apnea, certain forms of liver disease, Parkinson's disease, Alzheimer's disease, and osteoarthritis. Given various data that indicate some degree of potential effectiveness of GLP-1s for these indications, we expect considerable clinical activity to continue for these indications going forward.

Of these other potential indications, sleep apnea would appear to have the greatest near-term potential — notably, 30 million people in the U.S. suffer from sleep apnea according to the American Medical Association, and obese or overweight people are at heightened risk. This opportunity received a boost with the recent announcement of results from Eli Lilly's SURMOUNT-OSA Phase 3 clinical trial, which evaluated the effectiveness of a tirzepatide (Mounjaro and Zepbound) injection for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity, both with and without positive airway pressure (PAP) therapy. The results were very encouraging, with tirzepatide reducing moderate to severe OSA severity by up to 62.8% (the primary endpoint in the trial). In addition, when looking at a key secondary endpoint from two clinical studies, 43.0% and 51.5% of participants taking tirzepatide at the higher dose achieved the criteria for disease resolution, as defined by the apnea-hypopnea index and Epworth Sleepiness Scale measures.

This was followed within days by the results of a study at Oxford University that showed patients taking Ozempic for a year demonstrated a 48% lower risk of dementia as compared to patients taking an older diabetes drug called sitagliptin. The study also showed patients experienced a lower risk of "cognitive deficits" compared to patients taking either sitagliptin or another older medicine called glipizide. As if that wasn't encouraging enough, the same study suggested Ozempic patients had a 28% lower risk of smoking than those taking glipizide. This was a "retrospective" study, however, taking a backwards look at medical records from over 100,000 patients in the U.S. This was, unfortunately, not a prospective trial with patients randomly assigned to either GLP-1 therapy, a placebo, or another drug. As such, further studies will be necessary going forward.

Finally, we note that Eli Lilly recently reported topline results from the Phase 3 SUMMIT study of tirzepatide in adult patients with heart failure with preserved ejection fraction (HFpEF) in addition to obesity. In the study, tirzepatide demonstrated a 38% lower risk of heart failure outcomes. We would note that the study also met all key secondary endpoints. This appears to be yet another important clinical outcome that could help broaden the overall market and Medicare coverage for GLP-1 drugs.

Key takeaways

Going forward, we believe that acceptance of GLP-1s for indications other than obesity or in conjunction with obesity should allow for more widespread coverage and expanded usage.

GLP-1s are being studied for the following conditions, and we expect considerable clinical activity to continue for these indications going forward:

- Alcoholism
- Sleep apnea
- Liver disease (certain forms)
- Parkinson's disease
- Alzheimer's disease
- Osteoarthritis

5. "FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight," U.S. Food and Drug Administration, March 8, 2024.

Side effects and challenges associated with GLP-1 drugs

While the growing body of clinical data for GLP-1 drugs has generally been favorable, several notable risks and side effects have been associated with usage of GLP-1s over the past 20 years, and other issues have emerged as usage for obesity has expanded.

Most common side effects

The most common side effects are gastrointestinal symptoms, with estimates indicating that roughly 50% of users feel nausea, 20% experience vomiting, and 20% experience diarrhea and dehydration. Other common side effects include headaches, dizziness, and increased heart rate. Most side effects are mild to moderate and tend to occur shortly after injection, often easing or disappearing altogether as the patient continues usage.

While unpleasant in milder forms, more significant degrees of these complications cause a significant percentage of users to discontinue treatment. In fact, one long-term (10-year) study by Blue Cross Blue Shield suggested that nearly 60% of users failed to complete a prescribed 12-week course of GLP-1s.⁶ More recent studies focusing strictly on those taking GLP-1s for obesity suggest a dropout or discontinuation rate of roughly 33%.

Potentially severe side effects

While the data has been encouraging for GLP-1 drugs, we believe it remains too early to draw firm conclusions about their long-term safety and effectiveness, even though the drugs have been on the market for more than 20 years. Potential adverse complications remain a risk, with a growing list of rare but serious side effects associated with the drugs.

The growing list of more significant side effects includes pancreatitis, various forms of gall bladder disease, kidney problems, and certain types of thyroid tumors that have occurred in animal studies. Specifically, semaglutide has been shown to cause thyroid C-cell tumors at clinically relevant exposures, an unproven issue in humans though certainly one that will be watched closely. In addition, stomach paralysis, a condition in which the drug slows or stops the movement of food from the stomach to the intestine and can cause serious issues such as persistent vomiting, has been linked to GLP-1 usage by non-diabetic patients.⁷ More recently, GLP-1s have also been linked to a rare eye condition called non-arteritic anterior ischemic optic neuropathy, or NAION, which can cause blindness. While the condition is rare, initial studies suggest that patients taking semaglutide appear to be four to seven times more likely to suffer from NAION.⁸

The unknown remains a risk

While we are optimistic about the effectiveness of GLP-1s, side effects cannot be dismissed as a limiting factor on the market opportunity. Further, the question remains as to whether significantly severe side effects will emerge and change current market projections. While we believe the lengthy history of GLP-1 drugs would suggest that is unlikely, we have seen more serious side effects emerge, as noted above. In addition, as additional formulations and different compounds are introduced into this market, previously unforeseen side effects may emerge.

On a cautionary note, we would therefore remind investors of the example of Olestra. Olestra was a fat substitute that promised to remove fat and calories from junk food, and it was approved by the FDA in 1996. However, after significant gastrointestinal side effects became known, Olestra fell from grace and, thankfully, potato chips went back to their normal,

6. Finn Cohen, "FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight," Healthline, May 29, 2024.

7. Annika Kim Constantino, "Weight loss drugs may be linked to stomach paralysis, other rare but severe issues, study says," CNBC, October 5, 2023.

8. Deidre McPhillips, "Popular weight loss and diabetes drugs linked to increased risk of rare form of blindness," CNN, July 3, 2024.

unhealthy form. Olestra is now banned in many countries, though it still exists — as an industrial lubricant and paint additive.

Cost and reimbursement challenges remain obstacles

Cost is one of the most frequently mentioned topics when discussing GLP-1s, with some users absorbing significant out-of-pocket costs for the obesity indication. As mentioned earlier, a one-month supply typically costs between \$900 and \$1,350 before insurance and rebates negotiated by pharmacy benefit managers. Insurance coverage and reimbursement remain a challenge for pharmaceutical companies and patients, and while progress has been evident, cost does remain a potential limiting factor on an otherwise booming market. This is especially true in the U.S., where drug costs tend to run exponentially higher, a common theme and imbalance with respect to pharmaceuticals. That said, a recent study indicated that most patients have been successful in having their medication covered by insurance due to other comorbidities. Meanwhile, patients that had to pay out of pocket indicated that their average payment was slightly below \$200. This reflects various affordability programs as well as significant discounts and rebates paid by the pharmaceutical companies.⁹

The growing popularity of GLP-1s has clear implications with respect to Medicare. While Medicare is prohibited under law from covering drugs used for weight loss, Medicare Part D plans are able to cover GLP-1s for other indications. For example, the recent FDA approval of Wegovy to reduce the risk of cardiovascular death, heart attack, and stroke in adults with cardiovascular disease paves the way for Medicare Part D to cover the drug. As such, from the company perspective, the effectiveness of GLP-1s for multiple indications should play an increasingly important role in gaining reimbursement. Additional indications include diabetes, cardiovascular risks, sleep apnea, and a growing list of additional conditions that are currently being studied. Merck & Co., Inc. (Merck) has made it clear that its GLP-1 strategy involves focusing on drugs that show a benefit beyond simply weight loss, an effort intended to facilitate reimbursement. Ultimately, growing use of GLP-1 drugs offers the long-term potential of reducing costs associated with an aging population, including cardiovascular risks, diabetes-related conditions, and osteoporosis. This is, of course, the issue that weighed heavily on some elements of the Health Care sector during 2023, especially medical-device companies.

The trade off between cost and benefits for GLP-1s is a tricky one and complicates the situation. While the benefits are becoming increasingly clear, many critics remain, focused primarily on the high costs associated with the drugs. Jonathan Gruber, an economics professor at the Massachusetts Institute of Technology (MIT), suggests that drugs like Wegovy and Zepbound currently fail the cost-benefit argument given the significant number of potential users for GLP-1s. By his estimates, prescribing GLP-1s to all obese Americans could cost in excess of \$1 trillion. On a similar note, Senator Bernie Sanders is on record suggesting that a recently released study indicated that the growing use of GLP-1s had the theoretical potential to bankrupt Medicaid, Medicare, and the entire health-care system in the U.S.¹⁰ While that might come across as a bit hyperbolic, the high cost of GLP-1s for obesity is an obvious concern with respect to broader reimbursement. Bottom line, huge numbers of overweight and obese individuals in the U.S. coupled with the emergence of increasingly popular and very expensive drugs for obesity presents a challenging situation for the health-care system. We note that in early July, Senator Sanders and President Joe Biden published an op-ed in USA Today, pushing both Novo Nordisk and Eli Lilly to significantly lower the costs of GLP-1s in the U.S. and essentially threatening cost controls if they refuse to do so. We find anything along those lines to be unlikely, especially in the short term. More importantly, as mentioned previously, the actual cost paid by most patients is far below the significant list costs for the drugs.

9. Bruce Gil, "Biden and Sanders want Novo Nordisk and Eli Lilly to cut Ozempic and other weight loss drug prices," Quartz, July 2, 2024.

10. Ibid.

Sector implications

Health Care sector

The sector most directly impacted by the growing popularity of GLP-1s is obviously the Health Care sector. The two manufacturers, Eli Lilly and Novo Nordisk, have been two of the best performing stocks in the sector over the past 18 months or so, reflecting the runaway success of these drugs for their obesity indication. Meanwhile, other players in the Pharmaceuticals and Biotechnology sub-sectors are aggressively pursuing GLP-1 compounds, with Amgen recently announcing very encouraging (though limited) Phase 2 data on lead compound MariTide. Management commentary was very positive, however, and full data and details on the upcoming Phase 3 trial are expected later this year.

The very favorable results associated with Novo Nordisk's SELECT Trial in August 2023, which indicated a 20% reduction in cardiovascular risk for patients taking semaglutide (specifically Wegovy in this trial), significantly increased the excitement surrounding the GLP-1 opportunity and drove accelerating gains in the shares of related companies. On the downside, the SELECT Trial data caused widespread concern over the potential implications of GLP-1 usage on several medical-device markets, including orthopedics, cardiovascular, and diabetes markets. As a result, medical-device and medical-product stocks significantly underperformed the market for most of the second half of 2023. After a late-year rebound and a solid start to 2024, most of the Health Care sector has continued its underperformance through the first half of 2024. We believe it is much too simplistic to suggest that GLP-1 drugs will cure conditions such as cardiovascular disease, diabetes, or osteoarthritis, thus negatively impacting the size and growth of the medical-device markets focused on these conditions. At the same time, we think it is naïve to suggest that GLP-1 obesity drugs will not have at least some longer-term impact on these markets.

Meanwhile, we see a slightly positive impact on companies in the Life Sciences Tools & Services sub-sector as pharmaceutical companies look to develop more compounds in this area. However, we do not consider this a major catalyst for life-sciences companies at this point. While not a perfect indicator, we note that there are 142 clinical trials involving GLP-1s for obesity that are currently recruiting patients.¹¹

Consumer Staples sector

Another sector widely discussed as being impacted by the growing use of GLP-1s is the Consumer Staples sector and, more specifically, the makers of junk foods, snacks, and beverages. One source of investor concerns has been the notion that individuals taking GLP-1 drugs will tend to eat healthier going forward, thus weighing on the consumption of junk food. We find that concept a bit idealistic, but it could prove to be true. On the other hand, some users may continue to consume junk food as before, thinking they can simply take GLP-1s to offset the impact of unhealthy eating.

However, additional concerns revolve around the mechanism of action discussed earlier in the report. That is, GLP-1s reduce or slow the rate at which food leaves a patient's stomach, extending a feeling of fullness following meals and helping to reduce a patient's appetite. Concerns that GLP-1 usage could adversely impact the consumption of junk food have therefore arisen from a more mechanical point of view.

Similar to the overall Health Care sector, the Consumer Staples sector has continued to underperform over the past 12 – 18 months. While some of this can likely be explained by the interest-rate environment, we believe ongoing concerns about the possible impact of GLP-1s remains a drag on much of the sector. That said, we believe it remains too early to detect the impact of these drugs on the longer-term spending and consumption habits of consumers.

11. According to Clinicaltrials.gov, current as of July 29, 2024.

Investment ideas

The growth of the GLP-1 market opportunity is likely to remain one of the key topics, and likely the key topic, for the Health Care sector going forward. The growing body of favorable clinical data combined with increasing supply as Eli Lilly and Novo Nordisk ramp up their manufacturing capacity may very well lead to further increases in the estimated addressable market for GLP-1s. The expansion into additional indications, as discussed earlier in this report, could play a key role in the rapid growth of this market opportunity.

While many companies in the Pharmaceuticals and Biotechnology sub-sectors are eagerly pursuing GLP-1 compounds, the current market consists of essentially two companies, Eli Lilly and Novo Nordisk. Both had (and have) strong positions in the diabetes market and thus had GLP-1 drugs in their product lines. Amgen is poised to enter Phase 3 trials with what could prove to be a differentiated compound, with the company expected to release detailed Phase 2 clinical data and plans for Phase 3 late this year. Gilead Sciences, Inc. (Gilead), meanwhile, was in the news recently after reporting on a preclinical product that appears to have promise as an oral GLP-1.

While there are many pharmaceutical and biotech companies eagerly looking to develop GLP-1 compounds to allow them to eventually enter the anti-obesity market, we only mention those companies that are currently included on one or more of the Global Security Research (GSR) thematic lists.

Eli Lilly (LLY)

Diabetes revenues accounted for roughly 50% of Lilly's revenues before the rapid growth of the obesity market. Currently, Lilly features two key drugs, Mounjaro and Zepbound. Both are tirzepatide, with Mounjaro indicated for blood sugar control in people with type 2 diabetes while Zepbound is indicated for obesity or chronic weight management. While many companies are seeking to develop obesity compounds and enter this market eventually, Lilly is extremely well positioned to remain a leader in the market given its strong and deep pipeline.

Lilly's obesity pipeline includes next-generation, Phase 3 compounds such as retatrutide, which is a "GGG" (Glucagon, GLP-1, GIP) agonist. While Lilly's Zepbound targets GLP-1 as well as a second obesity-related hormone called GIP, retatrutide also targets a third hormone, glucagon, the third "G". In Phase 2 results released in 2023, retatrutide showed weight loss up to 24% after 48 weeks.¹² In addition, Lilly is also developing orforglipron, a once-daily oral nonpeptide GLP-1 receptor agonist, which showed weight loss of up to 15% at 36 weeks in Phase 2 studies published last year. In addition to being an oral formulation, orforglipron is expected to be easier to manufacture and thus potentially cheaper than GLP-1 drugs currently on the market.

Key takeaways

The growth of the GLP-1 market opportunity is likely to remain one of the key topics, and likely the key topic, for the Health Care sector going forward.

In our view, Novo Nordisk and Eli Lilly are likely to remain the dominant players in the GLP-1 market for the foreseeable future.

Other companies in the Pharmaceuticals and Biotechnology sub-sectors are aggressively pursuing GLP-1 compounds, some of which we discuss below.

12. Deena Beasley, "Lilly experimental 'triple G' obesity drug leads to 24.2% weight loss in trial," Reuters, June 26, 2023.

Novo Nordisk (NVO)

Similar to Eli Lilly, Novo Nordisk has been a leading player in the diabetes market, putting the company in a very strong competitive position for the rapid growth of GLP-1s for their obesity indication. The company's well-known drug Ozempic, or semaglutide, has been approved for type 2 diabetes since 2017. In 2021, the FDA cleared Novo's Wegovy for chronic weight management. While Ozempic and Wegovy are the same underlying compound, Wegovy contains higher doses of semaglutide. Ozempic is technically not approved for weight loss, though the name is used frequently when discussing GLP-1s for obesity.

Again, similar to Eli Lilly, Novo Nordisk has several next-generation obesity products in the pipeline.¹³ The key product in the pipeline is CagriSema, which is a combination of semaglutide and amylin analogue cagrilintide. The product is currently in Phase 3 trials for both obesity and type 2 diabetes. Based on previously reported Phase 2 data, we believe the product could deliver both glycemic control and weight loss that would be superior to semaglutide and as good as or better than Lilly's tirsepatide (Mounjaro and Zepbound). Novo Nordisk also has amycretin in development, with promising early data thus far. Amycretin is being developed in pill form, and it works differently from Wegovy as it is both a GLP-1 and amylin receptor agonist.¹⁴ As a result, amycretin could prove superior to Wegovy by further reducing hunger and slowing stomach emptying. The company completed the Phase 1 trial and expects to begin a Phase 2 trial on amycretin later this year, with results likely in early 2026.

Amgen (AMGN)

Amgen joined the GLP-1 parade, at least to an extent, in early May when the company made favorable (though very general) comments about its lead obesity product, MariTide (maridebart cafraglutide, originally known as AMG-133). Specifically, Amgen management suggested they were pleased with what they had seen from an internal review on interim Phase 2 results for the drug and that the compound offered a differentiated profile as compared to the current GLP-1 drugs on the market. In particular, MariTide may offer more durable weight-loss results and less frequent dosing over time (monthly dosing). Amgen management indicated the results will support a move into Phase 3 trials, with further details expected when the company reports full Phase 2 results in late 2024. Assuming favorable Phase 2 results, as Amgen has suggested, we believe an FDA clearance in 2027 is a realistic assumption. While Amgen has several other preclinical pipeline projects in obesity, we do note that the company recently announced that it was discontinuing its early-stage AMG-786 product, an obesity pill.

Pfizer Inc. (PFE)

Pfizer Inc. (Pfizer) has had an inconsistent experience with the GLP-1 development process thus far. In late 2023, Pfizer reported Phase 2 results for its oral GLP-1 danuglipron, with mixed results. As a result, the company elected to continue the development of a once-per-day version of the compound while discontinuing a twice-daily version. In recent weeks, Pfizer indicated that, after studying four separate formulations, it has selected its preferred once-daily modified release formulation and will conduct dose optimization studies during the second half of 2024.¹⁵ There are still uncertainties surrounding danuglipron given the high patient dropout rates witnessed with the twice-daily version of danuglipron, and even assuming positive clinical results going forward, we believe it unlikely Pfizer could have an approved product on the market before 2028 at the earliest.

13. R&D pipeline, Novo Nordisk, as of July 29, 2024.

14. Willow Shah-Neville, "Beyond Wegovy: Could Novo Nordisk's new experimental weight loss pill be even better?" Labiotech, March 27, 2024.

15. Damian Garde, "Pharma giant Pfizer is trying to cash in on the weight loss drug craze with a new pill that could be a welcome needle-free alternative to pesky GLP-1 shots," Fortune Well, July 11, 2024.

Merck (MRK)

Merck currently has a compound called efinopegdutide in clinical development. While efinopegdutide is a GLP-1 compound and has shown a promising weight-loss benefit in clinical data thus far, Merck is focusing on its development for non-alcoholic steatohepatitis (NASH), a liver disease. Merck Chief Executive Officer (CEO) Robert Davis has made it clear that the company is especially interested in drugs that show a benefit beyond simply weight loss as it will likely facilitate reimbursement for the product.

Gilead Sciences (GILD)

Gilead is a new name in the list of potential GLP-1 players based on recent preclinical data for Gilead's GS-4571 oral GLP-1 candidate. Data remains very limited at this point, though the development was largely unexpected and adds a potential new element to the Gilead story. Still, assuming everything goes well from a clinical perspective, this product remains years away from commercial development.

Johnson & Johnson (JNJ)

Johnson & Johnson CEO Joaquin Duato indicated at the company's investor day in late 2023 that the company had no plans to enter the market for weight-loss drugs due to the crowded field of companies looking to enter the market. At the time, Duato indicated that the company's priorities lied in its previously communicated plans to expand in areas such as neurology and oncology. In addition, we note that Johnson & Johnson has been very aggressive on the acquisition front in the medical-device business under Duato's leadership. As a result of the company's newfound aggressiveness since Duato assumed the CEO role, we do not rule out Johnson & Johnson ultimately entering the weight loss market. However, we suspect it would likely be through an acquisition.

Novartis AG (NVS)

Novartis AG (Novartis) has indicated interest in the weight loss market, though it has taken a longer-term view of the opportunity. Novartis CEO Vas Narasimhan has made it clear that the company does not see the wisdom in trying to play catch up with market leaders such as Lilly or Novo Nordisk, and thus Novartis will not seek to develop a similar GLP-1 product. Rather, Novartis has acknowledged that the company is involved in preclinical work on next-generation products that could be differentiated from the current products on the market. According to Narasimhan, that could take the form of a product that is much longer lasting or one that offers much greater tolerability and fewer side effects.

Overview of company recommendations

Ticker	Company name	Price	Market cap (billions)	Dividend	Dividend yield	Estimated NTM EPS	NTM P/E	Core	DSIP	Equity Select	Focus	Growth	High Yield	International	SMID	Value
LLY	Eli Lilly and Company	\$931.58	\$885.4	\$5.20	0.6%	\$19.97	46.7x			X	X					
NVO	Novo Nordisk A/S Sponsored ADR Class B	\$137.57	\$459.3	\$0.98	0.7%	\$3.92	35.1x							X		
AMGN	Amgen Inc.	\$325.39	\$174.8	\$9.00	2.8%	\$20.37	16.0x		X	X						
PFE	Pfizer Inc.	\$28.71	\$162.7	\$1.68	5.9%	\$2.77	10.4x						X			
MRK	Merck & Co., Inc.	\$113.31	\$287.2	\$3.08	2.7%	\$9.12	12.4x	X		X			X			
GILD	Gilead Sciences, Inc.	\$74.34	\$92.6	\$3.08	4.1%	\$5.93	12.5x									X
JNJ	Johnson & Johnson	\$159.09	\$383.0	\$4.96	3.1%	\$10.43	15.2x	X	X	X			X			
NVS	Novartis AG Sponsored ADR	\$113.31	\$221.7	\$3.17	2.8%	\$7.88	14.4x	X		X				X		

Sources: FactSet, Wells Fargo Investment Institute. Prices and data as of August 15, 2024. NTM – next-twelve-months. EPS = earnings per share. P/E = price-to-earnings.

Global Securities Research List Descriptions:

The **Core List** is comprised of blue chip, industry-leading companies. The objective is to provide a list of high-quality stocks that can be used to build a well-diversified portfolio or that can be used to supplement an existing portfolio.

The **Diversified Stock Income Plan (DSIP) List** focuses on companies that we believe will provide consistent annual dividend growth over a long-term investment horizon. Our objective is to provide a broad list of high-quality, industry-leading companies from which an investor can assemble a well-diversified portfolio. Through consistent dividend growth, our goal is to help investors stay ahead of the wealth-eroding effects of inflation.

The **Equity Select List** includes a wide range of what we view as high-quality securities. It has representation across all 11 economic sectors and exposure to stocks with varying levels of maturity, valuation, and cyclicity. The Equity Select List assumes a long-term holding period (five-plus years) and can be used to build or supplement a well-diversified equity portfolio.

The **Focus List** is a concentrated list of stocks that represents a combination of the equity sector guidance from Global Investment Strategy and security selection from Global Securities Research. The objective is to exceed the total return of the S&P 500 Index over an approximate one-year timeframe.

The **Growth List** focuses on companies that we believe offer above-average growth potential. Our objective is to offer investors a list of stocks that they can use to help build a well-diversified portfolio or fill holes in an existing portfolio.

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The **Small- and Mid-Cap List (SMID List)** includes stocks representing companies with market capitalizations ranging from \$1.0 billion to \$20.0 billion at the time of addition. The objective is to exceed the total return of the S&P 1000 Index over the long term (at least one year).

The **Value Equity List** focuses on companies that we believe are trading at a discount to their underlying fundamentals and have the potential to reduce or eliminate this valuation discount. Our objective is to provide investors a list of stocks that may generate attractive returns on a long-term basis as the stock price adjusts to better reflect the underlying fundamentals of the company.

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