

New diabetes and obesity drugs show promise for patients and investors



From the Field
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Key Insights

- GLP-1 drugs represent a watershed development in the health care sector, with broader implications for society and the economy.
- Evidence is emerging that they offer benefits beyond treating obesity and diabetes, thanks in part to their anti-inflammatory properties.
- The development of highly effective drugs in pill form will help unlock a massive potential market.



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Profound advances in a class of drugs that have proven successful at treating the twin epidemics of diabetes and obesity represent a golden age of health care innovation. The impact on improved health outcomes is likely to be significant in coming years as more therapies become available.

The investment implications are also enormous. Select drug developers are positioned to significantly grow their earnings from these drugs, called glucagon-like peptide-1 (GLP-1) agonists. At the same time, we expect downstream impacts across every health care segment, including biotechnology, pharmaceuticals, medical devices, and health care insurance. Because GLP-1s may meaningfully lower food consumption

in developed countries and allow it to be redistributed to poorer ones, they may also lower carbon emissions and serve important environmental, social, and governance (ESG) goals for investors.

How impactful could these new drugs be? For context, about 40 million people in the U.S. are living with diabetes and its consequences, such as heart disease, vision loss, and kidney disease. More than 100 million Americans struggle with obesity, which can be a precursor to diabetes and has an even wider range of comorbidities. Given current trends, the majority of children in the U.S. are expected to become obese in adulthood, threatening increased health care spending and shorter lifespans.

Unfortunately, established treatments for diabetes and obesity have come with adverse side effects; required significant effort and monitoring from the patient; and, in the case of the latter, exhibit limited efficacy. This is in part because the exact causes of obesity and insulin resistance have long remained unclear—and go far beyond an epidemic lack of willpower. Cheap and ubiquitous processed food is part of the problem, but it is not fully understood why some people are able to regulate its intake better than others.

Advances in GLP-1s represent a watershed in both our understanding of obesity and its treatment. GLP-1 drugs have been around for over a decade, but more potent and longer-lasting versions (sold under the

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brand names Ozempic and Wegovy) have come to market just in the past few years. Two even more recent versions (Mounjaro and Zepbound) also incorporate the action of gastric inhibitory polypeptide (GIP).

It is not surprising that the leading pharmaceutical companies are investing heavily in the development of GLP-1s as well as other new anti-obesity medications. At this point, the two with drugs already on the market—Novo Nordisk and Eli Lilly¹—have a significant head start, and we are closely monitoring the efforts of competitors to catch up.

Demand is outstripping supply

Given their robust efficacy in treating both diabetes and obesity, physicians are eager

to prescribe GLP-1 drugs and patients are enthusiastic to take them. Yet fewer than 1 million of the roughly 100 million non-diabetic people living with obesity in the U.S. who could benefit from GLP-1s are using them.

Availability in pharmacies has been the primary constraint as the manufacturing capacity for the most effective drugs cannot keep up with patient demand. Capacity is steadily increasing, but new plants to produce injectable GLP-1s cost billions of dollars and can take three to four years to build. Monitoring capacity is a key additional factor to consider when assessing investment opportunities, in addition to access/reimbursement, market share, and other factors we analyze.

GLP-1s in pill form will likely be a game changer

We are also focused on the expected release of effective GLP-1s in pill form, which we anticipate by 2026. This could be a game changer for the drug class as it could unlock a significantly larger market opportunity. While one GLP-1 product, Novo Nordisk's Rybelsus, is currently available in pill form, it is less effective compared with its injectable counterparts and has specific administration requirements that some patients find cumbersome.

Drug companies are investing heavily in creating small-molecule GLP-1s that can be taken in pill form. This could be significantly more cost-effective for drug companies as manufacturing a pill in large volumes is generally cheaper and

¹ As of December 31, 2023, Eli Lilly represented 3.8% of the Global Stock Fund and Novo Nordisk represented 1.3%.

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GLP-1s explained

GLP-1 agonists mimic the action of the body's naturally occurring GLP-1, a hormone produced in the gut. The biology surrounding GLP-1 is complicated and still not wholly understood, but in simple terms, the body naturally releases its own short-lived GLP-1 hormones after a meal to aid digestion and keep blood sugar in check.

Patients with Type II diabetes may not respond properly to their own, natural GLP-1, which can contribute to elevated blood sugar. Supplementing with long-acting GLP-1 "agonists" has shown outstanding efficacy in helping patients with diabetes to normalize their blood sugar levels. GLP-1 drugs have also shown a profound benefit on weight control since they both slow digestion in the gut and signal to the brain, promoting the feeling of fullness after a meal. The benefits of weight loss extend well beyond aesthetics, and large trials have demonstrated improved health outcomes in obese patients on GLP-1s, with patients on Novo Nordisk's Wegovy showing a 20% reduction in the risk of death from a cardiovascular event.

GLP-1 impacts beyond diabetes and obesity

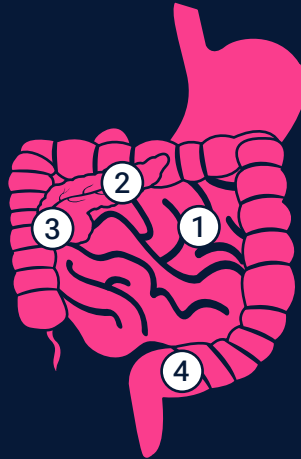
While much focus has been on the effect of GLP-1s on diabetes and weight control, increased attention is being paid to their effects elsewhere as the receptors where GLP-1s work are found throughout the body. For example, recent trials have suggested that these drugs can reduce fat buildup in patients with fatty liver disease and preserve kidney function in chronic kidney disease. Part of the widespread benefits may come from their ability to lower inflammation throughout the body—though it remains unclear whether this is simply the result of weight loss or from other properties of the drugs.

Of all the areas where GLP-1s have shown promise beyond diabetes and obesity, their potential influence on the brain is particularly interesting. Though the trials to date are small, there is increasing evidence that GLP-1s may have a positive effect in patients with alcohol use disorder and other dependencies by reducing cravings. Moreover, there is evidence that GLP-1s may have neuroprotective effects. An early study of a previous generation GLP-1 showed slowing of cognitive function decline in patients with early Alzheimer's disease. As a result, Novo Nordisk is running two Phase III trials of oral semaglutide in early Alzheimer's patients, with data expected in 2025. Thus, the applications for these drugs may span much broader than just diabetes and weight loss.

How GLP-1s work

GLP-1 agonists mimic the broad—and still only partially understood—action of natural GLP-1s, a hormone produced in the gut.

- 1 Although healthy bodies are constantly producing GLP-1s in small amounts, the small intestine ramps up their production in response to the presence of glucose in the small intestine following a meal.
- 2 GLP-1s then circulate in the bloodstream and bind with receptors in the pancreas, which they signal to produce insulin.



- 3 Insulin then encourages cells to absorb the stored glucose in the bloodstream and use it for energy—a process necessary for survival.
- 4 GLP-1s also appear to slow down the movement of food through the small intestine and colon. Slower and better absorption of food maintains the feeling of fullness after a meal and improves the uptake of nutrients.

What is diabetes, and how do artificial GLP-1s help?



People who develop Type II diabetes may not respond properly to the GLP-1s produced in their gut, resulting in elevated blood sugar.



Evidence suggests that artificial GLP-1s largely solve this problem, showing a high degree of efficacy in regulating insulin levels and achieving blood glucose homeostasis—the vital steady state that keeps our cells energized while regulating glucagon levels.

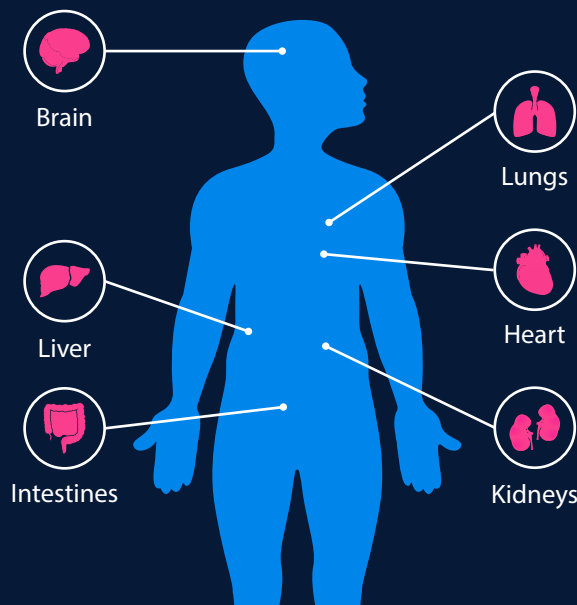
GLP-1 impacts beyond diabetes and obesity

While GLP-1 receptors are concentrated in the pancreas, they are spread throughout the body—and evidence is growing that GLP-1 drugs can interact directly with GLP-1 receptors found in other organs.

May reduce alcohol cravings, and early evidence suggests a possible role in avoiding neurodegenerative diseases such as Alzheimer's and Parkinson's.

May reduce fat buildup in those with fatty liver disease.

May speed the breakdown of fat cells to produce energy.



May reduce inflammation in the lungs and other organs, although it's unclear how much of this is due to weight loss.

May reduce inflammation in the heart and circulatory system.

May preserve kidney function in those with chronic kidney disease.

more straightforward than producing sterile pre-filled injectables. The cost savings, can in turn, be passed on to payors and patients, which may also help to improve access.

In addition to saving on manufacturing costs, pills can be more straightforward than injectables for primary care doctors to prescribe, as they are easier for patients to understand and administer. Indeed, given the production constraints on pre-filled syringes, GLP-1s in pill form are relatively easy to produce in essentially limitless quantities—making them the only way we can reach the underserved community of 100 million people in the U.S. alone who could benefit from their use.

Beyond pharmaceuticals, increased penetration of GLP-1s could have market implications for other health care segments, particularly once pricing comes down with the availability of oral products. As the downstream savings in other health care costs associated with diabetes and obesity begin to materialize, governments and private insurers will have increased incentives to broaden coverage. A GLP-1 prescription could save insurers from other health care costs, such as treatments for high blood pressure, high cholesterol, heart failure, sleep apnea, and kidney dialysis—let alone other significant costs such as strokes or liver failure.

Impact on other companies and industries

The second- and third-order effects of GLP-1s will also be important considerations for investors. Some

A unique combination of promise and safety

One of the most encouraging findings about GLP-1s in clinical trials so far has been the relative absence of serious side effects—indeed, the risk/benefit trade-off appears much stronger than for most other drugs. While some patients struggle with gastrointestinal discomfort, and roughly 10% of users drop off the medication within a month, it is reassuring that the main early safety concerns about these drugs have proven unfounded following reviews of large clinical trials and patient databases to date.

companies are already starting to see an impact, as diabetes patients continue to shift from other medications to newer GLP-1 drugs and more people with obesity initiate therapy. Reduced demand for bariatric surgery has already been noted by several companies.

And the impact is spreading beyond health care. Fast food companies are considering the potential impact on demand, as are makers of snack foods since GLP-1s not only reduce food intake, but may also influence a shift toward more healthy choices. Alcohol companies may also be vulnerable to more health-conscious habits among consumers as well due to GLP-1s' potential to combat addictive behaviors.

Looking further down the road, a healthier global population that consumes fewer calories and lives longer will have an

impact throughout the global economy. Workers are likely to be more productive as they take less sick time, but a longer-living population may also require more elder care and challenge pension systems.

We are active investors in health care's "golden age"

While we believe the advent of effective GLP-1 drugs is a momentous development for the health care system, economy, and markets, we are hopeful that this is only another step in what we believe is a dawning of a golden age of health care. The many billions of dollars spent in private and government-funded labs over the past few decades in understanding the genetics of disease is just now bearing fruit in new treatments. Advanced computing power and the recent advances in artificial intelligence promise that the pace of discovery and innovation will accelerate.

Profiting from these profound changes as investors will require looking beyond balance sheets and gaining a deep understanding of the science and technology behind their promise. We believe we were early in understanding the promise of GLP-1s, and we are confident that our team of portfolio managers and analysts—many of whom have medical and science backgrounds—will continue to aid us in the search for opportunities.

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