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HEALTHCARE MARKET REVIEW AND OUTLOOK

The third quarter was particularly volatile, and the reasons are not hard to identify. Markets were buffeted by, among other things, growing global economic concerns, the August downgrade of the US "Long-Term Foreign Currency Issuer Default Rating" (IDR) (from AAA to AA+) by Fitch Ratings, and a July interest-rate hike followed by a hawkish-hold in September, from the US Federal Reserve. As a consequence, after posting gains in July, markets cooled in August and declined in September.

Among sectors, healthcare closed the quarter in fourth spot. The MSCI World Healthcare marginally outperformed in Q3, declining 2.8%, and -2.0% year-to-date (YTD). Although the MSCI AC World fell 3.4% in the quarter, it remained up 10.1% YTD.

Within the sector, large-cap biotech led the way, as the MSCI World Biotech rose 4.7% (-3.6% YTD) with strong contributions from AbbVie and Amgen, this despite both companies' having economic interests in drugs selected by the Center for Medicare and Medicaid Services for entry into direct negotiation under the Inflation Reduction Act (IRA). On the other hand, the Federal Trade Commission cleared Amgen's pending acquisition of Horizon, offering a positive readthrough to pending and future M&A.

The MSCI World Healthcare Providers and Services Index also finished in the black, rising 0.8% (-6.4% YTD), as managed care stocks proved resilient to the strong medical-utilization environment and were further supported by the anticipated tailwind from higher-for-longer interest rates on earnings.

In the red, the MSCI Emerging Markets Healthcare Index fell 0.8% (-8.0% YTD) and outperformed the broad MSCI Emerging Markets Index, which was down 2.9% (+1.8% YTD). Strength in Chinese CRO/CDMOs and Indian healthcare equities were more than offset by weakness in South Korean, Brazilian, and Saudi Arabian healthcare.

The MSCI World Pharmaceuticals Index fell 1.0% (+2.1% YTD). Performance was led by Eli Lilly and Novo Nordisk after the latter reported that diabetes/obesity medication Wegovy reduced the risk of cardiovascular death, heart attack, and stroke by an impressive 20%. (See our accompanying review of the obesity market.) Most other pharmaceuticals were down in a period otherwise dominated by news identifying the initial list of 10 drugs for negotiation under the IRA, effective in 2026.

The MSCI World Life Sciences Tools & Services Index lost 5.1% (-9.7% YTD). Here, pockets of the industry continue to face destocking headwinds, with modest (at best) visibility on a trough.

Even more noticeable, the MSCI World Healthcare Equipment & Supplies Index fell a staggering 13.4% (-1.4% YTD). During the quarter, sentiment in medtech rapidly deteriorated, as investors debated the extent to which GLP-1 drugs may negatively affect the addressable markets for many medtech players, most notably in the fields of diabetes, cardiovascular disease, obstructive sleep apnea and orthopedics.

Worse still, small- and mid-cap healthcare, as measured by the Russell 2000 Healthcare Index, plunged 14.9%, erasing YTD gains (-7.1% YTD) and underperforming the broad Russell 2000 Index, which fell 5.1% (+2.5% YTD).

INDEX	CLOSE 9/29/2023	RETURN					ANNUALIZED VOLATILITY	
		1 MONTH	3 MONTH	6 MONTH	9 MONTH	12 MONTH	30 DAY	90 DAY
MSCI World Index (all country)	349.5	-4.1%	-3.4%	2.6%	10.1%	20.8%	10%	10%
MSC World Index	8,872.6	-4.3%	-3.5%	3.1%	11.1%	22.0%	11%	10%
MSCI World Healthcare Index	480.5	-3.3%	-2.8%	-0.4%	-2.0%	10.9%	9%	9%
MSCI World Pharma	338.6	-3.4%	-1.0%	4.3%	2.1%	16.4%	11%	12%
MSCI World Biotech	2,176.3	-1.1%	4.7%	-2.8%	-3.6%	14.3%	9%	11%
MSCI World Equipment and Supplies	706.2	-6.8%	-13.4%	-6.3%	-1.4%	12.2%	14%	13%
MSCI World Healthcare Prov & Srvs	1,040.8	3.2%	0.8%	4.4%	-6.4%	2.1%	13%	18%
MSCI World Life Sciences Tools & Srvs	8,226.1	-9.0%	-5.1%	-11.5%	-9.7%	-1.6%	18%	17%
MSCI Emerging Market Healthcare	456.6	-0.9%	-0.8%	-3.3%	-8.0%	4.1%	16%	16%
MSCI Emerging Markets	494.9	-2.6%	-2.9%	-2.1%	1.8%	11.7%	12%	13%

In stark contrast to the outperformance over the first half of 2023, our balanced approach and select idiosyncratic setbacks (without meaningful offsets in the period) weighed on third quarter performance. We do not take this lightly and continually respond to new information to challenge our assumptions.

Over the last 18 months, the market has frequently oscillated between hard and soft-landing scenarios, presenting a flip-flopping appetite for growth versus value, and across size and geographies. We retain conviction in the implications for healthcare regarding the "hard-versus-soft landing"—or even the no-landing—scenarios, in truth, the range of possible outcomes is relatively narrow, compared with other sectors. This stems from the non-discretionary nature of healthcare demand, which is supported by aging populations and the national investment in healthcare delivery, particularly in emerging markets.

As a consequence, we continue to believe that a focus on quality and a balanced approach across sub-industries, market capitalizations, styles, and geographies are suited to the challenges that lie ahead. Ensuring diversification within healthcare over time should mitigate the risks of anchoring to a specific macro or inflation outlook, while protecting the investor against future sector or style rotations.

Idiosyncratic setbacks will occur, although we are proud that our long-term track record shows the idiosyncratic breakthroughs continue to outweigh the setbacks. We are ever prudent in deploying capital, which we target only to the highest conviction investment opportunities. We also remain appropriately cautious on downside risks. Equally important, every year the healthcare sector, and biotech in particular, offers hundreds of clinical and regulatory catalysts carrying potential value-creation opportunities for investors. Many of these have the potential to materially change standards of care or unlock novel therapeutic options for patients who otherwise have no treatment options. Value creation from these catalysts is often uncorrelated with the overall market environment.

Capital markets catalysts are just as important. As dedicated sector specialists for more than 20 years, we know a rich pipeline of market leaders and innovative companies that have yet to enter public markets. These initial offerings are excellent opportunities for us. We expect several IPOs to be announced during the next six months.

The fall season is rich with events that will surely drive volatility and opportunity, as the two so often go hand-in-hand. On 2 October, we had the IRA drug-negotiation deadline pass in a backdrop of ongoing litigation. In addition, a US government shutdown could still occur later this year, despite

GROWTH P.A. 2023-2025E					
	SALES	EPS	PE24E	EV/SALES24E	COGS
MSCI World Pharma	2.5%	6.9%	15.1x	4.1x	26.8%
MSCI World Biotech	2.5%	0.4%	18.0x	5.5x	18.9%
MSCI World HC Equip and Supplies	8.3%	15.5%	21.6x	4.0x	40.8%
MSCI World HC Providers & Services	8.6%	12.4%	13.9x	0.5x	84.9%
MSCI World HC Life Sciences Tls & Srvs	4.0%	7.4%	23.3x	4.7x	52.2%
*Growth impacted by COVID-19 contibutions in 2022 base-year.					

the passage of the continuing resolution on 30 September. Third quarter earnings are only weeks away; these reports may offer clues on momentum into 2024 or add fodder to current investor debates which range from the impact of obesity drugs on medtech to the looming release of Medicare Advantage STAR ratings for 2025 and their ramifications. We will, of course, learn more about inflation trends and central-bank reactions, even as consumer strength will be tested by the continuing normalization of household savings and the resumption of student-loan repayments in the US, and, as noted above, demand for healthcare will continue to be supported by accelerating demographic trends, which will necessitate further innovation across the sector.

The key point is that, despite the myriad economic and geopolitical risks on the horizon, the healthcare sector offers investors diversification, downside protection, and durable growth with meaningful upside optionality. The diversity of the sector ranges across sub-industries, market capitalizations, valuation drivers, and geographies; taken together, healthcare offers opportunities in a variety of market scenarios. We remain focused on quality and maintain a balanced approach across healthcare sub-industries and geographies. We believe current valuations are reasonable, given the sector's resiliency and high potential for future growth.

Marco Cianflone, CFA
Senior Portfolio Manager

SOURCES:

Sectoral Asset Management

THE EXPANDING DEMAND FOR OBESITY DRUGS: HOW LARGE CAN THE MARKET GET?

We first highlighted advancements in medical-treatment options for obesity in our Q4 2020 newsletter. Novo Nordisk had just published a set of positive results from the STEP program using their long-acting GLP-1 (glucagon-like peptide 1) analogue, semaglutide. The drug, which belongs to a class of metabolic hormones called "incretins" that were previously approved for the treatment of Type 2 diabetes, had shown impressive efficacy in weight reduction in non-diabetic obese patients. At the time, we were hopeful that the approval of semaglutide for obesity would unlock a new market opportunity for Novo, while helping to address the global obesity epidemic and its many negative consequences on long-term health. Fast forward three years, and the outlook for the obesity market continues to improve: Novo's Wegovy (the brand name for 2.4mg semaglutide in obesity) was approved on schedule in 2021, and its initial launch was so successful that the company is still struggling to manufacture sufficient supply to meet the overwhelming demand. Eli Lilly, the other key player in the incretin space, released their own highly impressive weight-loss data in obese patients. Their drug, tirzepatide, is a long-acting dual agonist of GLP-1 and a second gastrointestinal incretin hormone, GIP (glucose-dependent insulinotropic polypeptide). Tirzepatide is expected to gain approval for obesity by the end of this year. Several other pharma and biotech companies, including a number in China (as highlighted in last quarter's newsletter), are rushing to develop follow-on products and novel incretin-based combination medicines, as well as oral (versus the current injectable) options for patients, in the hopes of capturing share in what is expected to be a huge global market. Demand for Novo and Lilly's Ozempic and Mounjaro (brand names for semaglutide and tirzepatide, respectively, in diabetes) continues to grow, together with patient and physician awareness of their benefits in both diabetes and obesity treatment. Ozempic is becoming a household name, with awareness fuelled in no small part by traditional and social media. Consider, as just one example, Oprah's discussion of weight loss, obesity, and Ozempic in a recent "The Life You Want" webcast, which featured multiple obesity experts and the CEO of Weight-Watchers. One would be hard-pressed to identify a better match between a prescription drug and the promotion of public demand.

Beyond celebrity endorsements and weight transformations, perhaps the most significant boost to the outlook for the obesity market came in August, when Novo released positive top-line Wegovy data from the SELECT cardiovascular outcomes trial (CVOT). This trial, enrolling over 17.5 thousand patients, is the first clinical demonstration of what any physician treating obesity knew intuitively all along: losing a significant proportion of excess body weight significantly reduces the risk of major adverse cardiovascular events (MACE) in obese patients. These positive results are being viewed as transformational for the obesity space, turning incretin-mediated weight loss from an aesthetic lifestyle choice into a medically validated treatment, with measurable long-term health benefits, in what is increasingly being recognized as a chronic disease. In other words, a treatment that should logically be broadly reimbursed to help avoid the condition's long-term negative health effects and their associated costs.

In this review, we will examine the implications of the recent positive SELECT CVOT data with Wegovy on broadening access and reimbursement for incretin-based weight-loss treatments and provide an overview of the pipeline of novel obesity products in development, from both from the incumbents Novo and Lilly, as well as a slew of potential new market entrants. We will also address what the broader adoption of weight-loss treatments could mean for adjacent healthcare segments, which have recently come under pressure. Will there still be a market for bariatric surgery, medical devices serving patients with type 2 diabetes, or those with obstructive sleep apnea (OSA), if everyone loses weight on a GLP-1 drug? The short answer? We tend to think yes.

Still A Worldwide Epidemic

The troubling data on the global spread of obesity assessed in our Q4 2020 newsletter have not shown any sign of improvement: obesity continues to affect over 764 million adults worldwide, and its prevalence is predicted to grow to 17.5% of the global population by 2030, more than 1 billion people (Figure 1).[1] These trends are disturbing because obesity not only affects a patient's quality of life, but the condition can also lead to premature mortality by increasing the risk of developing numerous chronic diseases, among them type 2 diabetes, hypertension, cardiovascular disease (heart disease and stroke), non-alcoholic steatohepatitis (NASH), OSA, osteoarthritis, and various types of cancer (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancer).[2]

	2010		2025		2030	
Adult obesity prevalence	% adults	number	% adults	number	% adults	number
Obesity (Class I, II and III) BMI ≥30kg/m²	11.4%	511m	16.1%	892m	17.5%	1,025m
of which, severe obesity (Class II and III) BMI ≥35kg/m²	3.2%%	143m	5.1%	284m	5.7%	333m
and of these, severe obesity (Class III) BMI ≥40kg/m²	0.9%	42m	1.7%	93m	1.9%	111m

Figure 1 Estimated global prevalence and numbers of adults living with obesity in 2010-2030

The public-health and socioeconomic burden associated with rising obesity rates remains substantial. The World Obesity Federation predicts that more than half the world's population will be either overweight or obese (defined as having a body mass index [BMI, weight in kg/height in m^2] greater than 25 and 30, respectively) by 2035; moreover, the economic impact of such high levels of BMI could reach $4.32 trillion, or 2.9% of total global GDP (Figure 2).[3] These figures consider both the direct medical costs of treating obesity-attributable diseases and the estimated loss of economic productivity caused by diminished on-the-job performance, inability to work, and premature death.

	2020	2025	2030	2035
Economic impact (US$ at 2019 value) (trillions)	US$ 1.96	US$ 2.47	US$ 3.23	US$ 4.32
Impact as proportion of total global GDP	2.4%	2.5%	2.7%	2.9%

Figure 2: Global economic impact of high BMI (BMI ≥25Kg/m^2) 2020-2035.

The US drives a large proportion of the global economic impact, a consequence of its high obesity prevalence and relatively high healthcare system costs. Over 40% of American adults have obesity,[4] and the associated direct medical costs have been estimated at more than $170 billion.[5] The economic burden is even higher if the cost of both obesity and overweight are considered. A recent report from the Milken Institute estimates that in 2016, chronic diseases driven by the risk factor of obesity and overweight accounted for $480.7 billion in direct healthcare costs in the US, with an additional $1.24 trillion in indirect costs due to lost economic productivity.[6] These are staggering numbers, which suggest a need for sustained strategies to help address obesity, both in the US and around the world. The magnitude of weight loss produced by incretin-based medications (15% and more) is known to have positive effects on many comorbidities associated with obesity, including hypertension, kidney disease, the prevention and even remission of type 2 diabetes, and cardiovascular disease (Figure 3). As a result, we expect that national strategies addressing obesity will soon include broader access to and reimbursement of incretin-based therapies to help prevent the development of secondary comorbidities and their associated costs.

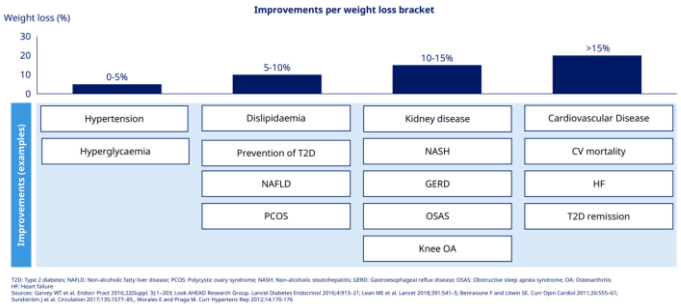

Figure 3 Many comorbidities of obesity can be improved with weight management.

GLP-1s: What's the Fuss About?

As highlighted above, obesity is associated with many serious health consequences, making it one of the most significant global public-health problems (Figure 4).[7] Achieving substantial weight loss through lifestyle changes such as diet and exercise is notoriously difficult. Maintaining weight loss for a sustained period has proven an even more elusive goal for most patients. The advance of GLP-1 therapies, which mimic the action of incretins, a group of gut hormones released during mealtimes, helps obese and overweight patients lose ≥15% of their body weight, and as important, maintain the loss over time. In short, GLP-1 agents make significant and sustained weight loss a more realistic goal.

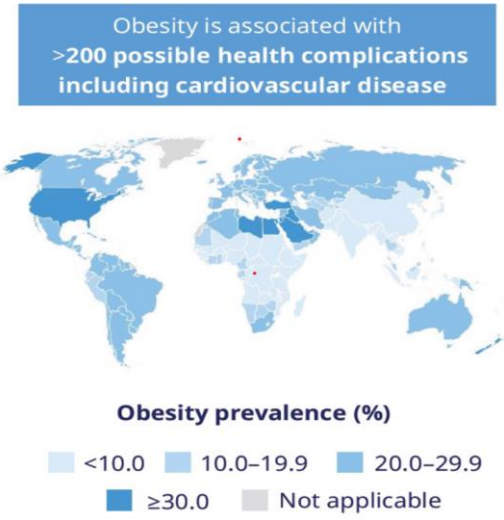

Figure 4: Map of Global obesity prevalence rates.

Semaglutide was first approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of type 2 diabetes under the brand name Ozempic and again in June 2021, at higher doses and under a different brand

name, Wegovy, for obesity. It is a once-weekly, injectable GLP-1 receptor agonist, which works by delaying gastric emptying and reducing gut motility, sending a satiety signal to the brain. In so doing the drug promotes weight loss. In the pivotal STEP-1 clinical trial, semaglutide 2.4mg demonstrated an almost 17% weight reduction in obese and overweight participants after 68 weeks of treatment.[8] This impressive efficacy led to the approval and launch of Wegovy for weight management in obese and overweight patients. Another drug, tirzepatide, developed by Eli Lilly and currently approved only for type 2 diabetes under the brand name Mounjaro, has also been studied for weight loss. Mounjaro is a dual agonist targeting both GLP1 and a second incretin hormone called GIP, which regulates energy balance through signaling in the brain and adipose tissue following food intake. In Lilly's pivotal SURMOUNT-1 clinical trial, tirzepatide 15mg demonstrated even stronger results than Wegovy, producing an almost 21% weight reduction in obese and overweight participants after 72 weeks of treatment.[9] Eli Lilly has filed tirzepatide for the treatment of obesity, with FDA approval expected by the end of this year.

Semaglutide and tirzepatide are the first two incretin-based therapies to demonstrate significant weight reduction in obese patients in pivotal clinical trials. Today, a multitude of earlier-stage drug candidates are in development, both by the two incumbents, Novo Nordisk and Eli Lilly, as well as other large-cap biopharma companies and a slew of smaller biotech players. All are hoping to capture a slice of what is expected to be a very large global market, one just starting to form. Key mechanisms of action under exploration in these programs are described in Figure 5.

Obesity was classified as a chronic disease by the American Medical Association only in 2013 and the European Commission in 2021, leading to a gradual change from the prevailing perception that it is a lifestyle condition to a recognition of obesity's underlying biological complexity. The advent of incretin-based weight loss drugs is pushing the treatment of obesity into mainstream primary-care management. Awareness of drugs like Wegovy, Ozempic, and Mounjaro from both physicians and patients is very high, the familiarity driven by traditional and social-media coverage, celebrity endorsements, and patient success stories. Patients are asking for these drugs by name, and many are paying out-of-pocket for access. Novo's launch of Wegovy, whose sales are already annualizing at over $4bn, despite well documented supply constraints, illustrates the potential of the obesity market once fully activated. Many analysts estimate that obesity medication sales could easily surpass $50 billion over the coming decade. No wonder that new entrants are looking to disrupt Novo and Lilly's current duopoly, with innovative pipeline medicines of their own.

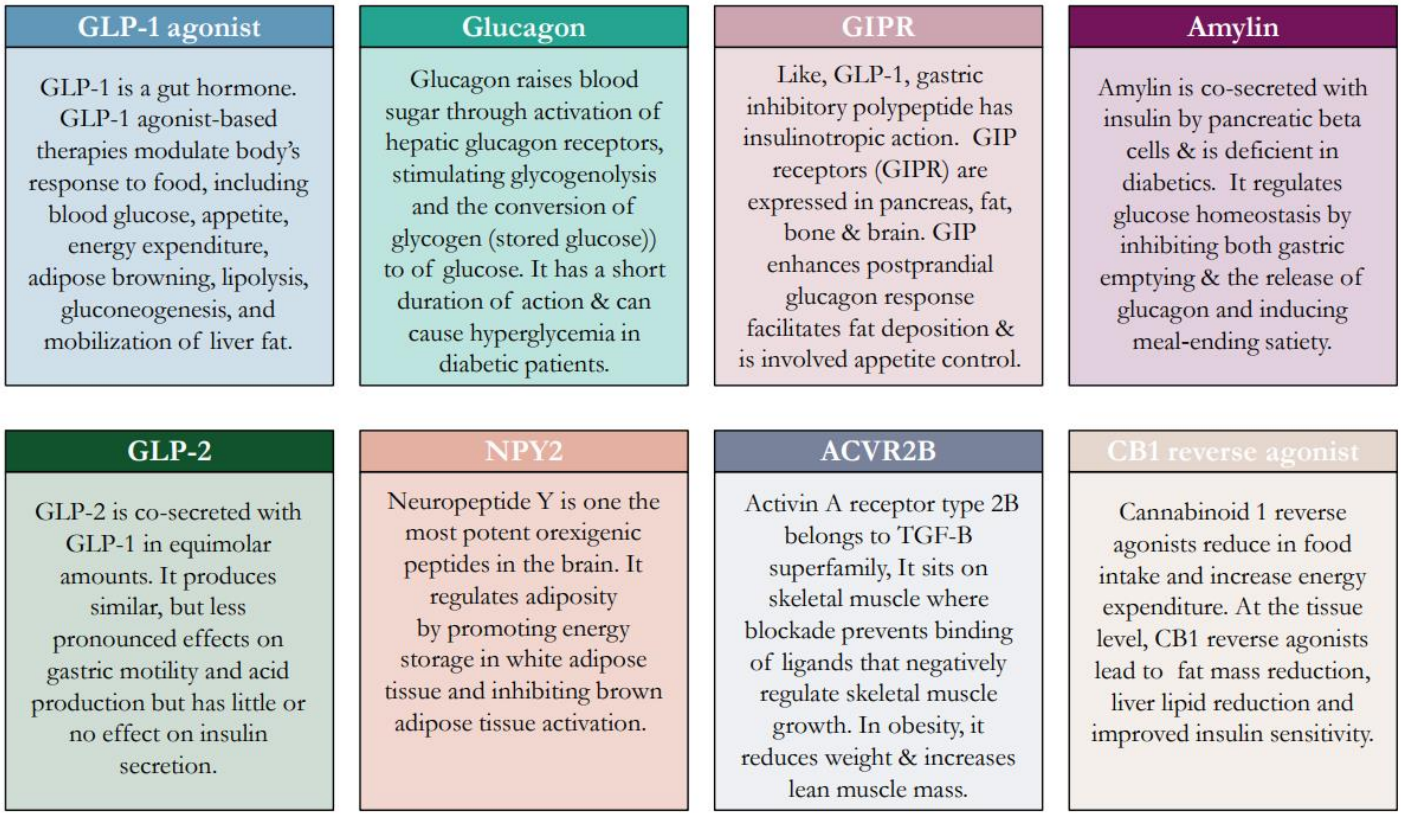

Figure 5: Key mechanisms of action of pipeline obesity drug candidates.

The next generation of obesity drugs aims to achieve one of four goals: (1) even higher levels of weight loss, usually achieved by combining multiple mechanisms of action. One notable example is Lilly's retatrutide, a triple hormone-receptor agonist targeting GLP-1, GIP, and glucagon, which recently demonstrated 24% weight loss at 48 weeks of treatment in a Phase 2 trial[9]; (2) oral administration, which has the dual benefit of offering patients a needle-free therapeutic option and the drug companies a potentially much easier and more scalable manufacturing process; (3) improved quality of weight loss, including a reduced loss of muscle mass while the patient loses weight, or the provision of additional benefits, such as the rapid lowering of liver fat; (4) improved safety and tolerability profiles, with fewer gastrointestinal side effects, which allows less complicated titration to the patient's optimal dose. A recent report from the broker Evercore ISI counted close to 50 new obesity medications with 25 unique modes of action in development across 34 large and small biopharma companies. Of these, approximately half were GLP-1 based and almost 30% were oral (Figure 6).

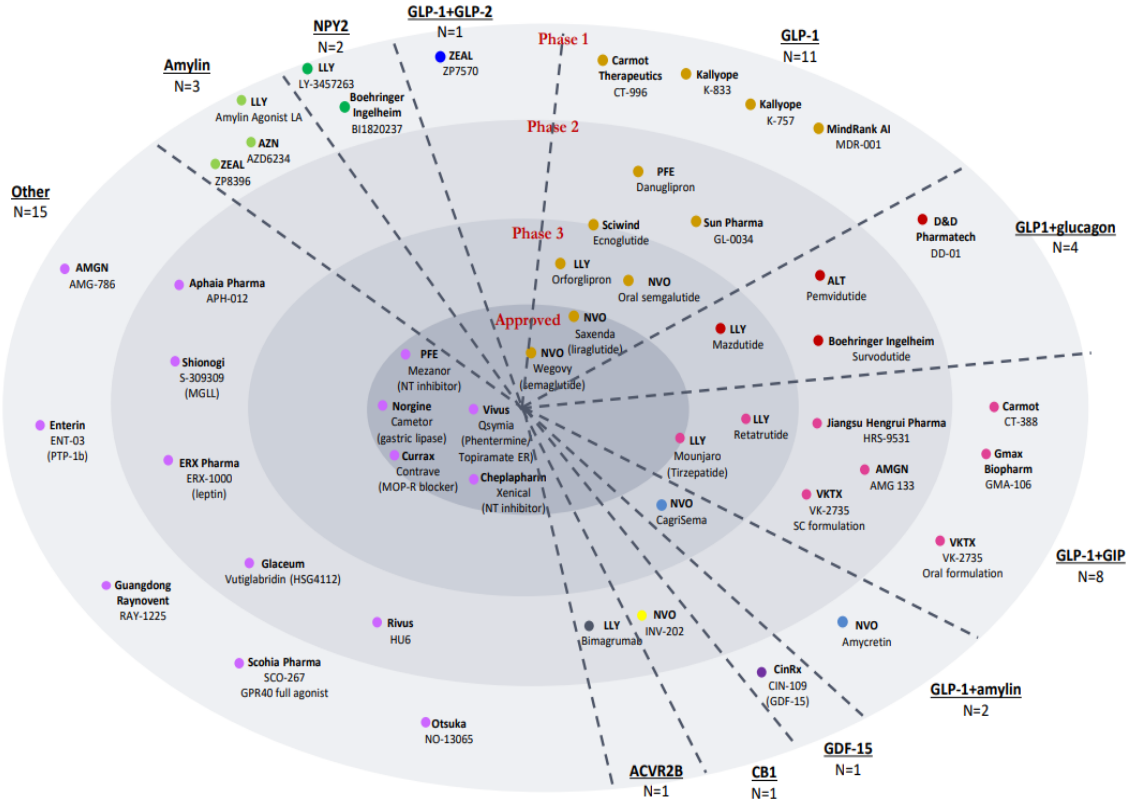

Figure 6: Obesity programs across biopharma: Most are early in development, half include GLP-1

A number of these programs will have validating clinical trials reading out between now and the end of 2024, as summarized in Figure 7. Many of these are still early-stage, proof-of-concept studies, whose outcomes will determine if the candidates are taken forward into larger trials. Of note are Novo and Lilly's phase 3 trials of their existing drugs, semaglutide and tirzepatide, in patients with obesity and existing comorbidities like knee osteoarthritis, sleep apnea, and heart failure. These studies are designed to demonstrate the benefit of weight loss in alleviating the comorbidities; if positive, the findings are likely to help drive adoption and reimbursement among these patient subgroups.

Company	Drug (Mechanism of Action)	Trial Description	Expected timing of data
Novo Nordisk	Semaglutide (weekly injectable GLP-1)	Ph3 in obesity with knee osteoarthritis	Q4/2023
Eli Lilly	LY3457263 (injectable peptide YY activator)	Ph1 proof of concept	Q4/2023
Pfizer	Danuglipron (oral GLP-1)	Ph2b interim obesity data	Q4/2023
Amgen	AMG 133 (monthly injectable GLP-1/GIP)	Ph2 obesity data	Q4/2023
AstraZeneca	AZD6234 (injectable long acitng amylin)	Ph1 proof of concept	Q4/2023
Altimmune	Pemvidutide (GLP-1/Glucagon)	Ph2 obesity data	Q4/2023
Viking Therapeutics	VK-2735 (oral GLP-1/GIP)	Ph1 proof of concept	Q4/2023
Novo Nordisk	Amycretin (oral GLP-1/amylin)	Ph1 proof of concept	Q1/2024
Novo Nordisk	Cagrisema (injectable GLP-1/amylin)	Ph3 in obesity	Q1/2024
Novo Nordisk	PYY1875 (injectable peptide YY activator)	Ph2 obesity data	Q1/2024
Eli Lilly	Tirzepatide (injectable GLP-1/GIP)	Ph3 in obesity with sleep apnea	Q1/2024
Aphaia	APH-012 (oral beaded glucose)	Ph2b obesity data	Q1/2024
Boehringer Ingelheim	BI 1820237 (injectable PNY2)	Ph1 proof of concept	H1/2024
Amgen	AMG 786 (oral D5D inhibitor)	Ph2 obesity data	H1/2024
Eli Lilly	Tirzepatide (injectable GLP-1/GIP)	Ph3 in obesity with HFpEF	H2/2024
Carmot Therapeutics	CT-996 (oral GLP-1)	Ph1 proof of concept	H2/2024
Novo Nordisk	INV-202 (oral CB-1 agonist)	Ph2 obesity data	Q3/2023
Zealand Pharma	ZP8369 (injectable amylin agonist)	Ph1 proof of concept	2024
Zealand Pharma	Dapiglutide (GLP-1 and GLP-2)	Ph1 proof of concept	2024
Rivus	HU6 (controlled metabolic accelerator)	Ph2 obesity data	2024

Figure 7: Summary of near-term clinical-trial readouts with novel anti-obesity drugs-

The most advanced of the new molecules is Novo's Cagrisema, a weekly injectable, fixed-dose combination of 2.4mg semaglutide (Wegovy) and 2.4mg cagrilintide, a long-acting amylin analogue, currently in phase 3. Amylin is a hormone produced by the pancreas and co-secreted with insulin, which regulates glucose homeostasis by slowing gastric emptying and inhibiting secretion of glucagon, thereby promoting the feeling of satiety. Novo presented impressive phase 1 obesity data, showing 17% weight loss after only 20 weeks of Cagrisema treatment, and started enrolling patients in phase 3 obesity trials in 2022. Data from the REDEFINE program (Figure 8) is expected in Q1 2024, [8] and Novo management has expressed optimism that the drug will deliver a more than 25% weight-loss benefit over the full treatment window of 68 weeks.

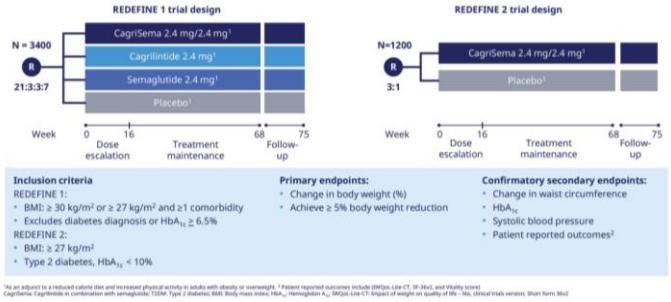

Figure 8: Design of Novo's REDEFINE Ph3 obesity clinical program.

A Large Market Requires Broad Access: The Effect of SELECT Should Help.

We have highlighted the scale and economic cost of the global obesity epidemic, as well as the emergence of first truly effective incretin-based weight-loss medicines and the extensive pipeline of next-generation products in development across biopharma. With an estimated 140 million obese adults in the US alone, there is no shortage of patients interested in getting access to effective weight-loss medicines. Unlike high blood pressure or cholesterol, obesity is a visible and symptomatic condition, one still associated with significant stigma. Thus, the patient base is highly motivated, suggesting the very real potential for high treatment-adherence rates. One could imagine incretin-based medicines being taken in every US household over the next few years.

Two things would need to happen to realize such high utilization rates. First, the manufacturing capacity will need to increase, so that companies such as Novo and Lilly can meet the demand for their products. At present, Ozempic, Wegovy, and Mounjaro are found on the FDA's Drug Shortage list, as the companies are struggling to meet volume demand for their drugs.[11]. Capacity expansion is already under way, with both companies investing heavily in securing additional supply – Novo expects constraints on Wegovy to gradually ease over the coming months. Over time, the expected market entry of additional players, as well as the development of oral drugs, which have a less complex manufacturing processes than injectables, should help to permanently alleviate the supply shortfall.

The second, and likely more crucial, gating factor for the ultimate size of the obesity market, is access and reimbursement. The out-of-pocket cost of Wegovy for patients without insurance coverage is approximately $1350 per month, a prohibitively high expense for most people for a chronic drug. Novo has been working to increase access to its obesity medications through the commercial-employer channel, with approximately 80% of payers providing formulary access to Wegovy and around 50% of employers opting-in to offer obesity treatment to their employees. This approach translates to coverage for close to 40 million US patients through health insurance at their place of employment. Another 10 million patients are covered through Medicaid. [8]

A major positive development that should lead to improved access to obesity medications for patients occurred on August 8, when Novo released highly anticipated, topline data from their SELECT CVOT with Wegovy. SELECT included over 17,500 participants across more than 800 sites in 41 countries and was designed to demonstrate the efficacy of weekly semaglutide 2.4 mg injections versus placebo in reducing the incidence of MACE in overweight or obese people with established cardiovascular disease and no prior history of diabetes. Patients enrolled in the trial were ≥45 years with a BMI ≥27 kg/m^2 (Figure 9). [8] The trial delivered impressively positive results, generating a 20% relative-risk reduction of major cardiovascular events (CV death, non-fatal strokes/heart attacks) in this patient population. Full results from SELECT will be presented at the American Heart Association Annual meeting in November; in the interim, Novo revealed the benefit was seen across all three components of MACE, and the 20% risk reduction exceeded expectations.

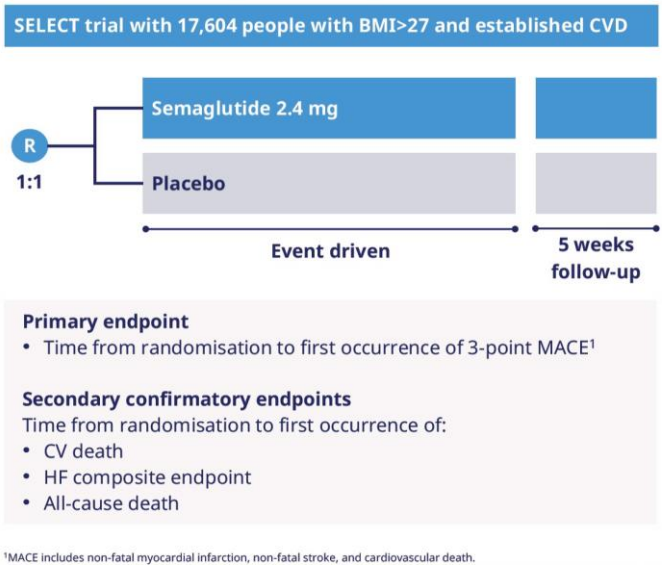

Figure 9: Trial Design for Novo's SELECT CVOT in people with overweight or obesity and established cardiovascular disease.

The highly positive SELECT results are being viewed as transformational for the obesity space as a whole, turning incretin-mediated weight loss from an aesthetic lifestyle choice to a medically-validated treatment with measurable health benefits. The market capitalizations of Novo and Lilly increased by 17% and 15% respectively on the day the results were released, adding over $100bn of value to the two stocks – a reflection of investor optimism that the CVOT data will drive adoption of obesity medications. The expectation is that the SELECT results will make it difficult for payers not to cover incretin-based therapies for weight loss, and utilization will surge as a result. While it is likely to take some time, we expect more US insurance companies to add obesity drugs to their formularies and more employers to opt-in and offer coverage for employees. This conclusion is in line with a recent employer/plan survey conducted by PSG, showing an additional 28% of payers are considering adding coverage over the next 1-2 years (Figure 10).[12]

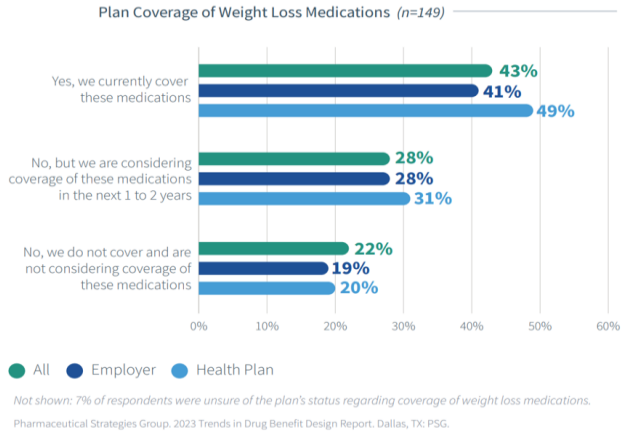

Figure 10: Insurance plan survey results on obesity coverage.

SELECT may also help to increase the likelihood that Medicare, the US government's health-insurance program for seniors, which is currently prohibited from reimbursing prescription obesity medications, will expand coverage. At present, the only efficacious obesity treatment covered by Medicare is bariatric surgery. Draft legislation, called the Treat and Reduce Obesity Act (TROA), was recently reintorduced in the US Congress with bipartisan support. If passed, the TROA would expand Medicare coverage to include screening and treatment of obesity by a diverse range of healthcare providers and introduce coverage of behavioral counseling, FDA-approved prescription drugs for long-term weight management, and other prevention and treatment options. This bill was first introduced in 2013, but it now seems to have a better chance of passing, as weight loss has been shown to lead to tangible health benefits for obese and overweight patients. The Congressional Budget Office has yet to score the bill, so the cost of the added coverage is not yet known.

However, as evidence of the downstream benefits of weight loss continues to roll in, with additional study findings anticipated in the coming years, it seems inevitable that Medicare will eventually cover obesity drugs. This step would have positive implications for access across the US, as health-insurance companies traditionally model their coverage plans after Medicare. Wegovy is approved only in a handful of countries outside the US, . and Novo has been very prudent about launching in new markets, given the ongoing suply shortages. As stated above, we expect these issues to be resoved over the next 6-12 months, once additional manufacturing sites come online and ramp up production. We also anticipate that payers outside the US., particularly in countries with a single-payer system for healthcare, are also likely to provide reimbursement. For example, the UK government recently unveiled a £40 million two-year pilot program that will allow Novo's Wegovy to be prescribed to outpatient obese patients with BMI over 35 and one related condition, even though the treatment has yet to be launched in the country.[13]

Will Obesity Drugs Solve All Downstream Health Problems?

The aftershocks of the SELECT data release were felt well beyond current market leaders Novo and Lilly and other biopharma players involved in the development of new obesity drugs, most of which saw their market valuations increase. A slew of medtech companies saw their stock prices decline significantly on the SELECT data release, as investors worried about the long-term implications of

the expected broader use of weight-loss medicines on adjacent markets. Hardest hit were companies serving patients with type 2 diabetes, such as Tandem Diabetes Care (TNDM), Insulet (PODD), and Dexcom (DXCM), which, at the time of writing, were down 35%, 40%, and 29%, respectively, since the SELECT data were released on August 8. The main concern is that the total market opportunity for devices like insulin pumps for people with insulin-dependent diabetes (TNDM, PODD) and continuous glucose monitors (DXCM) may well shrink, if many obese patients lose weight on incretin-based therapies and either reverse the course of their disease (such that they are no longer insulin-dependent), or do not progress to develop diabetes. Similarly, given that OSA is a known complication of obesity, companies including ResMed and Inspire Medical Systems, which serve OSA patients with continuous positive airway pressure (CPAP) devices and implantable neurostimulation, also saw their stocks decline more than 25%. Another negatively impacted medtech company, Outset Medical, which develops hemodialysis systems for kidney-failure patients, another complication of obesity, is down 35% since the SELECT data release.

Is the market right in its assumption that the rise of incretin-based obesity medications spells doom for the outlook in adjacent markets? Will there still be a need for bariatric surgery, insulin pumps, or CPAP if everyone loses weight on a GLP-1 drug? We agree some impact on these adjacencies will be felt, but the long-term growth outlook for these medtech companies will likely be much less dire than their recent value decline might suggest. Several points should be considered. The first is patient access and reimbursement – as highlighted above, we expect access to obesity medications to increase over time. However, given the sheer volume of potential patients, it is reasonable to expect this access will be somewhat gated and limited, at least initially, to patients with very high BMI or existing comorbidities, who may need the medications most. The second is patient compliance – how long patients will stay on treatment. As subset of patients are unable to tolerate GLP-1 medication due to side effects such as nausea and vomiting and discontinue use before achieving substantial weight loss. Given substantial co-pays, even for patients with insurance, and the fact that the weight loss for those who tolerate the treatment, while impressive, eventually plateaus, the percentage of patients who will stay on incretin therapy for the long term is uncertain. It is also not clear whether payers will continue to reimburse the medicines beyond the initial period of weight loss. What is known, however, is that patients who lose weight on GLP-1 therapy regain two-thirds of their lost weight one year after discontinuing the use of the drug and their cardiometabolic improvements revert towards baseline for most variables (Figure 11).[14] These findings suggest continuous treatment is required to maintain weight and health improvements with incretin therapies, and there will be a subset of patients for whom treatment will serve to delay, rather than prevent, the onset of obesity-related comorbidities such as diabetes or OSA.

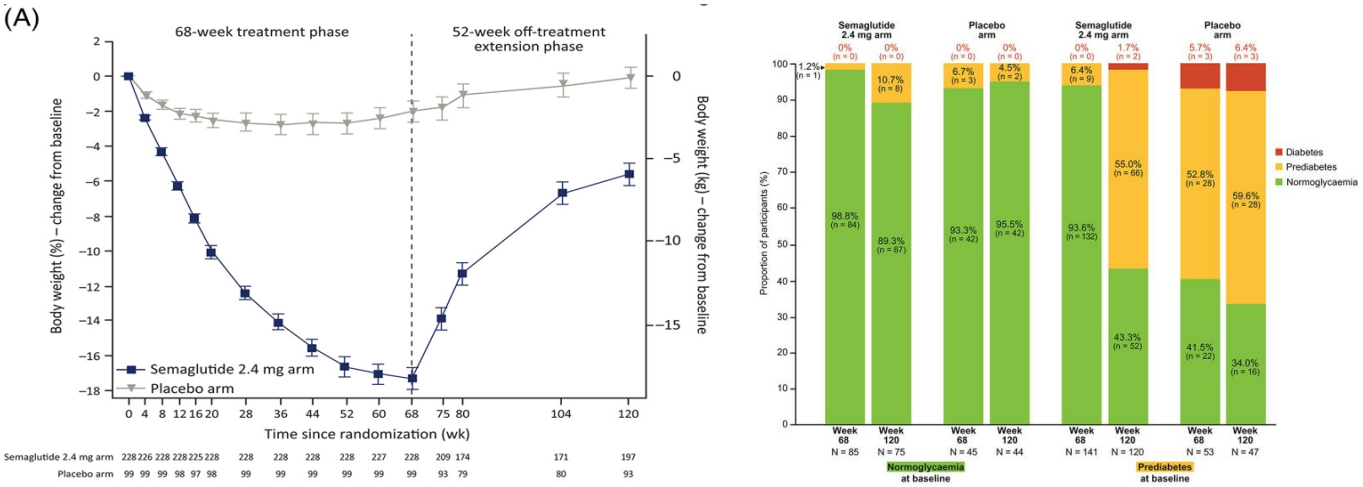

Figure 11: Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP1 trail extension.

The final point to consider is the efficacy of current obesity medications. So far, the most efficacious pipeline products, Lilly's retatrutide and Novo's Cagrisema, have approached 25% weight loss in obese patients in phase 2 studies. Clearly, those results are very impressive; if confirmed in pivotal trials, the drugs will offer many patients the means to achieve a healthy weight or a BMI of 25 or below. Still, for those who are morbidly obese, even a 25% weight loss would not achieve this goal. Consider a patient who starts at a weight of 100kg and is 165cm tall, which implies a BMI of 36.7. Losing 25kg would likely generate significant health benefits, to be sure, but would still leave the individual with a BMI of 27.5, which is overweight and carries an elevated risk of downstream complications.

Conclusion

Novo's impressive results from their SELECT cardiovascular outcomes trial are hard to ignore. The 20% risk reduction in MACE in obese patients who lost weight on Wegovy may be transformational for the growth of the obesity market. We expect access to and reimbursement of first- and second-generation incretin-based therapies to grow as new data are published and the range of choices expands. The demand for conventional treatments for obesity and related conditions, including bariatric surgery, insulin pumps, glucose monitors, and CPAP devices, may shrink in the short term, but over time, a not insubstantial demand is likely to remain, due to such factors as cost, limits to insurance coverage, and treatment compliance. Many patients may also find it difficult to maintain the primary and secondary benefits from the new drugs over time, especially those who are morbidly obese. In short, although many questions remain to be answered, the sheer volume of motivated patients (140 million in the U.S. alone!) suggests that this already large market is likely to continue expanding, thereby assuring robust growth for biopharma players for the coming decade and beyond.

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