

Global Equities

April 2024

Quarterly Insight

Can GLP-1s solve the world's obesity problem?

The obesity epidemic presents a formidable challenge globally, with more than 16% of the world's population grappling with its consequences. The impact of obesity extends far beyond an individual's health, affecting societal productivity and ultimately escalating healthcare and economic costs. Traditional approaches focusing on lifestyle and dietary changes have proven insufficient in curbing this growing issue. However, the rise of GLP-1 agonists (GLP-1s), a class of drugs initially used for diabetes management, has marked a turning point in obesity treatment. These drugs have shown not only promising results in weight management but also in improving associated health risks, leading to an extraordinary surge in demand.

The integration of GLP-1s into healthcare systems has the potential to revolutionise the landscape of obesity management and create healthier societies, but the question lies in whether they have the power to solve the obesity epidemic? In this report we will delve into the background of the obesity crisis; present the advantages and hurdles of this new therapeutic approach; and finally, we will explore ways that we as investors can invest in the opportunity.

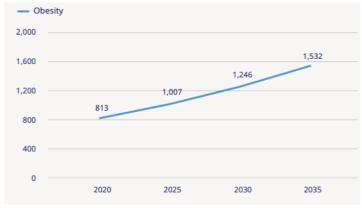
THE RISING PREVALENCE OF OBESITY

The rising prevalence of obesity has fast become one of the greatest health challenges we will likely experience in our lifetime. Since 1975, obesity rates have nearly tripled worldwide, with a substantial increase in the number of adults and children affected by this condition. Over 900 million adults or 16% of the global population are living with obesity today but this is substantially higher in many countries including the US at 45%, highlighting the pervasive nature of this issue. Unfortunately, this is not the endpoint as the global obesity rate is projected to double by 2035.

The impact of obesity is extensive, contributing to over 200 medical conditions, including cardiovascular diseases, sleep apnea, kidney disease, osteoarthritis, diabetes, and various forms of cancer. It's crucial to

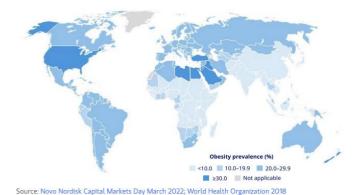
note that obesity is not just a matter of weight but a complex health issue with multifaceted causes and consequences.

Global prevalence of Obesity (adults in millions)



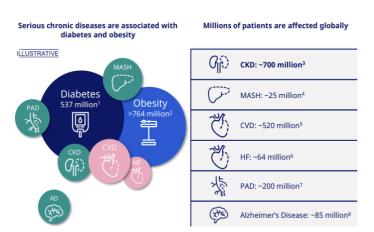
Source: Novo Nordisk, Obesity Atlas

Global obesity epidemic prevalence



Source: Novo Nordisk, WHO 2018

Strong overlap across several chronic diseases



Source: Novo Nordisk, 2022

The fact that over 90% of individuals with obesity experience multiple comorbidities underscores the urgency for effective prevention and treatment strategies to improve health outcomes and quality of life for those affected. But addressing this epidemic requires a multifaceted approach, including public health initiatives, policy changes, cultural adjustments and perhaps most importantly a paradigm shift in the treatment of the condition as a chronic disease.

COST BURDEN TO SOCIETY

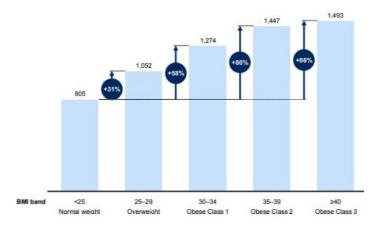
Beyond the health consequences for an individual, obesity has far-reaching consequences on societies.

The increased risk of health conditions leads to higher associated direct medical costs. Moreover, obesity has indirect economic costs associated with mental health issues, reduced productivity and greater

socioeconomic disparities, which can place strain on public health budgets and impact global economies. We will address each of these below.

Paying extra pounds for the pounds: The societal cost of obesity is extensive and difficult to measure, as it includes both the direct medical costs as well as the indirect economic burden. A Milken Institute study conducted in 2016 estimated that the US annual economic cost from obesity (including direct and indirect costs) was over \$1.72 trillion (9.3% of GDP), which is likely higher today given the 3-4% rise in prevalence since then. Unsurprisingly, the direct medical cost burden rises exponentially with higher rates of obesity, with 60-80% higher costs or ~\$1,500 per annum for those with obesity. The World Health Organisation (WHO) estimates that obesity has a staggering 2.4% impact on global GDP.

Rising medical costs with increasing levels of obesity

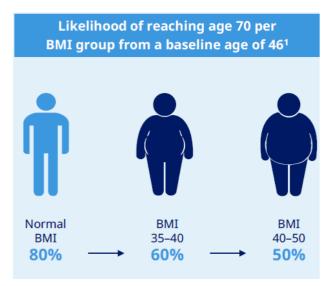


Source: Morgan Stanley Research, McKinsey study (2014)

Tipping the income inequality scale: Obesity has been shown to exacerbate socioeconomic disparities. There is a growing prevalence of obesity in lower and middleincome socioeconomic groups, where access to healthy food alternatives is limited and packaged and unhealthy foods are sadly often more affordable. Furthermore, an economist study highlighted a concerning pattern of pay inequality linked to obesity, with overweight women earning lower salaries and those with severe obesity experiencing up to a 10% income reduction.

Downsizing life expectancy: Research shows that being overweight or obese, radically reduces life expectancy in adults by around 5-10 years, due to the health-related consequences. According to WHO, obesity is responsible for 5% of global deaths and is the second most preventable cause. Lower quality of life in the latter years is also highly probable.

Lower life expectancy with obesity



Source: Novo Nordisk

Given the extensive health and financial consequences of obesity on both an individual and to society, it is essential that additional steps are taken to address this growing problem.

SOLVING THE OBESITY EPIDEMIC

Despite being recognized as a chronic disease by the American Medical Association in 2013, obesity has been viewed by the general population and policy makers as a consequence of poor lifestyle choices and **overeating.** Until recently, the obesity treatment options have been largely limited to recommended lifestyle and dietary modifications, with the other health consequences separately addressed with appropriate therapeutic care. There have been very few successful obesity therapeutic care options to date given the underwhelming observed weight loss benefits including a maximum of 5% of body weight; little-known positive health benefits; significant longer term safety concerns

e.g. weight loss drug Belvig/Lorcaserin was withdrawn in 2020 due to increased risk of cancer; and high out-ofpocket costs due lack of reimbursement. As such, only 10% of these individuals tended to seek help, and less than 2% received medical treatment. It is therefore no surprise that only a quarter of patients persisted with treatment for more than a year.

The FDA's approval of Wegovy in 2021 marked a significant milestone in obesity management, recognizing it as a serious medical condition and reshaping how it is treated. Developed by Novo Nordisk, Wegovy is part of a new class of GLP-1 drug treatments designed for chronic weight management. It builds upon the legacy of Saxenda, a less effective GLP-1 weight loss drug and shares the active ingredient Semaglutide with diabetes medication Ozempic, albeit in varying dosages. In part thanks to social media, the demand for these new 'miracle drugs' has been unprecedented, highlighting the desperation of those strugaling with obesity and its consequences to find a solution beyond just lifestyle modifications.



Key GLP-1 drugs and approval dates for Novo Nordisk and Eli Lilly				
	Obesity	sity Diabetes		
Novo Nordisk	Wegovy (2021)	Ozempic (2017)		
Eli Lilly	Zepbound (2023)	Mounjaro (2022)		

As the market for GLP-1s expands, with estimates suggesting it could reach \$100 billion by 2030, there are exciting investment opportunities emerging. Before delving into these, we will discuss the background to GLP-1s and outline both the benefits and disadvantages of their ability to solve the world's obesity epidemic.

What is a GLP-1?

GLP-1 agonists are a revolutionary class of medications that have transformed the management of type 2 diabetes and more recently obesity. By emulating the natural hormone "glucagon-like peptide 1", they play a crucial role in regulating blood sugar levels post-meal. Their ability to slow gastric emptying not only helps in controlling blood sugar spikes but also aids in weight management by reducing appetite and caloric intake. Furthermore, they contribute to the health of pancreatic beta cells, which are essential for insulin production, thus delaying the progression towards full insulin dependency.

It is worth noting that these drugs have been around since 2005, for the treatment of type 2 diabetes. Their surge in popularity over the last 2 years can be attributed to their effectiveness in weight reduction, a significant advantage over legacy diabetes medications that could lead to weight gain. But perhaps more importantly, the overall health benefits they offer and initial breakthrough expansion of insurance coverage in the US, along with reimbursement policies in other countries, have made them more accessible to patients seeking both diabetes treatment and weight management solutions. We will review each of these benefits in more detail.

Benefits of the new wave of obesity treatment

1) Larger weight loss outcomes

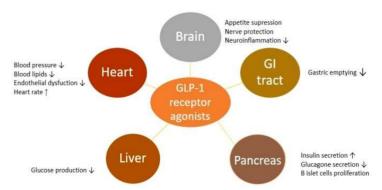
One of the more significant benefits of the newest class of drugs is the improving weight loss outcomes. The evolution of GLP-1 treatments for obesity and diabetes represents a significant advancement in medical therapies. The newer generation of these drugs, such as Novo Nordisk's Wegovy and Ozempic, and Eli Lilly's Zepbound and Mounjaro, have demonstrated remarkable improvements in weight loss outcomes, nearly tripling the efficacy of previous treatments towards 15-20% weight loss. With ongoing research and development, these companies are not only

enhancing drug effectiveness towards 20-25% but also focusing on patient-centric treatment options, including oral medications and various injectable dosages, to better meet individual health requirements.

2) Big gains in health benefits

GLP-1 receptor agonists have been shown to not only slow gastric emptying and improve insulin secretion, but there are other positive health impacts on the heart, liver, brain and kidneys.

The positive effects of GLP-1 receptor agonists

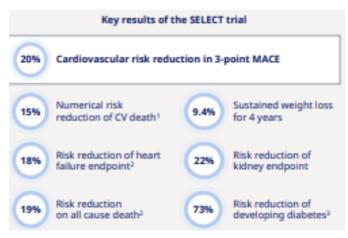


Source: National Library of Medicine (2023)

Novo Nordisk's SELECT trials of Wegovy have shown several improved healthcare outcomes. These include a 20% improvement in risk of developing cardiovascular diseases, which includes lowering blood pressure and blood lipid levels; an 18% reduction of heart failure; 22% reduction of progression towards kidney disease/dialysis; and a 19% reduction on all causes of death. Most encouragingly, there was a notable 37% reduction in a broad composite of diseases, including stroke, cardiovascular disease and diabetes etc.

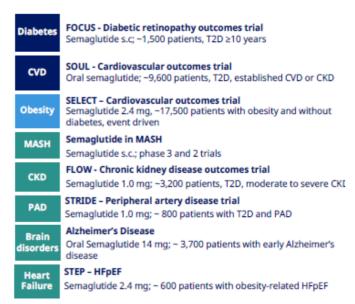
These benefits are considerable but this is only the beginning, as both Novo Nordisk and Eli Lilly are undergoing further clinical trials to understand the impact on other comorbidities including Parkinsons, Alzheimer's, osteoarthritis and sleep apnea.

Strong SELECT data trial outcomes



Source: Novo Nordisk CMD (2024)

Far reaching studies underway for other comorbidities

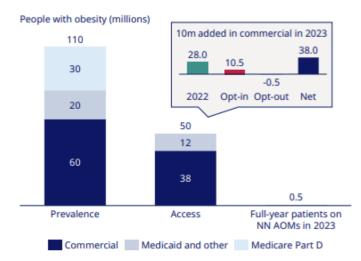


Source: Novo Nordisk, 2022

3) Insuring the masses

As demand for GLP-1s has surged, fueled by their profound improvement in health outcomes, we have seen a shift in corporate and government willingness to provide coverage. In the US, there are currently 50 million people with access to Wegovy, including 38 million through commercial insurance plans and 12 million through Medicaid within 18 states.

50mn people in the US have access to Wegovy



Source: Novo Nordisk CMD, 2024

In March 2024, we began to see the first signs of hope for broader obesity reimbursement, when the FDA widened the approved use of Wegovy to include a reduction in the risk of heart conditions in people with obesity/overweight following the positive trial data. As such, Medicare Part D drug-benefit plans announced plans to cover Wegovy for overweight patients at risk of heart disease. While this covers subset of around 11 million people, directionally it shows that selective reimbursement is likely to expand.

Currently 80% of adults with type 2 diabetes are also overweight or obese. GLP-1s are reimbursed in the US and in many other countries, for the treatment of diabetes and therefore may be the most obvious route to access for these individuals until such time that reimbursement for obesity improves. In the meantime, for those that are not diabetic, coverage is likely to broaden through greater corporate insurance and selective reimbursement based on favourable trial outcomes.

The landscape of anti-obesity medication is evolving, with Wegovy now available in several countries outside of the US, including the UK, Denmark, Norway, UAE, Japan, Switzerland, Iceland and Germany with varying reimbursement policies influencing access. While around 80% of treatments are currently borne by individuals, efforts are underway to enhance insurance

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coverage, which could lead to broader usage and accessibility. As an example, in the UK GLP-1s are reimbursed for those with a BMI over 35 or 30 with other related comorbidities. Pharmaceutical companies like Novo Nordisk and Eli Lilly are actively working to expand global availability, which will likely be facilitated as production scales up to meet demand. This expansion is crucial in addressing the global obesity challenge by making them more accessible to those in need.

Strong uptake of Wegovy internationally



Source: Morgan Stanley research

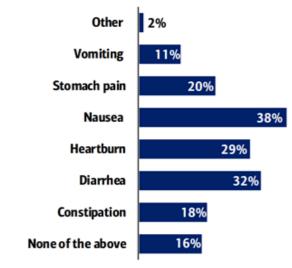
Challenges to solving the epidemic

Given the significant opportunity to address one of the greatest heath concerns of our lifetime, it is important to understand the challenges of GLP-1s. We will discuss 3 of the main ones below.

1) Nauseating side effects

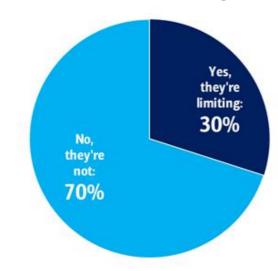
A key barrier to GLP-1s solving the world's obesity problem is the tolerability of these drugs. The more common short-term side effects include nausea, diarrhea, heartburn, and stomach pain. A Bank of America study showed that most patients taking Wegovy experience some form of side effect, particularly in the first 2 months. Encouragingly, around 70% of patients found these side effects to be manageable, perhaps suggesting that tolerability is less of a prohibiting factor to persisting with treatment.

Majority of patients experience side effects



Source: Bank of America

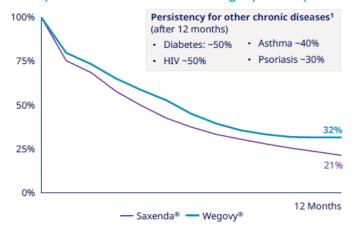
Most found the side effects to be manageable



Source: Bank of America

Adherence to long-term medication regimens, such as those for weight loss, is crucial for achieving the desired outcomes. Novo Nordisk data indicates that a third of patients have maintained their treatment with Wegovy over a year which is encouraging, as it aligns with adherence rates for other chronic conditions. Addressing common barriers to treatment continuation, like drug availability, side effects, and financial factors, is essential for improving patient compliance and ensuring sustained benefits from these medications.

32% of patients have remained on Wegovy after 1 year



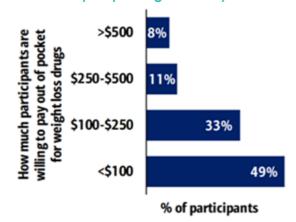
Source: Novo Nordisk CMD, 2023

When it comes to the longer-term implications of the treatment, which some argue is unchartered territory, we should recall that GLP-1s have in fact been in the market for almost 20 years. Therefore, the long-term side effects are well documented and appear to be limited. Amongst some of the more serious potential longer term concerns are that they are not recommended for those predisposed with a history of thyroid or pancreatic cancers as early studies suggested an increased risk of thyroid and pancreas tumors.

2) No free lunch

As a precursor to improving societal healthcare outcomes, the drug will need to be made more widely available and affordable. The price of these drugs is currently high, particularly in the US, where 55% of those living with obesity are paying out-of-pocket. The same study conducted by Bank of America showed, over 70% of US participants had annual household incomes below \$100k and unsurprisingly most participants were only willing to pay up to \$250 or less per month for treatment. The cost of Wegovy, presents a significant financial consideration for patients, with a list price of \$1,350 per month of supply. While insurance coverage and manufacturer discounts can reduce this cost, that seems a 'hard pill to swallow.' Encouragingly, with over 50 million lives covered, 80% of US patients are paving substantially less than that at around \$25 per month.

Cost sensitivity to spending on obesity treatment



Source: Bank of America

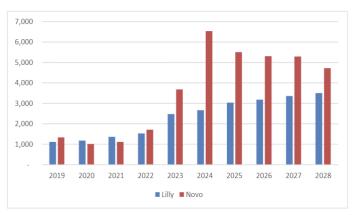
The financial implications of fully reimbursing antiobesity medication in the US are indeed significant and frankly unattainable. Based on the current list price, the estimated cost of full reimbursement would cost \$1.6 trillion, a substantial portion of the US healthcare budget. As we see it, the only way to fully integrate these treatments into the healthcare system sustainably is for pharmaceutical companies to substantially reduce their prices, which seems unlikely near term in the face of supply constraints, or for selective reimbursement targeting specific comorbidities to gradually improve access. Studies are beginning to show that coverage for new obesity treatments could generate cost offsets to Medicare over time, potentially easing the financial burden, but the benefits of these will need to be assessed.

In Germany and Denmark, legislation currently prohibits general coverage of weight loss drugs by the public health insurance programs, forcing those in need to stomach a hefty Eur170-300 per month. In Denmark, the government has an arrangement to reimburse a certain number of severely overweight individuals. Encouragingly, despite Denmark being primarily an out-of-pocket market, they have managed to penetrate around 7% of the obese population and most have remained on it a year later. A key differentiator in this small market, which could explain part of the impressive persistency, is the lack of supply chain bottlenecks which has been a constraint to meeting soaring demand levels in the US and other larger markets.

3) Building supply inch by inch

The unprecedented demand is outstripping supply. It is fair to say that the main challenge shorter term will be to meet the demand with sufficient supply. The main bottlenecks to date are related to the 'fill and finish' capacity, rather than sourcing of ingredients. As such, both Novo Nordisk and Eli Lilly have been accelerating capex investments with a combined \$50bn to improve supply over the next 5 years. A typical organically built 'fill-finish' manufacturing plant takes around 3 years to reach full capacity, due to the complex and technical nature of filling the auto-injector device in a sterile environment. Novo Nordisk has focused efforts on outsourcing these capabilities with contract manufacturing and development organisations (CDMOs). A more creative and less time-consuming way to navigate the supply challenges is to buy capacity outright. In February 2024 we saw this in action as the parent company of Novo Nordisk, Novo Holdings, entered into an agreement to acquire Catalent, a leading CDMO with 50 sites where Novo Nordisk will acquire 3 of these for \$11bn. We estimate that Novo will have sufficient supply to serve 4-5 million patients by 2026, with a new wave of supply coming through the Catalent sites thereafter.

Novo and Eli Lilly capex investments to ramp supply



Source: Morgan Stanley Research, 2023

FINDING INVESTMENT OPPORTUNITIES IN THIS **NEW ERA OF THERAPEUTIC CARE**

The obesity drug market, currently valued at \$6 billion, is projected to experience a significant expansion, exceeding \$100 billion by 2030. This growth is driven by the increasing demand for innovative treatments and the development of new drugs that offer more effective weight management solutions. Investment opportunities are diverse, ranging from direct investment in pharmaceutical companies leading the charge, to indirect investments in the supply chain. Additionally, the market's evolution is expected to influence various sectors, with companies experiencing varying degrees of impact based on the resulting behavioral changes and health outcomes associated with obesity management. We will explore each of these in more detail.

1) Pharmaceutical companies

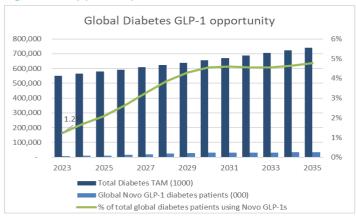
The investment opportunity that excites us most, as global investors, is the direct pharmaceutical beneficiaries. Danish listed Novo Nordisk (NOVOB DC) and US listed Eli **Lilly (LLY US)** are the frontrunners dominating the GLP-1 market. While we believe both companies are set to see tremendous growth from the revolutionary obesity opportunity, we added Novo Nordisk (NOVOB DC) to the Northcape Global Equity Fund. While both Novo Nordisk and Eli Lilly meet our 5 quality principles and could be considered for our Approved List, we prefer Novo Nordisk for its comparatively attractive valuation.

Novo Nordisk's century-long expertise in diabetes care and their strategic investments in innovation and manufacturing capabilities have positioned them as a market leader. Despite the potential entry of new competitors, which are only in clinical trial phases of drug development, the current duopoly has strengthened their competitive moat and created a sustainable advantage. They are arguably years ahead in the development of products, which continue to improve with each new class, and have invested significant capital in shoring up manufacturing capacity which as we know is no quick process.

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The company has 2 primary growth drivers. Firstly, Diabetes care is an attractive growth opportunity, given it is 75% of current revenues and core to their strateay. Around 537 million people are living with diabetes which is expected to grow to 650 million or to 1 in 8 people by 2030. Only 15% of these patients are under good care and 50% remain undiagnosed. GLP-1s are in the very early innings of penetration, with only 6% of the US diabetic population using them (and only 1.2% globally!). We expect this to rapidly expand given the broad array of health benefits offered over alternative treatments. Given they are primarily reimbursed for diabetes, we believe the company will gain significant share of the \$75bn diabetic drug market which is expected to grow to \$100bn by 2030.

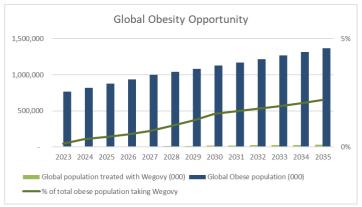
Significant opportunity in diabetes care



Source: Bloomberg, Northcape estimates

Secondly, within obesity care, we believe Novo Nordisk is one of the best positioned companies to capitalise on this opportunity. Only 1 million people are currently using GLP-1s for obesity treatment today which is 0.1% of the total addressable market. What's more, our assumptions imply only 2% penetration by 2030 so there is a very long runway for growth. We believe that Novo can easily dominate 35% of the \$100bn obesity drug market by 2030. Supply will continue to expand, organically and through the Catalent acquisition, and we expect pricing to reduce significantly across all markets allowing more people to access the drugs at a more affordable price.

Early days in the global obesity opportunity



Source: Bloomberg, Northcape estimates

2) Indirect beneficiaries: contract manufacturers and suppliers

We view **Thermo Fisher (TMO US)**, held in the Northcape Global Equity Fund, as another beneficiary of this new wave of obesity care. Thermo Fisher is a global leading life science company with a strong contract manufacturing (CDMO) business. It was a strong beneficiary of COVID, given its ability to supply covid vaccinations around the world, however as the need for this supply wanes they have been able to repurpose some of the excess supply capacity to 'fill-finish' the GLP-1 injectable products. While this is not a significant part of their business, they are uniquely positioned with their global scale and capacity.

Secondly, **Becton Dickinson (BDX US)**, a long-standing fund holding, is a key provider of GLP-1 autoinjector syringes for both diabetes and obesity. They can produce at a reduced cost given their significant global scale benefits. Becton has around 60% share of the \$3bn market which is expected to grow strongly with the emergence of obesity drugs. While a small part of Becton's total revenues, it should provide a tailwind to growth over the medium term.



Source: Becton Dickinson

3) Calories shifting to healthier lifestyle choices

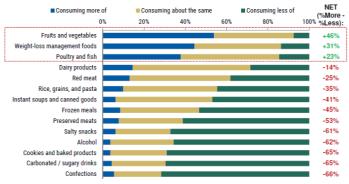
As a hunger suppressant, GLP-1s have been shown to significantly reduce patient calorie intake by 20-30%. In an effort to tackle the obesity crisis, it is important that individuals support weight loss efforts with healthier lifestyle choices. We were encouraged to see that studies by Morgan Stanley indicated that GLP-1 patients appear to be reducing the number of daily meals and snacks and have doubled their weekly exercise quotient. The study further showed that consumption declined across most food categories, but particularly in foods high in sugar and fat. It also indicated that around 70% of patients moderated eating at restaurants and ordering of fast food.

GLP-1 patients reduced calories and exercise more

-			
	Total		
	Before	Currently	Impact
Average Number of Daily Meals	2.8	2.2	-0.6
Average Number of Daily Snacks	3.5	2.1	-1.4
Average Number of Daily Calories	3,196	2,280	-916
Weekly Exercise	35%	71%	36%

Source: Morgan Stanley Survey

GLP-1s patients consume less packaged/unhealthy foods



Source: Morgan Stanley Survey

While the number of patients taking GLP-1s is too small to 'move the needle' on demand at this stage, greater penetration longer term could detriment sales of consumer-packaged goods companies and restaurants. Our exposure to these sectors is limited. On our Approved List, we see Nike (NKE US) as a beneficiary of the shift to more frequent exercise, with its dominant position in active and sportswear.

4) Weighing up the health outcomes

Within the healthcare sector, several companies have seen harsh share price reactions to the potential health outcomes from GLP-1s. CSL (CSL AU), a small holding in the Global Equity Fund, is one example of a company that was placed in the GLP-1 'loser' camp when Novo Nordisk's Phase 3 trial data indicated a significant slowing in the onset of chronic kidney disease. Given Nephrology is only 7% of sales, we believe the potential impact to CSL was more than reflected in the share price. As with our Australian Equity Team, we too saw this as an opportunity to add to the stock on the undue weakness and attractive valuation.

Conclusion

As one of the greatest healthcare challenges of our lifetime, which has up until now largely been neglected, the emergence of therapeutic drugs to treat obesity as a chronic disease presents a very exciting investment opportunity. The improving weight loss outcomes along with extensive and far-reaching health benefits will continue to improve with new emerging drugs and therefore should provide significant benefits to overall societal health outcomes. As responsible investors, we believe that addressing the obesity problem is essential to align with UN Sustainability goal 3 which ensures healthy lives and promotes well-being for all at all ages.

While we don't believe that these drugs will solve the entire world obesity epidemic, due to the risks around tolerability, reimbursement and high drug costs, we do think it will be a meaningful growth driver for the direct pharmaceutical beneficiaries, namely Novo Nordisk, given the size of the total addressable markets and multifaceted benefits these products offer. We further see indirect opportunities to invest in companies building capacity through Thermo Fisher and in the syringes through Becton Dickinson. Additionally, several healthcare companies have been oversold due to the mispriced negative long-term consequences, for example CSL, which has created a buying opportunity.

At Northcape Capital, our investment philosophy is rooted

in finding companies that meet our 5 key quality principles. We are focused on investing in companies with a greater degree of earnings certainty and structural growth. Novo Nordisk, Thermo Fisher and Becton are just a few examples of companies that meet our stringent quality requirements and present attractive growth opportunities over the long term.

Northcape Capital Global Equity Team



Fleur Wright, CFA

Portfolio Manager | Analyst

Before joining Northcape, Fleur was a Managing Director doing Global Equities at UBS in Sydney, running the APAC team. Prior to this, Fleur lived and worked in the UK focusing on European equities. She also has experience in valuing infrastructure securities.

Years of industry experience: 25



Theo Maas, CFA

Portfolio Manager | Analyst

Before joining Northcape, Theo worked at Arnhem Investment Management where he was Portfolio Manager for Arnhem's Global Equity Strategy. Theo worked at ABN AMRO in Amsterdam from 1994 to 2007 as a PM in the Global Equity team with a focus on the TMT sectors.

Years of industry experience: 29



Calvin Lim, CA

Portfolio Manager | Analyst

Before joining Northcape, Calvin was an Investment Analyst at Fidelity International and has covered a range of sectors including Financials. He was also the Asia ex-Japan consumer sector lead analyst. Prior to this Calvin worked at PwC in Audit; Corporate Finance and Valuations.

Years of industry experience: 17



Wendy Herringer, CFA

Portfolio Manager | Analyst

Before joining Northcape, Wendy was portfolio manager at Barings Asset Management in the Global Equity team based in London. Wendy worked at Barings from 2011 covering a wide range of sectors including Consumer Staples, Consumer Discretionary, Financials, Healthcare and Industrials.

Years of industry experience: 17

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