Baillie Gifford™

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Novo Nordisk: how weight-loss drug Wegovy can drive further growth

Your capital is at risk.

Malcolm Borthwick (MB): In 1973, a Japanese biochemist discovered a new class of molecule that lowers cholesterol. His finding led to the creation of one of the most prescribed drugs ever. Statins. Half-a-century on, over 200 million people take them daily, and they've prevented countless heart attacks and strokes. Well, we could be on the precipice of another blockbuster class of drugs. And what's more, they could dwarf statins' $15 billion market.

These medicines mimic the hormone GLP-1 and you've probably heard about an early product. Wegovy helps people lose weight, and keep it off, so long as they continued injections. The UK's NHS recently began prescribing it. The market for an effective slimming treatment is huge. But there are also early signs that these drugs could tackle Alzheimer's, Parkinson's, liver disease and more.

Welcome to *Short Briefings on Long Term Thinking*. I'm Malcolm Borthwick managing editor at Baillie Gifford, and I'm joined by Ross Mathison, who's an investment manager in our Global Income Growth team. Ross is also co-manager of our Global Income Growth Fund and deputy manager of the Scottish American Investment Company, also known as SAINTS. Ross will explain why one Danish firm could take a large share of these GLP-1 profits.

But first a quick reminder, as with all investments, your capital is at risk and your income is not guaranteed.

Ross, welcome to *Short Briefings on Long Term Thinking*. Great to have you with us on the podcast.

Ross Mathison (RM): Hello. Good to be here.

MB: So, let's start with a sizable general question. What are GLP-1s?

RM: GLP-1s is this new class of drugs, originally thought of as a class that was really suitable for patients with diabetes. And then more recently, in the last couple of years, great excitement has built because we found that these drugs bring significant weight loss. And so, this has become a topic of the mainstream media, because people now think we have got potentially a solution for the obesity challenge that we as a society face.

When you look through the data on how many people globally fall into that categorisation, the World Health Organisation estimate that's somewhere between 750 to 800 million. So, a large population globally. And then when you think about how this population will change over the next 10 or 15 years, there's huge growth still to come. So, when you look at prevalence of obesity in children, adolescents, this leads to continued growth in his population. So, estimates ranging between 1 billion, some people say in 2030, some people 2 billion in 2035, huge numbers out there. So, this is a big, big problem. And this is a huge cost to society. It costs society in terms of putting strain on our food supplies, putting strain on productivity, and then the healthcare burden, the costs around that are absolutely massive. So, in my opinion, this is one of society's greatest challenges that faces us over the next 10, 20, 30 years that we need to get on top of.

And then at an individual level, this is also a huge challenge. When you think back over the last 20 years, from the Atkins diet to raw, vegetable diet to soup diets, people want solutions for this problem. We have had drug therapy available in the past, but there's always been really quite nasty side effects. So, what we've got is potentially a drug therapy, which is really quite exciting.

So, what are GLP-1s? When you eat your stomach releases a group of hormones, which are known as incretins. And one of those hormones is called GLP-1, and that has multiple jobs, such as controlling your blood sugar levels, sending signals to your brain about how hungry you are. Now that the pharma industry has learned how to replicate these naturally occurring hormones, we have a way to start to tackle this problem that sits in front of us.

MB: Oh, that's really interesting. So, it convinces the brain that you're fuller, faster?

RM: Exactly, So, you get this feeling of 'okay, I don't need to go and eat'. The signal's telling you your appetite is no longer there.

MB: They have been around for quite a while, haven't they? Which many listeners might not realise.

RM: The science breakthrough came in early 1980s, 1982, this was discovered. And then, when you discover something like that, it takes a while to actually find a drug to fit. With the GLP-1 products, they have been on the market since 2005. So, I would broadly categorise us as being on around the third wave of these products.

So, say the first drugs tended to be less effective at reducing blood glucose levels, not as much weight loss, and were twice daily injections. Then we had the second wave, around the 2010s era, where we got products, which were still daily injections, but much more effective at reducing your blood sugar levels and also, giving more weight loss.

What's made this really exciting is, when you look in the last five or so years, we've got onto wave three, which is what we've moved to, once weekly, and we've got very, very good blood sugar control. But we've also got weight loss, which is around the 15 per cent level. And that's closing the gap with bariatric surgery, which is kind of roughly 30 per cent weight loss. And so, we're seeing meaningful weight loss and what that means for other health outcomes.

MB: And I think what's really interesting is we're seeing a mindset shift where weight is no longer seen as a lifestyle choice but more as a disease?

RM: Yeah, this is something that has come a long way in the last five years, but it has more to go. So, if I think about the root causes of obesity, what we're learning more about in the science is that there are genetic mutations, which will show from early on that you are more likely to go down the route of becoming obese. It's not simple as where we used to think this is just bad lifestyle choices, not doing enough exercise, eating too much. There's often a combination of the two. But this is not just as simple as people not having the willpower, and so choosing to become obese.

And then there's a second bit to the science that people call the set point theory. Whenever you try and lose weight, your body is naturally trying to get back to its peak weight, just something that's built up in humans over multiple, multiple generations. And that is difficult to change, that set point, and so that is where a belief is building that treating this is needing to be done in a chronic therapy. You need to be taking these treatments for the rest of your life because your body will always naturally try and spring back to that higher weight that you once were. So, this is really moving things forward. But we've still got a long, long way to go.

And I remember a conversation I had with one of the more sophisticated US healthcare insurance and hospital providers. And they were still very much of the mindset, this is even two or so years ago, that this is a disease where people who are not obese should not be paying for people who are obese – this is a lifestyle condition. They were still of that mindset. So, we've still got a long, long way to go. But that mindset is tipping over, and tipping over because of recent trials which show how these drugs are impacting other parts of people's lives beyond just the visible appearance change, from no longer being as obese.

MB: And one of the best-known drugs in this area is Wegovy. Tell me more about that.

RM: Wegovy is a drug from Novo Nordisk, a Danish pharmaceutical company. It's a brand name of a underlying molecule, which is called semaglutide. This was a huge development when this came through. This was one of two very, very effective once-weekly medicines. We've seen the success of this drug under a brand name Ozempic in diabetes patients, and now it's on the market for obesity as Wegovy. Patients are seeing great weight loss, around about the 15 per cent level, which is meaningful.

And what's really, really important in the recent trial that we've just had revealed – a trial of 17,000 patients, so it's a huge trial over five years, the biggest trial in the history of Novo Nordisk as a

company – if you take this drug, and if you stay on this drug, not only do you get the weight loss, but your probability of having a cardiovascular event, like a stroke, or a heart attack reduces by 20 per cent. And that makes people who have to pay for these drugs sit up and notice, because we know the healthcare burden of caring for patients who have those conditions. And so, it's not just people thinking, 'okay, this is not about making someone feel a bit better or look a bit better', this has actually got real, real consequences if we do start treating this as a drug therapy.

MB: You mentioned the health care burden there, and we've seen a number of US insurers commit to this and also the NHS is prescribing it. What's the significance of that?

RM: The payers are starting to take notice. One thing that's interesting is, the restrictions they put around being able to take this drug means that it's not yet getting prescribed in a way that is written on the label. So, where the regulator would say this should be for patients with a BMI above 30, or patients with a BMI above 27, and other conditions, the payers are saying, well, actually, we are going to give this to people above 35 or so. So, there's way to come to be reimbursed for this for the whole patient population that it should be.

And there are some restrictions as well that will need to change around the amount of time. This is a chronic therapy; you need to be taking this for the rest of your life. When you stop taking this, your weight will go up again and the cardiovascular benefits that you're seeing are reversing. So, for the system, it doesn't make a huge amount of sense to reimburse this for two years, bear all that cost, but not see the benefits down the line of having less patients with heart attacks or strokes, and the costs that are attached to that.

But this is still early. People are nervous. Healthcare budgets can be destroyed by this. When I talk about the 750 million people, these drugs, if you believe the headline costs around $1,000 a month in the US, you get the calculator out as a healthcare payer, and you start to get quite nervous about where this can go. And so, it's natural that people are just taking a bit of time to understand how to get the benefits for a broad population without destroying healthcare budgets.

MB: We've talked about the benefits, but what about the side effects?

RM: So, the main side effects that we think about are gastrointestinal side effects. Things like nausea, at the outset, when you're getting used to taking this therapy. This is actually a very clean class of drugs. We know there are risks with all drug therapy, we've got millions of years of patient data now on the GLP-1 therapies, particularly in this latest round. So, there are no main side effects that particularly give me cause for concern. But what I would say is, these are still drugs that are far from perfect, there's a lot of room for improvement.

And that's exciting because when you think about insulin, which has seen innovation for 100 years, we're only less than 20 years into the innovation cycle here. And so yes, that nausea is an important one that will be sorted with future iterations. There are other things that can be improved

upon such as losing less of your lean mass when you take these drugs, or making them no longer injectable, or having a therapy that they combine with, that means you sustain the weight loss, and you don't rebound if you stopped taking therapy. So, a very imperfect class of drugs now, but a fantastic base from which to combine and grow.

MB: And have Novo Nordisk been able to meet the demand?

RM: No, not yet. So, they've got a lot of latent demand in there that they can't serve. This company is a mission-driven company, and so, what they're doing is they're being very careful to make sure that those who desperately need it and are on therapy can continue with therapy. While taking the decision to make sure people who are starting are maybe not as easy to get hold of the drug. So that's bad for commercials just know, but the right thing to do for patients.

MB: How long have you been looking at Novo Nordisk and how do you how did you come about it?

RM: Probably about 15 or so years, it's kind of been on the radar. I've been over to visit them in Denmark multiple times. Met with management, I would guess, maybe 50 times in multiple different settings. So yes, it's a company we've followed for a long time.

MB: Founded 100 years ago, probably best known for insulin, I guess?

RM: Correct. Absolutely. Yeah.

MB: And paint a picture of what the manufacturing process is like at Novo.

RM: Novo Nordisk in insulin have got a huge market share in manufacturing. And in GLP-1s, I expect it to be absolutely the same. I break it down roughly into three main stages. There's the production of what's called the active pharmaceutical ingredient, the raw materials. There's then the manufacturing of the pens that are used to inject these. And then there's the finishing and filling of those pens.

So, what is interesting, when you see huge spikes in demand, these manufacturing steps take a long time to get ready. And Novo Nordisk is committing a huge amount of capital expenditure in many of their manufacturing plants. They've got plants all around the world, but they've had recent investments in the US, in Denmark, and just committed to more investment in France as well. So that, to me, is something that will perhaps go on to become a really important competitive advantage, that the investment that needs to go in ahead of time is something that many will struggle to compete with.

MB: Will this give them an advantage when the drug goes off patent?

RM: It's something that I'm thinking about a lot just now, in whether life past patent expiry in 2032 does look very, very different. There's not only the fact that there's a scale, and the company likely

spending somewhere in the region of $20-to-£30 billion dollars building that capacity – that's a barrier. There's also a lot of technology know-how that's gone into this.

I remember very early on, maybe 2013, visiting their site in Denmark and having a conversation with one of the engineers there who was studying this, from what I could see, was just a metal pipe, it looked very plain vanilla to me. But hearing him passionately talk about how important this was for the marginal improvements in yield. That was something that at the time, I wasn't able to really place that.

But now when looking back and thinking about the manufacturing edge they've got, it's all of those 0.01 per cent things that they focus on, that really mean that they can produce these products, and potentially a far lower cost than most. So, it's a hypothesis I'll do more work on to try and understand. But I think it is something that's really exciting, and is a very different way to look at this company to typical patent expiries

MB: And presumably hard for other companies to replicate?

RM: Very, very, very hard. They've actually got very different technology using yeast cells, when others are doing a different process altogether, quite often, synthetic chemistry. That is something that they again, do, because they've focused on that for 20-plus years and mastered that. That means they've got a continuous process where many others are doing batch processing. And that is all something that adds into this pot of ‘very hard to compete with’.

MB: And it's their culture that really helps that, isn't it? Because they're partly owned by a foundation.

RM: Yeah, that's correct. The foundation has got about a quarter of the capital, but nearly 80 per cent of the votes. And that is really, really important. When I think about the pharmaceutical companies that I've been following for a number of years, it's interesting to observe how many of them go down these strategies, which takes them away from their roots. I remember 15 years ago, everyone was thinking about, ‘we've got this great pharmaceutical business, but what I'm going to do is I'm going to add on a vaccines business, or I'm going to add on a consumer health business, or an animal health business’, this diversification for stability point but taking away from what was your core. Interestingly, if you look at the last five years, everyone's been shedding off those assets and going back to their core.

What's happened here, I think, with Novo Nordisk and having that foundation, that they've been giving out huge scientific grants for decades. They want to be doing that decades forward. So, they want to make sure that Novo Nordisk is investing for the long term and keeping a focus on what they're good at. And through all that turbulence within the pharmaceutical sector, Novo Nordisk have been very focused on, ‘well, we're just going to stick to pharma’ and, within that, the vast majority of time and R&D budget is dedicated towards diabetes and the closely related subject of obesity. So that focus, the long-termism, I think that's hugely enabled by having that kind of cornerstone investor that's protecting them and making sure they're thinking long term. And rather

than having investors asking, ‘what's next quarter's gross margin going to be?’ ’Could you cut that capex because things are looking a little bit weak?’ That just never comes into the boardroom of Novo Nordisk. And so that focus is really, really helpful.

MB: And who are their competitors?

RM: So, this is this is something that will evolve quite a lot. So, their main competitor is Eli Lilly, within the GLP-1 space. So, they are a very, very credible, very strong competitor, great innovator. Beyond them, this is where it gets interesting. People have taken notice of this opportunity, people now think this is really, really exciting. So, within the last wee while alone, we've seen companies like Roche acquiring assets, or AstraZeneca acquiring assets, many, many biotechs going after this, which is absolutely to be expected.

Something to put in context is when you look on the clinical trials registration, you can see how many trials are going on for various classes of therapy. So, in obesity, just now there are 12,000 trials going on, just under that, so as a large number. But in oncology, There's well over 100,000. So, it's still a fraction of what's out there. And I think it's very, very understandable that people want to be interested in investing here. But it's also very, very difficult to come in when companies like Novo Nordisk have been focused on this class of drugs since the 1990s. So, they understand the disease. And importantly, they understand how to engineer a molecule to go after the pathways that they've identified.

And then I guess one slightly interesting technical point to think about is, for Novo Nordisk and Eli Lilly, who have been here at the start of this obesity category, when they're doing their trials it’s fair enough to do the comparison with placebo. If we now know that the standard of care is these, for these drugs like Wegovy, 15 percent weight loss, you get into some kind of more ethical challenging decisions to make. Like, is it fair to be saying, well, we know the standard of care is 15 per cent weight loss, and that therefore means you're 20 per cent less likely to have a cardiovascular event, is it reasonable to say we're not going to use that as a comparator, we're going to use placebo?

So there's things that come as an advantage of being early into this market that gives me confidence that Eli Lilly and Novo Nordisk will continue to be the leader, but the only way you stay leaders is by continuing to innovate. And when we go back to all the issues that I mentioned with these current drug therapies that need to still be resolved, Novo Nordisk, and Eli Lilly need to be focused on making sure that they're the ones closing down these opportunities.

MB: That requirement to continue to innovate is absolutely crucial. Is there enough competition in the market to ensure that's the case?

RM: The history of Novo would be they've never needed to be motivated by outside threats to do innovation. They are a company that has been very early on and been very mission driven in wanting to serve more patients. So, this is something that is at the heart. And again, that's guided by the Foundation and what the Foundation wants to achieve. So, I don't think it's one that they would have ever let their foot off the gas on because there was less competition. But what you've

seen them do is acquire a few of these early-stage assets where they think they can combine these with semaglutide or bring in new technologies, new platforms in house for them.

I think more competition is helpful but when we're thinking as investors, it is also a risk. Just as semaglutide has been this wonder drug, somebody could come out with a completely different modality and suddenly be a real competitive threat. So, there's always risk to that. The risk to that is a risk to our investment case. It's fantastic for society if we get that next stage developed. But when you look at a lot of the trials that are going on, it's people combining things with semaglutide. So, it's almost like semaglutide is setting itself out as a base therapy now, and we're putting stuff on top of that.

MB: Where else could we see benefits apart from just weight loss?

RM: Things that are closer to being tangibles, we've seen improvement on cardiovascular health, we've also seen for people suffering from chronic kidney disease. We saw a trial have to be stopped early because the efficacy was so good.

MB: How does that come about? How do they stop a trial because the efficacy is so good? Tell me more about that.

RM: Yeah, so if you gather enough events in a trial, and you have a board that looks at the data, they can make a judgement call on whether it is ultimately becoming, we've got enough information, it doesn't make sense to be giving some people placebo here anymore, and we've got something which, if you've got chronic kidney disease, if you're on actual active arm rather than the placebo arm, you would be benefiting and this would be helping your health. So, it's almost like a safeguard there would step in.

MB: And what else apart from kidney disease?

There's growing excitement about what this might mean for various liver diseases. Back to the point about this sending signals to your brain about cravings, there's a feeling that within addiction, different addiction-related conditions, this may work. And Alzheimer's is a very large opportunity and an opportunity that has been very, very difficult to develop drugs for. We've been looking at this for a very, very long time. And people have had really strong theories about if you clear certain amyloid plaques, this will lead to better cognitive function. It's never quite come through just yet. So, it's one that I would never have baked into an investment case that it would be dependent upon that.

It's almost like when they announced the trial, I remember having conversations with them about just how much you're going to spend. This was very expensive trial to run there were limited to 5 per cent of R&D. But I think it's the right thing to do to try this. I've seen some data in a Danish registry that gives them confidence that there is something there. But yes, I would have that as just

an ability to extend the hype cycle, if that does come, rather than this is what you need to make good returns for your clients.

MB: What I always find fascinating with our investment floor is you need a huge degree of knowledge of science and medicine to understand the firm light never noticed. Did you naturally gravitate towards these type of investment opportunities? Or are you quite wide ranging in the company as you research?

RM: I'm very wide ranging and whether you need deep scientific knowledge, I'd say it's debatable. I've been in and around many pharmaceutical companies in many events for investors where I've seen a lot of people so far in the weeds and their inability to separate what matters from what doesn't matter really struck me in the past. What I do is have a tendency to lean on conversations with experts.

So, when I think about where the excitement for obesity came from, for me here, it came from reading an article in the *New England Journal of Medicine*, finding the co-author and tracking him down, having a conversation with him, he'd been studying GLP-1s for decades, getting him to put the context about what this latest data was. And that set me off on a path thinking, right, this feels really material, this feels different. And so, I should be going and doing more work.

But I would typically lean on the academics that are out there, rather than me try and get up the learning curve and pretend that I can read and understand exactly what's going on at that low low level of detail. There are people out there that can do that. Because one day, I'll be looking at a pharmaceutical company. Next day, I'll maybe be looking at a company in a completely different sector. You can't afford to get too granular. But I think what's important is understanding what matters in the analysis.

MB: And you've worked at other asset managers. What's different about working at Baillie Gifford?

RM: The biggest change for me, and it's been a more impactful change than I even imagined, was being truly long term. One thing that I find quite funny, having been at a couple of other places is, within this industry, the vast majority people are getting the same emails from the same people with the same information. Being long term, most of the information that's out there, provided to this asset management industry, is not information that's useful for our time horizon. So, we're talking, 10 years is what we're looking to invest for. And so, we need to go away and do our own research, generate our own insights to come up with that. And that means, therefore, that we can invest the time to have these conversations with academics, do really long thematic bits of work.

And when I actually come back to the very root of when we invested in Novo Nordisk, it was a time when the company was going through some challenges. And we on our team have an investigative researcher, a former journalist, who goes away and speaks to lots of former employees and experts that aren't within the traditional networks of the asset management industry and gathers a picture of what a company is like. She did a bit of work on Novo Nordisk to really get to the heart of the R&D culture and see whether this is a culture that was still as strong as ever, but was just not

having a productive output for a small period in time. And that was what she came back with. She came back saying, you shouldn't be giving up on his company because we've got one product which has not been as innovative as many of their other products. You should be expecting this company to continue to have breakthroughs. And lo and behold, that's exactly what we've continued to see.

So doing that bit of work, having that type of resource, that's not something that I'd ever come across before in my career and that's really different. It's really empowering as well. And also, being long term is really interesting in how you can use that to build better relationships with companies. So many bits of work that I've done on Novo Nordisk have been shared with the board of Novo Nordisk.

For example, our analyst who looks at companies through our sustainability lens had done a bit of work on how Novo Nordisk had provided access to medicines in low- and middle-income countries, spoken to various people at the UN and WHO. Built up a picture of what best in class access looked like, worked out some things that Novo Nordisk weren't doing that could be best in class. We did that bit of work, fed it back, had a conversation with their team on that. And these little bits of back and forth make it feel like a partnership or a relationship, rather than kind of transaction where I come along and once a year I sit down, I try and grill you for information and then disappear, never to be seen again.

MB: One question we always finish the podcast with is, what book are you reading at the moment, Ross?

RM: It's a book about cricket. I have, in my LinkedIn profile, attempted several times to make a tenuous link between investments and cricket. But I think I'd be stretching a little bit here. It's called *Hitting Against the Spin*. And it's really, really interesting, because there's so much data available in cricket. And what this is doing is using this data to go and challenge some of the default assumptions, such as in test cricket, if you win the toss, should you bat first? Should you bowl first? Why are left-handers typically over-represented in top batting orders? I read that as a left-hander who plays cricket hopelessly thinking, well, there's maybe hope for me yet. But it's just a really interesting way of putting data over assumptions. It's not something I would say was necessarily going to make me a better investor. But maybe it made me more marginally better cricketer.

MB: Maybe there's a there's a link there in terms of marginal gains in data as with investment?

RM: Possibly. In fact, having said I will not make on, let's try and make a tenuous link. I think just the fact of using data to challenge some of your assumptions, something we always have to do. Every company has got a narrative that you can avoid being drawn into just by going back and refreshing your memory of what the actual data tells you. And I often say it can disrupt a good story, but it's for good reason as well.

MB: Ross, great to have you on. Thanks for joining us.

RM: Thanks very much.

MB: And thanks for investing your time in *Short Briefings on Long Term Thinking*. You can find all our episodes at baillliegifford.com/podcasts or subscribe at Apple Podcasts, Spotify and other platforms. And if you enjoyed listening and would like to discover more insights from our income team, then check out 'Looking back: the long-term case for dividend growth', which is a paper by Ross's colleague, James Dow, which you can find at baillliegifford.com/insights. Until next time, goodbye.

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