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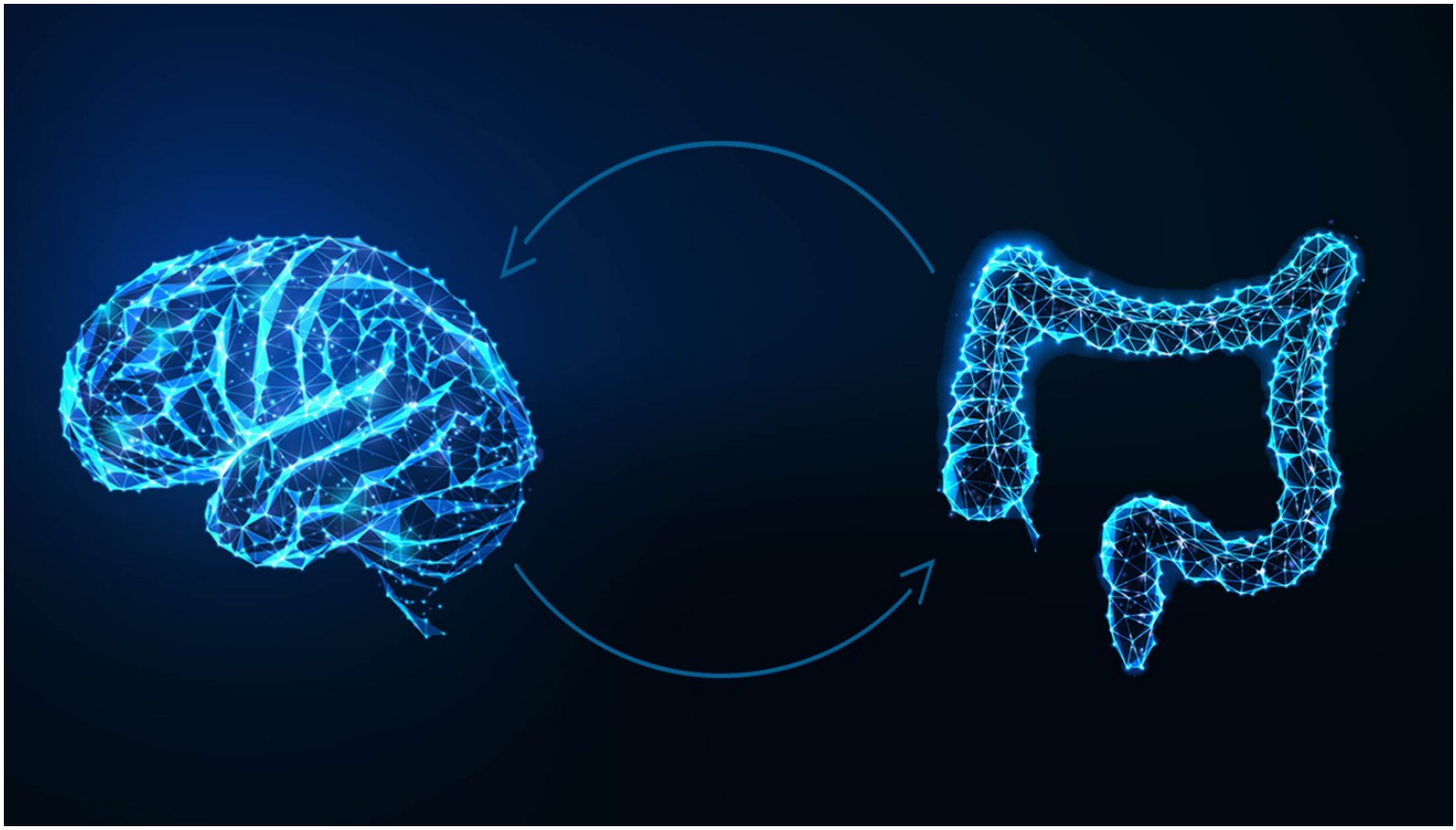
Pharmaceuticals

Unlocking the Obesity Challenge: a >$50bn Market

We have built a detailed bottom-up global obesity model focusing on the key bottle-necks - patient activation, physician engagement, payer recognition - and incorporating all the key biopharma stakeholders based on a full review of the industry's pipeline. With conservative pricing assumptions, we believe global obesity sales could reach >$50bn in 2030. This would lift obesity from a $2.4bn category to a top-12 therapy area by global spending.



Contributors

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Mark D Purcell

Equity Analyst

+44 20 7677-8557

Mark.Purcell@morganstanley.com

MORGAN STANLEY & CO. LLC

Terence C Flynn, Ph.D.

Equity Analyst

+1 212 761-2230

Terence.Flynn@morganstanley.com

MORGAN STANLEY & CO. LLC

Matthew Harrison

Equity Analyst

+1 212 761-8055

Matthew.Harrison@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Edward Stanley

Equity Strategist

+44 20 7425-0840

Edward.Stanley@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Jasper De Maere

Research Associate

+44 20 7425-3602

Jasper.De.Maere@morganstanley.com

MORGAN STANLEY MUFG SECURITIES CO., LTD.+

Shinichiro Muraoka

Equity Analyst

+81 3 6836-5424

Shinichiro.Muraoka@morganstanleymufg.com

MORGAN STANLEY ASIA LIMITED+

Sean Wu

Equity Analyst

+852 3963-0755

Sean.Wu@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Thibault Boutherin

Equity Analyst

+44 20 7425-9688

Thibault.Boutherin@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

James P Quigley

Equity Analyst

+44 20 7677-1963

James.Quigley@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Sarita Kapila

Equity Analyst

+44 20 7425-1320

Sarita.Kapila@morganstanley.com

MORGAN STANLEY & CO. INTERNATIONAL PLC+

Philippa K Pritchard

Research Associate

+44 20 7425-1422

Pippa.Pritchard@morganstanley.com

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Unlocking the Obesity Challenge: a >$50bn Market

Obesity is the new hypertension and looks set to become the next blockbuster pharma category. We believe the treatment of obesity, classified by the American Medical Association (2013) and now the European Commission (2021) as a chronic disease, is on the cusp of moving into mainstream primary care management and that the obesity market is where the treatment of high blood pressure was in the mid-to-late 1980's before it transformed into a $30bn market by the end of 1990's. Focus is shifting to the upstream cause as opposed to the downstream consequences of diabetes and cardiovascular disease. Therefore we expect excess weight and fat loss to become treatment targets for obesity and for treatment guidelines to adopt obesity as a primary target ahead of other associated diseases.

A confluence of catalysts should begin to unlock the potential over the next 6 months:

1) We expect Novo's landmark obesity study, SELECT, to conclude that "weight management saves lives". An interim analysis is anticipated in 3Q22 and our work suggests that Novo's obesity medicine Wegovy will deliver a 27% reduction in the risk of heart attacks, strokes and cardiovascular deaths, a key factor to improve obesity market access.

2) Progressive removal of Wegovy supply constraints starting in 3Q22. The US launch of Wegovy has been held in check by supply constraints and once these shackles are removed, underlying patient demand will be released in the second half of 2022.

3) Social media: early signs of an exponential virtuous cycle. Our analysis shows that social media is already creating a recursive cycle of education, word of mouth and heightened demand for weight-loss drugs. The launch of Wegovy in mid-2021 has created a "halo effect" centred on the patient-physician axis of obesity treatment, with the prescription growth rate of weight-lowering GLP-1 medicines in diabetes more than doubling.

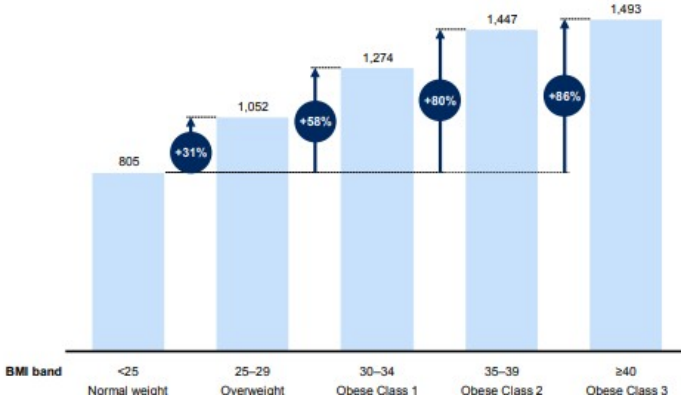
4) Diabetes treatment guidelines are actively evolving after a long period of inertia. Cardio-centric goals were incorporated in 2020 and a greater emphasis on weight-centric goals is anticipated in 2023.

Our new proprietary obesity model suggests >$50bn revenue potential. We have built a detailed bottom-up global obesity model focusing on the key bottle-necks (patient activation, physician engagement, payer recognition) and incorporating all the key biopharma stakeholders based on a full review of the industry's pipeline. Over time, we expect one quarter of obese individuals will engage with physicians (up from 7% today; compares to circa 80% for high blood pressure and diabetes) and 55% of these patients will receive a new anti-obesity medicine. Mirroring hypertension in the 1980's, our analysis shows that the biopharma pipeline of obesity medicines is expanding rapidly, enhancing our understanding of the disease biology and promising higher quality weight loss solutions in the future. With conservative pricing assumptions, we believe global obesity sales could reach $54bn in 2030. This would lift obesity from a $2.4bn category to a top-12 therapy area by global spending.

Novo Nordisk and Eli Lilly seen as category winners. We project Novo and Lilly to each capture a circa 40% share of the obesity revenue opportunity, supported by 12 obesity medicines in clinical development between them. There are many derisking clinical, regulatory and commercial steps in the development of the obesity market and we adjusted our company forecasts accordingly. **For Novo**, we have raised our obesity sales forecasts by >26% 2024-29 to reflect our increased confidence in market dynamics ahead of the Wegovy SELECT study interim analysis in 3Q22 and project obesity revenues of $11.7bn in 2030 (see our accompanying upgrade note here). **For Lilly**, we leave our above consensus obesity sales forecast of $6.5bn ($5.4bn for tirzepatide alone) in 2030E unchanged ahead of the SELECT readout, but we see significant upside potential with total revenues of $22bn projected by our obesity model and every $1bn of incremental revenues adding 4-5% to our long-term earnings estimates. We expect large-cap biopharma companies with established commercial platforms in cardio-metabolic disease will seek to break Novo's and Lilly's "duopoly", with innovative pipeline medicines from biotech players such as **Altimmune, Zealand Pharma, Hamni,Regor Therapeutics**, **Sciwind Biosciences** and **vTv Therapeutics** generating proof-of-concept data over the next 6-12 months. We highlight that **Polypeptide Group**, **Chugai** and **Innovent Biologics** have partnerships with Lilly, providing diabesity revenue leverage for investors ahead of the SELECT study readout.

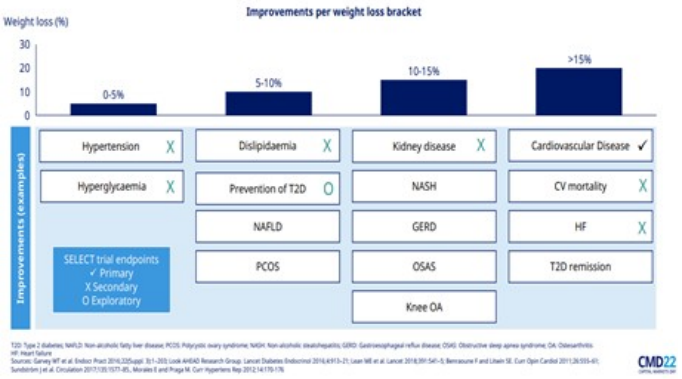
Unlocking the Obesity Challenge

Exhibit 1: Cost to society: medical costs rise with increasing levels of obesity (£ per capita)



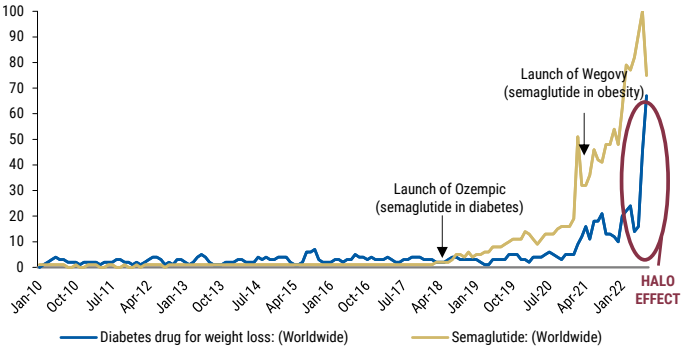
Source: McKinsey Global Institute 2014

Exhibit 2: Positive impact of weight loss drugs: a broad range of health benefits



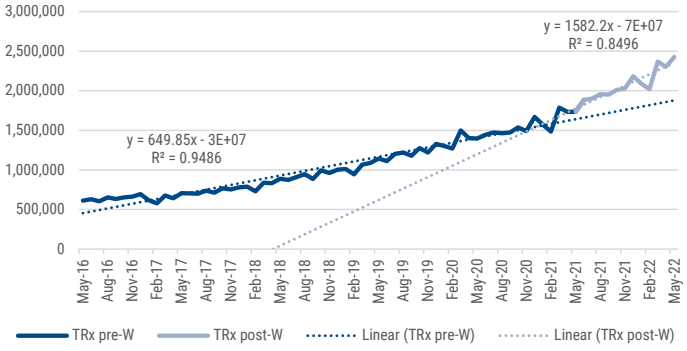
Source: Novo Nordisk Capital Markets Day 2022

Exhibit 3: Social media activity from Wegovy is driving patient engagement...



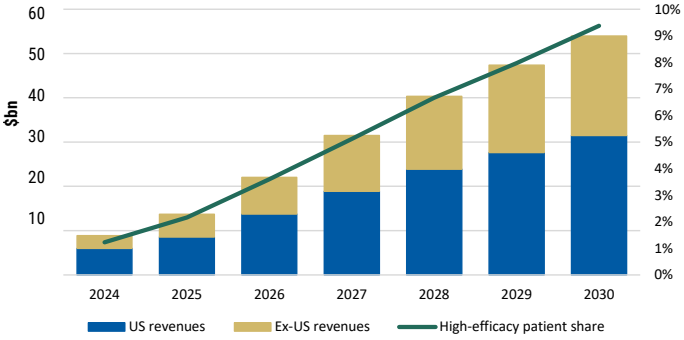
Source: Google trends, Morgan Stanley Research

Exhibit 4: ...and physician prescribing of weight saving GLP-1 medicines for diabesity



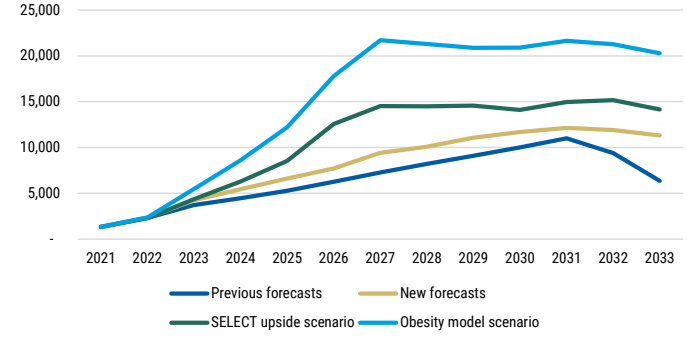
Source: IQVIA, Morgan Stanley Research

Exhibit 5: The New Obesity Model: $54bn global revenue potential in 2030E



Source: Morgan Stanley Research estimates

Exhibit 6: SELECT outcomes study: key near-term catalyst for Novo Nordisk



Source: Morgan Stanley Research estimates

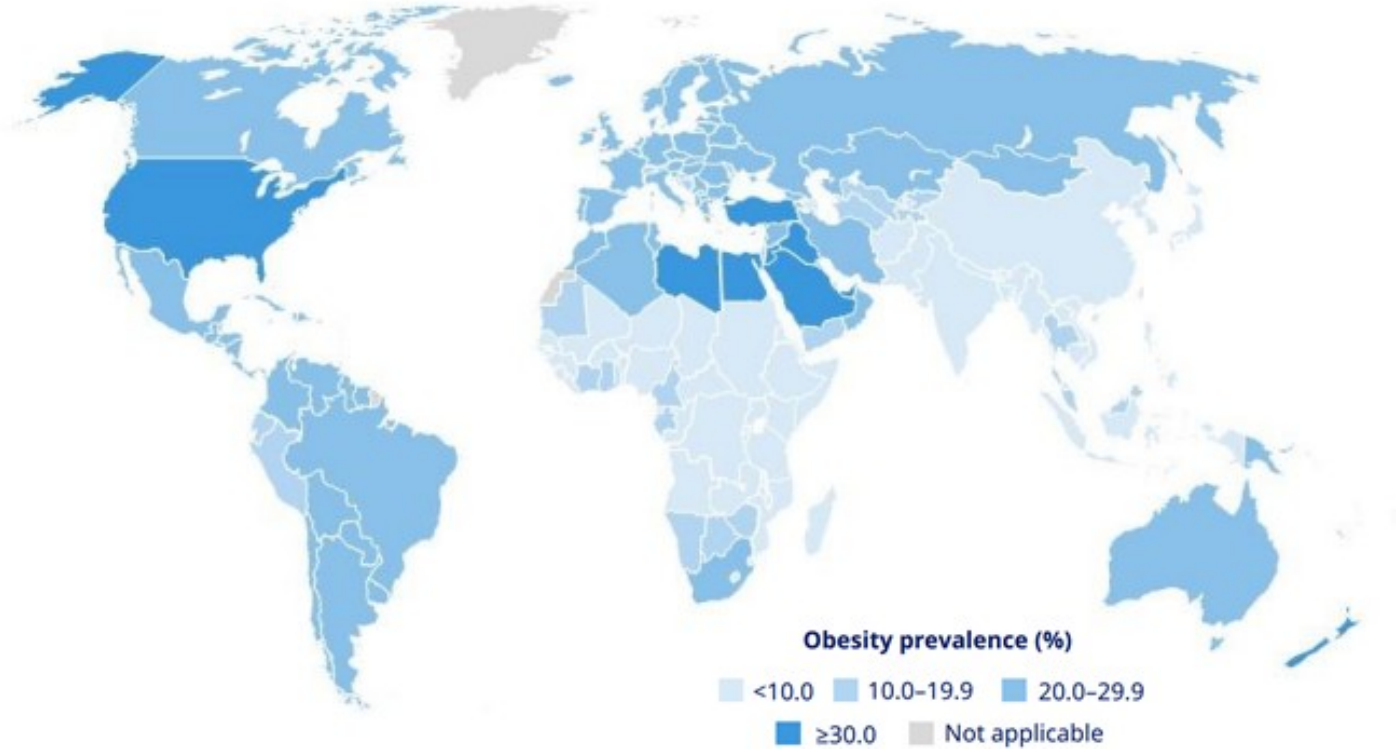
Executive summary

It is estimated that more than 650m people are living with obesity. The associated personal, social and economic costs are huge, with the World Health Organization estimating obesity to be responsible for 5% of all global deaths, which impacts global GDP by circa 3% (McKinesey Global Institute). Obesity is associated with >200 health complications from osteoarthritis to kidney disease to early loss of sight, so tackling the obesity epidemic would indirectly impact orthopedic surgery, dialysis care, the food industry and the leisure sector.

We believe the narrative around obesity is changing, with a more empathetic media tone, exponential social media growth and increased recognition across healthcare professionals and policy-makers. Biopharma is focused on a patient-centric strategy to encourage patients (Truth About Weight) to engage with physicians (Rethink Obesity), supported by outcomes data and improved market access.

Novo's landmark obesity study, SELECT, has set out to prove that "weight management saves lives". An early stopping decision for overwhelming efficacy for the SELECT study is anticipated in 3Q22, and we believe that anti-obesity medicine Wegovy will deliver a 27% reduction in the risk of heart attacks, strokes and cardiovascular deaths, and with it a step-change in unlocking obesity revenue potential.

Exhibit 7: Obesity is a preventable global pandemic affecting more than 650m people



Source: Novo Nordisk Capital Markets Day March 2022; World Health Organization 2018

What's new?

In this Global Insight report we have built a detailed bottom-up global obesity model focusing on the key bottle-necks (patient activation, physician engagement, payer recognition) and incorporating all the key biopharma stakeholders based on a full review of the industry's pipeline. Reflecting the scale of the patient demographics, we have 'top-down sense-checked' our obesity forecasts ($54bn revenue potential in 2030) against how chronic markets such as hypertension have evolved in the past and the revenue scale of the cholesterol lowering / non-insulin diabetes markets if they were fully branded today. Diabetes treatment guidelines are actively evolving after a long period of inertia, incorporating cardio-centric goals in 2020 and with a greater emphasis on weight-centric goals anticipated in 2023.

Our analysis shows that the launch of Wegovy in mid-2021 has created a "halo effect" centred on the patient-physician axis of obesity treatment, with social media activity showing showing early signs of exponential growth and the prescription growth rate of weight-lowering GLP-1 medicines in diabetes more than doubling. Mirroring hypertension in the 1980's, the biopharma pipeline of obesity medicines is expanding rapidly, enhancing our understanding of the disease biology and promising higher quality weight loss solutions in the future. The next step in the journey will be the landmark obesity study, SELECT, which we expect will accelerate these trends.

Obesity is the new hypertension

Treatment of obesity is on the cusp of moving into mainstream primary care management. We believe that the obesity market is where the treatment of high blood pressure was in the mid-to-late 1980's. Obesity and hypertension were both initially believed to consequences of lifestyle choice as opposed to true diseases. Blood pressure became a treatment target backed by proven mortality benefits from 1979 onwards requiring long-term management to effectively control it. Combination therapy was critical to achieving consistent, robust blood pressure lowering and following the launch of next generation medicines in the mid-1980's, the global hypertension market reached $30bn in sales ($54bn today, CPI-adjusted) at the end of the 1990's.

We anticipate the first landmark obesity study, SELECT, will shortly prove that "weight management saves lives". We expect excess weight and fat loss to become treatment targets for obesity and, in the pursuit of more consistent and greater weight loss, we believe that obesity will become a combination treatment market, benefiting from a wave of new treatment approaches. As explored in detail in this report, modest uptake rates for obesity medicines and conservative pricing assumptions point to obesity becoming >$50bn global market. Whilst this might sound a stretch ahead of a series of key catalysts, it is important to consider the considerable healthcare savings that effective obesity treatment could deliver, with obesity estimated to account for >8% of healthcare budgets and impacting global GDP by circa 3%.

Exhibit 8: Market dynamics for selected chronic cardio-metabolic diseases

	Obesity	Cholesterol	High blood pressure	Diabetes	Obesity (raised awareness)
Prevalence	142,228,850	94,000,000	116,000,000	37,300,000	142,228,850
Diagnosed/rec. medical treatment	9,800,000	85,923,218	91,700,000	29,314,956	56,891,540
% patients diag / rec. medical treatment	7%	91%	79%	79%	*40%*
Actual treated	3,920,000	47,000,000	33,600,003	24,243,469	31,290,347
% treated	40%	55%	37%	83%	*55%*
% patients treated, controlled	n/a	56%	70%	51%	na
Total prescriptions	10,240,782	249,039,740	636,660,671	218,856,941	250,322,777
Current gross sales ($m)	1,613	2,207	8,514	85,278	na
Revenues ($m) assuming $350/script	3,584	87,164	222,831	76,600	87,613
At $350/script (where statins got)	3,584.27	87,163.91	222,831.23	76,599.93	

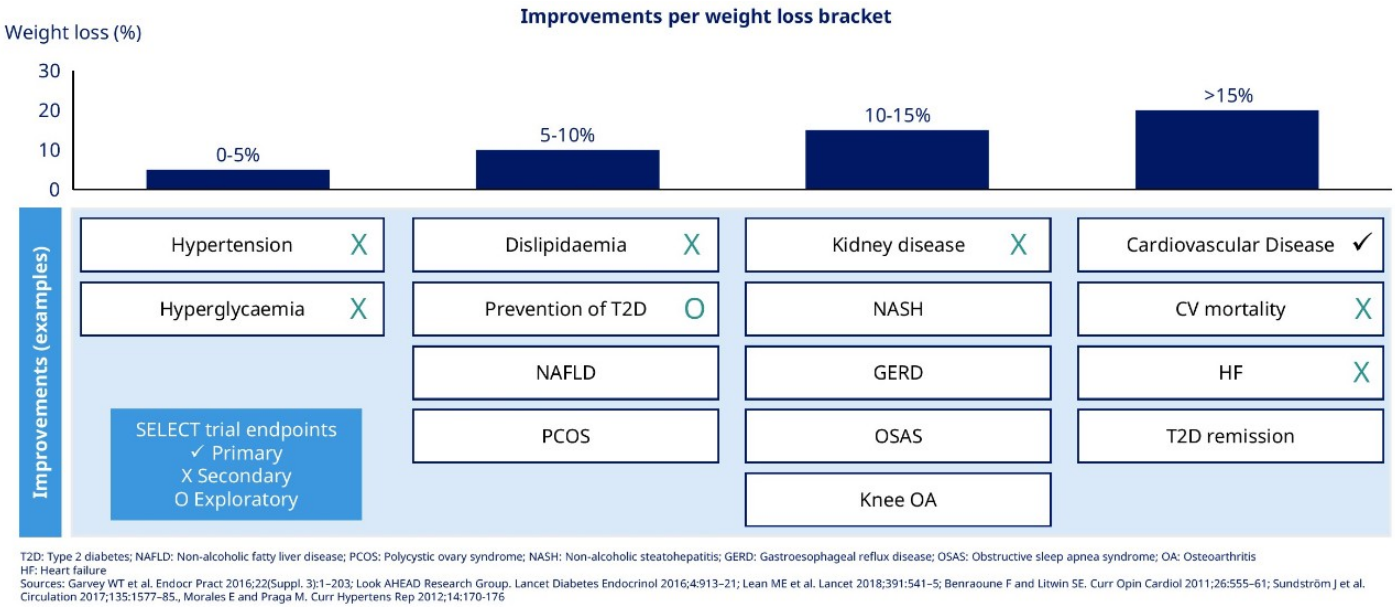
Source: IQVIA; CDC; Morgan Stanley Research

An early stopping decision for overwhelming efficacy for the SELECT study is anticipated in 3Q22. Our analysis suggests that Novo Nordisk's obesity medicine Wegovy will deliver a 27% reduction in the risk of heart attacks, strokes and cardiovascular deaths. We expect this will act as an extremely powerful message for physicians, national treatment guideline policies and payers alike, opening up the patient-physician engagement bottleneck. We would expect positive SELECT data to be incorporated into treatment guidelines in the US no later than the end of 2023, targeting >15% weight loss in diabetics. The increased focus on weight loss following the launch of Novo's Wegovy and positive data for Eli Lilly's tirzepatide has already created a halo effect behind the use of GLP-1 medicines, with the rate of prescription growth more than doubling over the past year.

Focus is shifting to the upstream cause as opposed to the downstream consequences of diabetes and cardiovascular disease. Obesity, or more formally the abnormal accumulation of fat tissue (adiposity), is a key upstream driver of downstream complications such as diabetes and cardiovascular disease; as such, we expect obesity will over time become a primary focus in treatment guidelines. If caught early enough, substantial weight reduction can reverse the progression of diabetes and patients can achieve remission. Importantly, the management of diabetes has undergone a major conceptual change recently with a focus on cardio-centric goals. Therefore we believe the door is already very much ajar to support a shift in clinical care to include weight-centric goals and support the uptake of obesity medicines.

It's a just a matter of time before the key bottleneck for obesity - the activation of patients to seek treatment and engagement with physicians - is addressed. Key inflection points ahead for investors in the obesity market journey include: (1) the interim analysis of the Wegovy SELECT trial in 3Q22, which is the key near-term catalyst; (2) treatment guideline updates anticipated at the end of 2022 and 2023; (3) supportive co-morbidity trials across obesity-related diseases from 2023-onwards for both semaglutide and tirzepatide (Exhibit 28); (4) a wave of next-generation obesity medicines generating proof-of-concept data over the next 12 months and launching in 2025/26; (5) improving reimbursement dynamics, with Wegovy commercial formulary access circa 80% (circa 20m individuals with access post employee opt-in) and a potential TROA (Treat and Reduce Obesity Act) decision opening up Medicare/Medicaid channels 2025-onwards. Important upcoming "reality checkpoints" include whether: (1) the "relaunch" of Novo's Wegovy drives an expansion of the US obesity market in 2H22/2023; (2) Eli Lilly adopts a flat pricing strategy for tirzepatide across diabetes and obesity (which is what we model).

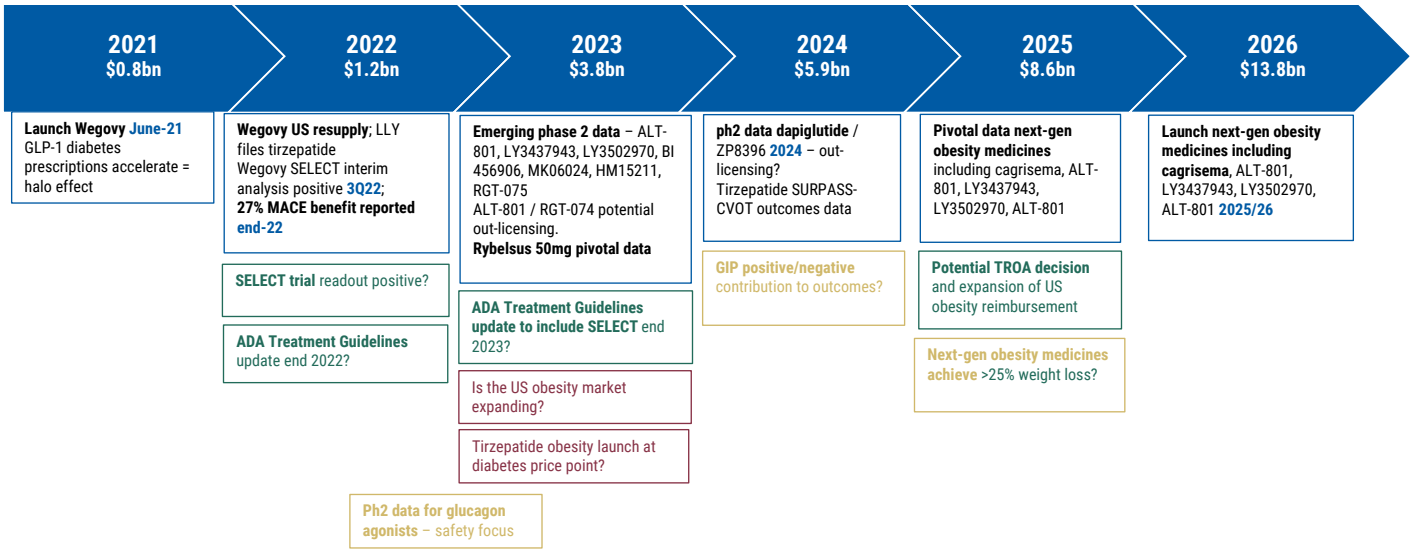
Exhibit 9: Greater and more consistent weight loss delivers a broader range of health benefits



T2D: Type 2 diabetes; NAFLD: Non-alcoholic fatty liver disease; PCOS: Polycystic ovary syndrome; NASH: Non-alcoholic steatohepatitis; GERD: Gastroesophageal reflux disease; OSAS: Obstructive sleep apnea syndrome; OA: Osteoarthritis
HF: Heart failure
Sources: Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–5; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85., Morales E and Praga M. Curr Hypertens Rep 2012;14:170-176

Source: Novo Nordisk Capital Markets Day 2022

Exhibit 10: US obesity market expansion checkpoints; 2023-25 represent key transition years

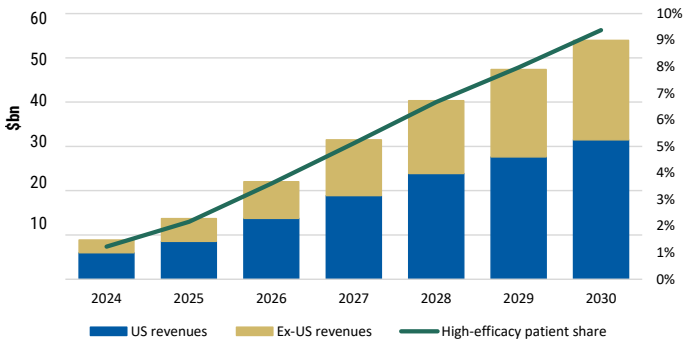


Source: Morgan Stanley Research

Our proprietary analysis suggests $54bn global revenue potential

We have remodelled the obesity medicine opportunity based on positive SELECT trial data driving positive treatment guideline changes at the end of 2023. We believe the domino effect of this will be to unlock the patient-physician engagement bottleneck and broaden payer engagement. We have assumed that the percentage of the obese patient target population which is actively managed increases from 10% to 25% in 2035E (equivalent to two-thirds of the severely obese target population being actively managed) and that the proportion of actively managed patients who receive an anti-obesity medicine rises from 40% to 55% in 2035E (a similar adoption rate to cholesterol lowering medicines). We have assumed that patients stay on the new, more-effective anti-obesity medicines for longer (8 months average treatment).

Exhibit 11: Obesity market projections: $54bn global revenue opportunity in 2030E



Source: Morgan Stanley Research estimates

We expect increased competition to drive obesity medicine prices down. Greater competition in the diabetes market means that GLP-1 medicines are priced at $890-970/month and attract >50% rebates, whereas essentially the same medicines are priced at $1,349/month and attract closer to 30% rebates for the treatment of obesity. We have perhaps conservatively assumed that Eli Lilly adopts a flat pricing strategy for tirzepatide across diabetes and obesity such that pricing converges. We expect the net price of GLP-1 medicines in obesity to fall to $450/script in 2025E and $350/script in 2030E (ahead of increased visibility, we model a flat tirzepatide net price of $505/script). The potential entry of new players into the obesity/non-alcoholic fatty liver disease (NAFLD) market, including Pfizer, Merck, AstraZeneca and Novartis, especially in the small molecule space has potential to further potentiate pricing pressure.

Novo Nordisk and Eli Lilly are seeking to strengthen their largely "duopoly" GLP-1 position with 12 obesity medicines in clinical development. Eli Lilly's tirzepatide has raised the efficacy bar in obesity with up to a 21% weight reduction sustained over 72 weeks in the SURMOUNT-1 trial (see here) compared to 15% with Novo's Wegovy in the STEP-1 trial. We expect Lilly to explore a fast route to market for tirzepatide in obesity (i.e., filing on a single Ph3 trial) with more details in 2H22. We expect Novo to fight back and conduct a head-to-head trial against tirzepatide with Wegovy in combination with cagrilinitide, targeting 25% weight loss comparable to bariatric surgery. Both companies have additional combination and oral obesity medicines expected to launch from 2024-onwards.

Exhibit 12: Leading approaches for the treatment of obesity

	GLP-1/GIP weekly inj.	Glucagon-focused weekly inj.	Amylin weekly inj.	Oral GLP-1 approaches	Long-acting GIPR inj.
Obesity focus	Weight & glycemic centric	Weight, cardio & glycemic centric	Weight centric	Weight & glycemic centric	Weight centric only?
Indications	Diabetes, obesity	NASH, obesity, diabetes	Obesity	Diabetes, obesity	Obesity
Weight loss	++	+++	++	++	+++
HbA1c	++	++	neutral	++	?
LDL-C	+	+++	+	+	?
SBP	+	++	neutral	+	?
Liver fat	na	+++	na	na	?
Safety	Nausea, diarrhea	Nausea, diarrhea, **heart rate?**	Nausea, diarrhea	Nausea, diarrhea	?
Companies	Novo Nordisk, Eli Lilly, Zealand Pharma, Sci	Eli Lilly, Altimmune, Boehringer/Zealand Ph	Novo Nordisk Zealand Pharma, Eli Lilly	Novo Nordisk, Eli Lilly, Pfizer, Regor Therap	Amgen

Source: Morgan Stanley Research

Can Novo and Lilly "duopoly position" be challenged in obesity? We expect large-cap biopharma companies with established commercial platforms in cardio-metabolic disease and research interests in obesity will be in competition to in-license the current crop of unpartnered innovative obesity medicines in development. We believe combination approaches will be required to improve the depth, consistency and quality of weight loss in obesity and that two to three credible challengers to Novo and Lilly will emerge. Attractive pipeline opportunities: (1) weekly injectible foundational assets include Altimmune's ALT-801, Hamni's HM15211, Zealand Pharma's dapiglutide; (2) Zealand Pharma's weekly amylin analogue AP8396 offers a combination option; (3) oral GLP-1 assets from Regor Therapeutics, vTv Therapeutic and Sciwind Biosiences.

Glucagon represents a disruption risk to Novo. Targeting glucagon receptors has received relatively limited attention, with Novo abandoning the target based on safety concerns arising in early stage clinical trials. With the exception of heart rate increases, these safety issues have not been seen with medicines developed by other pharma companies which target glucagon (GLP-1R/GCGR dual agonists) ahead of phase 2b data involving >2,200 patients reading out before the end of 2022. Glucagon resistance appears to be a critical first step in the development of diabetes and cardiovascular disease and the quality of weight loss achieved could be superior to other approaches. We note that after 12 weeks, Altimmune's ALT-801 has shown 10% weight loss (trending towards circa 20% at 24 weeks), striking reductions in blood pressure and LDL-C cholesterol, >90% removal of liver fat and no increase in heart rate.

Exhibit 13: Global anti-obesity medicines revenue projections

$m	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US revenues										
Novo	780	1,572	3,935	5,798	7,606	11,101	13,032	12,598	12,175	12,208
Lilly	-	-	-	171	841	2,304	4,833	8,515	10,858	12,599
Altimmune	-	-	-	-	42	134	531	1,493	2,348	3,099
Amgen	-	-	-	-	-	-	19	119	276	630
Other	-	-	-	23	84	219	493	1,139	1,989	2,973
TOTAL	**780**	**1,572**	**3,935**	**5,992**	**8,574**	**13,758**	**18,908**	**23,866**	**27,647**	**31,509**
Ex-US revenues										
Novo	554	790	1,531	2,815	4,587	6,706	8,674	8,697	8,699	8,702
Lilly	-	-	-	73	479	1,378	3,201	5,859	7,743	8,969
Altimmune	-	-	-	-	24	80	352	1,028	1,675	2,206
Amgen	-	-	-	-	-	-	12	82	197	448
Other	-	-	-	10	48	131	327	784	1,418	2,117
TOTAL	**554**	**790**	**1,531**	**2,899**	**5,138**	**8,295**	**12,566**	**16,450**	**19,732**	**22,442**
Global revenues										
Novo	1,335	2,362	5,466	8,614	12,194	17,808	21,706	21,295	20,874	20,910
Lilly	-	-	-	244	1,320	3,681	8,033	14,374	18,601	21,567
Altimmune	-	-	-	-	66	214	884	2,521	4,023	5,306
Amgen	-	-	-	-	-	-	31	201	473	1,078
Other	-	-	-	33	132	350	820	1,924	3,408	5,090
TOTAL	**1,335**	**2,362**	**5,466**	**8,891**	**13,711**	**22,054**	**31,474**	**40,315**	**47,379**	**53,951**

Source: Morgan Stanley Research estimates

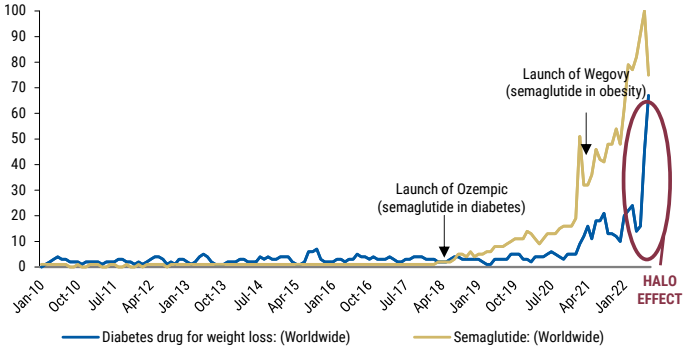
Social media and obesity: from linear to exponential demand. Once obesity treatment is understood and more widely accepted, with the patient-physician bottleneck addressed, it can catalyse a step-change in demand. Our analysis shows that social media is already creating a recursive cycle of education, word of mouth and heightened demand for weight-loss drugs as they become more widely available to the public and is re-accelerating interest / prescription growth in weight-lowering GLP-1 medicines for diabetes. Simply put, if calorie counting apps are the linear growth route to obesity management, social media combined with medicines like Ozempic and Wegovy are already showing the early signs of an exponential virtuous cycle.

We project the global obesity market to reach $54.0bn in 2030E, split $31.5bn US and $22.5 ex-US. This would represent an out-sized revenue uplift for the obesity market from outside the top-20 therapy areas by global spending ($2.4bn category in 2022E) into a top-12 position. We have assumed that Novo Nordisk and Eli Lilly will each hold a circa 40% share of the obesity market in 2030, reflecting their largely "duopoly" GLP-1 position and deep development pipelines which offer a broad range of combination treatment options. Ahead of proof-of-concept data for over 10 competitive medicines over the next 6-12 months, we have assumed that Altimmune's ALT-801 captures an 8% peak share and that Amgen's potentially disruptive long-acting antibody AMG833 captures a 5% peak share. Our analysis suggests that with a focus on combination approaches, Wegovy will represent <20% of Novo's obesity franchise ahead of patent expiry in 2031.

Stock implications

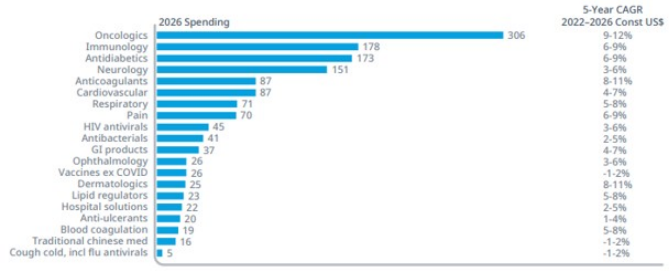
Novo Nordisk: raising earnings estimates by 7-9%, upgrading to Overweight. We have raised our Novo obesity revenue forecasts to reflect our increased confidence in market dynamics ahead of the Wegovy SELECT study interim analysis in 3Q22 (Exhibit 18). Importantly, we have raised our pipeline sales estimates for the semaglutide injectible combinations and for the oral obesity options in recognition that the obesity market is likely to move towards combination approaches with deeper, more consistent and higher quality weight loss reductions. As a result of this, Wegovy represents <20% of our obesity franchise revenues ahead of patent expiry in 2031. So whilst the uplift to our obesity forecasts is >26% and our group earnings is 7-9% from 2024-28, our DCF valuation is raised from DKK805/share to DKK915/share to reflect increased revenue durability.

Exhibit 14: Google search activity globally for the terms "semaglutide" and "drug for weight loss"



Source: Google trends, Morgan Stanley Research

Exhibit 15: Top-20 therapy areas in 2026 in terms of global spending



Source: IQVIA Institute, Nov 2021

Exhibit 16: Novo Nordisk obesity revenues scenarios

$m	2021	2022	2023	2024	2025	2026	2027	2028	2029
Previous forecasts	1,335	2,330	3,728	4,464	5,267	6,257	7,263	8,209	9,088
New forecasts	1,335	2,352	4,241	5,448	6,616	7,716	9,419	10,086	11,069
SELECT upside scenario	1,335	2,298	4,369	6,281	8,535	12,569	14,529	14,502	14,580
Obesity model scenario	1,335	2,362	5,466	8,614	12,194	17,808	21,706	21,295	20,874
Consensus	1,335	1,887	2,845	3,780	4,831	5,850	6,838	7,803	8,796

Source: Morgan Stanley Research estimates, Visible Alpha consensus

We have made a number of conservative assumptions including: (1) an increasingly competitive obesity market, with Novo's value share falling to circa 40% from an initial "monopoly" position and (2) the pricing of GLP-1 medicines in obesity converging with diabetes pricing and continuing to soften as competition increases. The key risk from a competitive standpoint remains the successful development of glucagon-targeting medicines, although Novo could return to be a fast-follower. Relative to Novo's strategic aspiration of >DKK25bn in obesity sales in 2025, we forecasts DKK47bn and consensus DKK35bn.

The key upside risks to our forecasts include: (1) a positive SELECT study interim analysis 3Q22, where we expect Wegovy to reduce the risk of cardiovascular events by 27% and (2) de-risking of the obesity pipeline based on positive proof-of-concept data. Positive top-line SELECT study data (>20% cardiovascular risk benefit) released as early as 4Q22 could increase our long-term obesity forecasts by a further 19-27% and lift our DCF valuation to DKK1025/share. Therefore, reflecting the positive risk-reward balance going into the SELECT study interim analysis, we have upgraded our Novo Nordisk rating to Overweight.

Despite an increasing focus from diabetes treatment guidelines on weight centric targets, we have assumed the halo effect from the launch of Wegovy fades such that the growth rate of Novo's GLP-1 franchise in diabetes, spearheaded by Ozempic, normalises from a mid-30% growth rate to an 11% CAGR 2022-28. We have removed cagrisema in diabetes from our forecasts ahead of phase 2 data in 2H22, leaving Novo's diabetes franchise increasingly reliant on higher doses of semaglutide and the icodec-sema combination program for growth.

Exhibit 17: Novo Nordisk earnings estimates raised by 7-9% 2024-28E (DKKm)

New forecasts	2021	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Sales	140,800	171,975	200,926	224,000	247,856	272,220	297,852	313,731
Operating profit (published)	58,644	74,233	93,910	107,608	120,247	136,718	152,427	158,356
Adjusted Net profit	47,757	55,847	73,768	84,794	94,779	107,791	120,201	124,885
EPS diluted (adjusted)	20.74	24.62	33.01	38.51	43.67	50.40	57.02	60.10

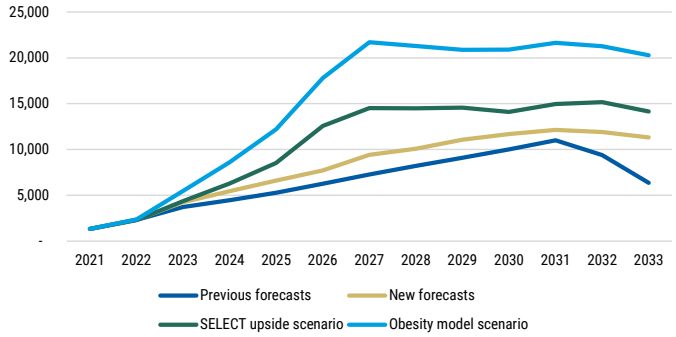
% growth	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Sales		22.1%	16.8%	11.5%	10.7%	9.8%	9.4%	5.3%
Operating profit (published)		26.6%	26.5%	14.6%	11.7%	13.7%	11.5%	3.9%
Adjusted Net profit		16.9%	32.1%	14.9%	11.8%	13.7%	11.5%	3.9%
EPS diluted (adjusted)		18.7%	34.1%	16.6%	13.4%	15.4%	13.1%	5.4%

Previous forecasts	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Sales		171,819	197,308	217,061	238,435	262,197	283,199	301,401
Operating profit (published)		73,577	89,279	99,820	110,185	126,501	138,576	147,591
Adjusted Net profit		55,325	70,109	78,641	86,830	99,719	109,258	116,381
EPS diluted (adjusted)		24.39	31.37	35.71	40.01	46.62	51.83	56.01

% change	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e
Sales		0%	2%	3%	4%	4%	5%	4%
Operating profit (published)		1%	5%	8%	9%	8%	10%	7%
Adjusted Net profit		1%	5%	8%	9%	8%	10%	7%
EPS diluted (adjusted)		1%	5%	8%	9%	8%	10%	7%

Source: Morgan Stanley Research estimates

Exhibit 18: Novo Nordisk obesity revenue forecast scenarios



Source: Morgan Stanley Research; Visible Alpha consensus

Exhibit 19: Novo Nordisk revenue breakdown for the obesity franchise

US											
$m	2020	2021	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e
Saxenda	494	560	544	435	305	102	67	45	30	20	13
Wegovy	-	220	1,075	2,829	3,856	4,721	4,792	4,615	3,491	2,748	1,627
Cagrisema/GIPsema	-	-	-	-	-	84	604	1,417	2,346	3,357	4,338
Rybelsus 50mg, GLP-1+amylin, GLP-1+GIP	-	-	-	-	4	29	87	293	442	474	653
PYY1875/LA-GDF15	-	-	-	-	-	-	-	31	93	164	271
Total	494	781	1,619	3,264	4,164	4,935	5,550	6,401	6,403	6,763	6,902
Ex-US											
$m	2020	2021	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e
Saxenda	364	554	644	564	445	300	106	71	48	33	22
Wegovy	0	0	90	413	836	1,315	1,622	1,732	1,547	1,280	819
Cagrisema/GIPsema	0	0	0	0	0	48	383	991	1,703	2,518	3,247
Rybelsus 50mg, GLP-1+amylin, GLP-1+GIP	0	0	0	0	2	17	55	203	318	352	484
PYY1875/LA-GDF15	0	0	0	0	0	0	0	21	68	123	202
Total	364	554	734	977	1,284	1,680	2,166	3,018	3,683	4,306	4,775
Global											
$m	2020	2021	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e
Saxenda	858	1,115	1,187	999	750	402	173	116	78	53	36
Wegovy	-	220	1,165	3,243	4,692	6,036	6,414	6,347	5,038	4,028	2,446
Cagrisema/GIPsema	-	-	-	-	-	132	987	2,408	4,049	5,875	7,584
Rybelsus 50mg, GLP-1+amylin, GLP-1+GIP	-	-	-	-	6	47	141	496	760	826	1,137
PYY1875/LA-GDF15	-	-	-	-	-	-	-	52	161	287	474
Total	858	1,335	2,352	4,241	5,448	6,616	7,716	9,419	10,086	11,069	11,676

Source: Company data, Morgan Stanley Research Research estimates (e)

Eli Lilly (Overweight, top pick): maintaining our above consensus stance on tirzepatide; obesity revenue upside less appreciated compared to Novo. We have not changed our above consensus tirzepatide forecasts and await the SELECT study interim analysis decision in 3Q22 / potential top-line SELECT study data as early as 4Q22 as well as further details on the filing path for tirzepatide in obesity. Under our base case we forecast tirzepatide 2030 sales of $18.9bn ($13.5bn in diabetes and $5.4bn in obesity), or $28bn under our bull case, compared to consensus c.$13.9bn, with a flat $505/ script net pricing assumption ahead of further visibility. Focusing purely on the obesity opportunity, our Eli Lilly model forecasts combined revenues of $6.5bn (tirzepatide, GGG-agonist and small molecule GLP-1RA) compared to the $22bn revenue opportunity projected by our obesity market model. Therefore relative to Novo where consensus already forecasts >$9bn in obesity sales in 2030, we view Eli Lilly to be the best large-cap biopharma stock to play the diabesity thematic. Our Eli Lilly EPS estimate is circa 5% above consensus in 2030E. The initial launch of tirzepatide (Mounjaro) in diabetes supported by a bridge-program has shown strong momentum as discussed in our *Mounjaro Script Tracker* (here).

If the SELECT study reads out positively, we would expect Eli Lilly shares to react favourably (up 2-6%), reflecting the positive impacts for our long-term obesity forecasts and therefore our outer-year tirzepatide estimates. We note that every $1bn in tirzepatide sales translates into an incremental 4-5% long-term earnings impact. In the event it is recommended that the SELECT study continues through to completion in 3Q23, implying the reduction in cardiovascular risks is not substantially above the 17% benefit targeted in the study, we would expect Eli Lilly shares to trade off slightly as investors debate the magnitude of the outcomes benefit GLP-1 medicines provide in obesity (Exhibit 45). If the SELECT study ultimately fails to achieve a significant reduction in cardiovascular morbidity in 3Q23, we would expect Eli Lilly shares to trade down 4-6%, whilst noting that tirzepatide generated more robust weight loss than Wegovy in the SURPASS-2 trial (8-11kg weight loss versus 6kg). Eli Lilly has yet to finalise the design of its equivalent morbidity/mortality outcomes trial for tirzepatide in obesity and could optimise the design based on learnings from the SELECT study. We also note that Eli Lilly is conducting a broad obesity development program for tirzepatide across a range of related conditions (Exhibit 28), which we believe will help to build the long-term commercial opportunity.

Polypeptide Group (Overweight): upside risk to consensus based on our above consensus tirzepatide (Drug E) forecasts and additional peptide pipeline opportunities. We believe that Polypeptide is a supplier of the drug substance for tirzepatide ("Drug E"), a synthetic peptide with non-natural amino acids, as well as potentially for the GGG-agonist and mazdutide peptides in phase 2 development. On the basis that the contract manufacturing revenue for peptide intermediates could be around 1-1.5% of reference product sales, we estimate that Eli Lilly's diabetes and obesity peptide pipeline will represent c.30% of Polypeptide's long-term revenues. Assuming a $5bn peak sales uplift for Lilly's obesity peptide franchise based on read across from positive SELECT study data would point to c.7-8% upside to Polypeptide 2030E group sales.

Exhibit 20: Eli Lilly forecasts - our company model versus obesity model

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Eli Lilly model											
Diabetes											
Trulicity	5,068	6,472	7,542	7,567	6,811	7,172	6,992	6,489	3,221	2,059	1,137
Mounjaro	-	-	305	2,309	4,485	4,938	5,577	6,797	10,008	11,540	13,491
Obesity											
Trulicity											
tirzepatide	-	-	-	-	301	698	1,234	1,928	2,867	4,032	5,427
Pipeline											
GGG-agonist (diabetes and obesity)				-	-	18	108	303	548	756	902
GLP-1RA (diabetes and obesity)				-	-	24	144	404	730	1,008	1,203
Diabesity sales	5,068	6,472	7,847	9,876	11,596	12,849	14,055	15,920	17,373	19,394	22,160
Obesity sales	-	-	-	-	301	719	1,360	2,281	3,506	4,914	6,480
Obesity model											
tirzepatide	-	-	-	-	244	1,317	3,003	5,301	7,924	8,851	9,285
GGG-agonist / mazdutide (obesity)	-	-	-	-	-	643	2,356	5,042	6,437	8,401	9,370
GLP-1RA (obesity)	-	-	-	-	-	3	35	376	1,408	3,313	3,882
Obesity sales					244	1,963	5,394	10,720	15,769	20,564	22,537

Source: Morgan Stanley Research estimates

Exhibit 21: Polypeptide Group revenue sensitivity

$m	2022	2023	2024	2025	2026	2027	2028	2029	2030
tirzepatide (Drug E)	305	2,309	4,786	5,635	6,811	8,724	12,875	15,572	18,918
GGG-agonist/mazdutide				18	108	303	548	756	902
Lilly peptide obesity sales	305	2,309	4,786	5,653	6,919	9,027	13,422	16,328	19,820
Est. PPGN revenues from Lilly	4	29	60	71	86	113	168	204	248
Drug E and pipeline % of sales	*1%*	*8%*	*14%*	*15%*	*17%*	*19%*	*25%*	*28%*	*30%*
Additional $5bn obesity sales	1	7	15	18	22	28	42	51	63
Upside to PPGN group revenues	0%	2%	4%	4%	4%	5%	6%	7%	8%

Source: Morgan Stanley Research estimates

Chugai (Equal-weight): an under-appreciated diabesity play based on the leading small molecule GLP-1 medicine. Chugai is the originator of the oral small molecule GLP-1 medicine LY3502970 and out-licensed worldwide rights to Eli Lilly in September 2018 before human trials began. Economic terms have not been disclosed beyond the $50m upfront in-licensing payment, but we believe the royalty rate on sales could be high single digit percent (up to 10%). On the basis of a 10% royalty rate and peak sales of $4bn, LY3502970 revenues of $400m would correspond to more than 12% of Chugai's current core operating profits (company guidance for F12/22 is Yn440bn).

Proof of concept data for LY3502970 are expected to read out for both diabetes (370 patients) and obesity (270 patients) in 4Q22. The early data for LY3502970 suggested a similar efficacy and tolerability profile to high-efficacy injectible GLP-1 medicines (HbA1c reduction -1.77% versus -0.45% for placebo; 4.71kg weight loss versus 0.48kg weight gain for placebo at 12 weeks), without the food or water restrictions associated with Novo Nordisk's Rybelsus.

Chugai has experienced a lack of new drug launches since Hemlibra in 2019, but several new medicines are expected to report phase 3 data over the next 1-2 years including LY3502970, nemolizumab for atopic dermatitis, crovalumab for PNH and GYM329 for SMA. We argue that LY3502970 is particularly interesting given the size of the market opportunity, first-in-class status and limited investor expectations.

Innovent Biologics (Overweight): an opportunity to gain exposure to the diabesity market in China. Innovent has in-licensed rights to commercialise one of the leading GLP-1R/GCGR dual agonists, Lilly's mazdutide, an oxyntomodulin analog, in China. Mazdutide has demonstrated category-leading weight reduction of up to 11.2kg (12.7% change from baseline) and HbA1c reduction of up to -1.72% (versus -0.7% for placebo) at 16 weeks in individuals with Type 2 diabetes. From a tolerability perspective, mazdutide requires 3-4 week dose titration steps to manage the gastrointestinal side-effects and increases in heart rate.

Innovent initiated phase 2 trials with mazdutide (IBI362) in China for both obesity and diabetes in 3Q21, with proof-of-concept data from a combined 492 patients anticipated towards the end of 2022 / early 2023. From a commercial perspective, the obesity market remains relatively under-developed in China with Saxenda sales of circa $10m in 2021. Furthermore, Novo's semaglutide loses patent protection in China in 2026, the first market where biosimilars are expected to launch. Taken together, this places an increasing onus on mazdutide to demonstrate category leading efficacy without any significant compromises on safety.

Exhibit 22: Oral GLP-1 medicine LY3502970 provides a royalty revenue opportunity for Chugai

$m	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Obesity model										
LY3502970 Global sales					3	35	376	1,408	3,313	3,882
Lilly model										
LY3502970 Global sales (risk adjusted)					18	108	303	548	756	902
LY3502970 Global sales (non-risk adjusted)					60	360	1,010	1,825	2,519	3,007
Chugai - Royalty contribution to EBIT										
Assuming 10% royalty rate										
Core OP (Ynbn)	434.1	438.5	446.0	484.5	525.5	561.0				
Core OP ($m)	3,955	3,571	3,568	3,876	4,204	4,488				
USD JPY	110	123	125	125	125	125				
GLP-1 royalty contribution to EBIT										
Risk adjusted					0.0%	0.2%				
Non-Risk adjusted					0.1%	0.8%				

Source: Morgan Stanley Research estimates

Obesity - the new hypertension

Hypertension and obesity are both complex diseases, initially believed to be consequences of lifestyle choice as opposed to true diseases, requiring long-term management.

Blood pressure has evolved as a treatment target associated with proven morbidity/mortality benefits; likewise, we expect excess weight/body fat reduction and body mass index (BMI) will become treatment threshold targets in obesity supported by proven outcomes data.

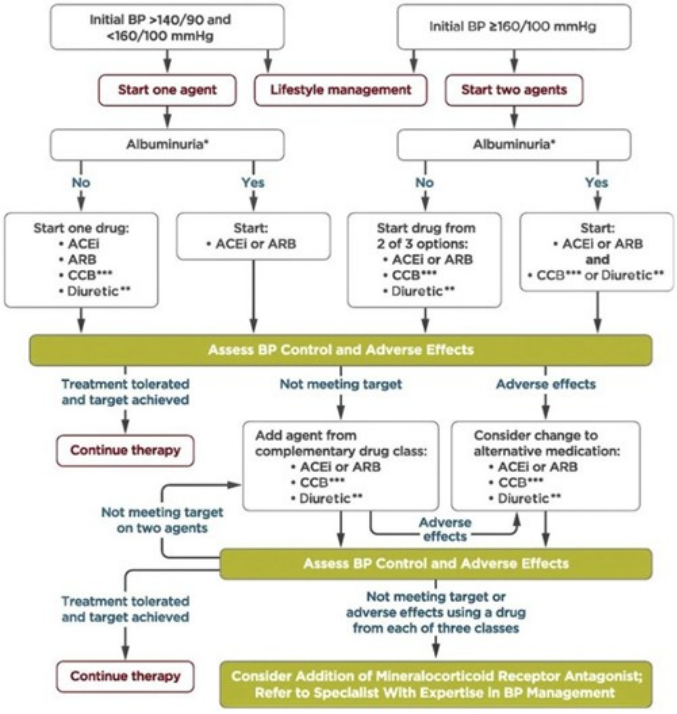
Combination therapy is required to achieve treatment goals in hypertension; we expect the same will hold true for obesity in the pursuit of more consistent and greater weight loss benefits accompanied by excellent tolerability.

The global hypertension market reached $30bn circa 14 years after the launch of the initial (ACEi) combination treatments ($54bn today, CPI-adjusted). Modest penetration and conservative pricing assumptions point to obesity becoming >$50bn global market.

Umashanker et al have argued that the treatment of obesity will evolve in parallel with how the treatment of hypertension developed in the 1980's and 1990's. Both obesity and hypertension are complex diseases that respond to lifestyle change, as well as medicines, and were initially believed to be consequences of lifestyle as opposed to true diseases. The prevalence of both diseases is high - the Centers for Disease Control and Prevention (CDC) estimates that 140m Americans are living with obesity and circa 120m with hypertension. The impact of both diseases on the healthcare system is also high, with the McKinsey Global Institute (MGI) estimating that obesity accounts for >8% of healthcare budgets and impacts global GDP by circa 3%. The prevalence of obesity in Europe is estimated to be >18% and the COVID-19 pandemic may have worsened the situation. A long-term treatment approach is essential to maintain lasting benefit, with blood pressure and weight returned to their pre-treatment set-points once therapy is withdrawn.

Hypertension was recognised as a disease in the 1970's but remained undertreated until the 1980's. The current generation of medicines including ACE inhibitors and Calcium Channel Blockers emerged in the 1980's and at that point the treatment of hypertension moved into mainstream primary care. By the end of the 1990's, 14 years after the approval of Merck's Vasotec, hypertension had evolved into a $30bn global sales category with four main treatment approaches. Fast forward to today and there are >120 anti-hypertensive medicines approved across eight different drug categories used in dual and triple combinations - this equates to close to 650m prescriptions in the US each year, which if branded would generate c.$100bn in sales. Outcomes trials support well established hypertension treatment guidelines based on the initial level of blood pressure, co-morbidities and tolerability considerations. A 10mm/Hg reduction in systolic blood pressure has been shown to reduce the risk of cardiovascular events by circa 20%.

Exhibit 23: The treatment of high blood pressure: multiple mechanisms, dual/triple combination therapy



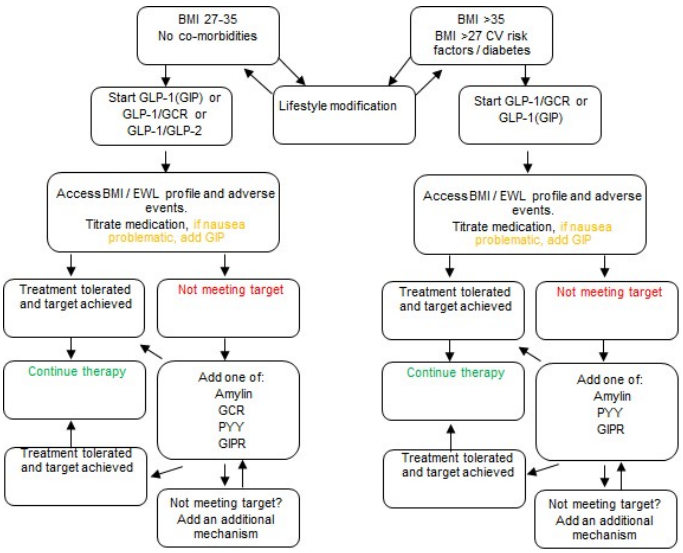
Source: ADA 2020 guidelines for hypertension

The American Medical Association only classified obesity as a chronic disease in 2013. Whilst the WHO recognised obesity as a chronic disease in 1997, it has taken the European Commission until 2021 to define obesity as a "chronic relapsing disease". As such, disagreement remains across physician and payer eco-systems as to whether obesity requires treatment. It has become increasingly clear that it is environmental factors (e.g. proliferation of high calorie affordable food options, sedentary lifestyles) that lead to the body's fat set-point becoming elevated to abnormally high levels, which in

turn leads to obesity. In the majority of cases, medicines are required to reset the feedback loop between the brain and digestive system and lower the body's fat set-point. In the 1960's, the medical community debated whether hypertension was a behavioural disorder caused by stress or an unavoidable consequence of ageing, until drugs that reset blood pressure feedback loops, starting with the diuretics, established morbidity and mortality benefits in the 1970's. Novo Nordisk's SELECT trial for Wegovy is expected to establish a proven link between weight loss and important health outcomes in obesity.

Novo Nordisk's Wegovy looks set to be a ground-breaking new treatment for obesity. The treatment of obesity is currently limited to seven FDA-approved medicines, the majority of which target serotonergic, dopaminergic or noradrenergic signalling pathways in the hypothalamus region in the brain to reduce appetite. These include Contrave (a combination of bupropion and topiramate) and Qysymia (a combination of phentermine and topiramate), as well generic phentermine which is the most widely prescribed anti-obesity medicine. Xenical works differently, blocking the absorption of fat. The most efficacious approach to date is to target appetite suppressing hormones (incretins), with GLP-1 the most widely studied target. GLP-1 agonists such as Novo's Saxenda and Wegovy interact with the hypothalamus to reduce appetite, but also have glycemic, cardio-protective and anti-inflammatory benefit.

Exhibit 24: Hypothetical future guidelines for the treatment of obesity through combination approaches



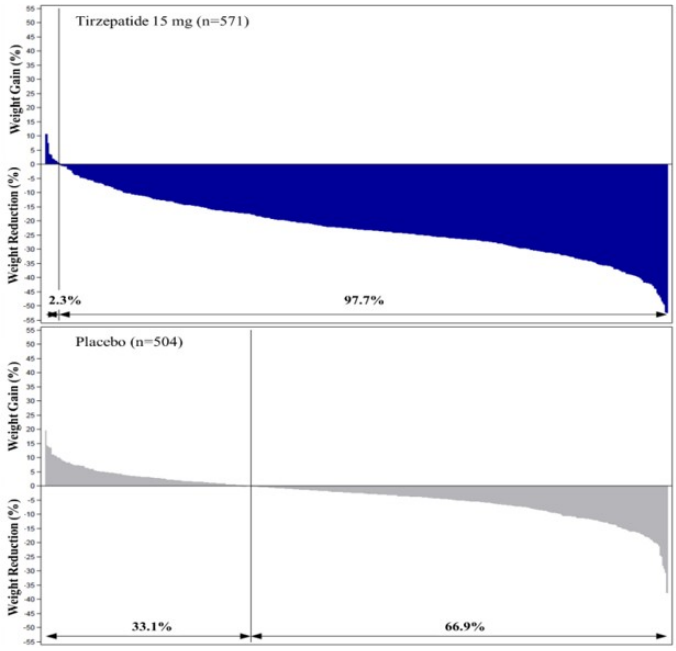
Source: Morgan Stanley Research

For chronic diseases such as hypertension and obesity, side-effects associated with medicines can reduce adherence to treatment. The broad range of anti-hypertensive medicines available means that treatment can be tailor-made to limit side-effect issues and medicines can be used in combination to provide both greater efficacy and improved tolerability. The same has been shown in obesity already, with both Qysymia and Belviq demonstrating superior efficacy over their respective component parts without increasing the incidence of adverse events. It has been hypothesised that GIP receptor agonism of tirzepatide might reduce nausea and allow higher dosing of the GLP-1 action.

There are five additional incretin targeting medicines beyond GLP-1 and GIP in clinical development for the treatment of obesity, which could come to market by 2026/27. Combinations of these medicines are likely to be important in addressing the heterogeneity of obesity and providing a more consistent weight loss benefit. Put another way, it is likely that a combination of mechanisms is required to mimic the coordinated release of appetite suppressive gut hormones after a meal. Whilst tirzepatide 15mg demonstrated an impressive 22.5% average weight loss in the SURMOUNT-1 trial, 2% of patients gained weight and a further 27% of patients failed to achieve 15% weight loss. Some patients might respond better to an alternative appetite suppression approach such as amylin, whilst the enhanced energy expenditure from glucagon might be important for other patients.

Phase 2 and planned phase 3 trials for these different incretin targeting medicines will help to identify how to tailor-make treatment plans for different subgroups based on co-morbidities, age and other risk factors. The development of oral small molecule medicines, which can be combined with complementary categories including SGLT2s and statin, as well as long-acting injectables, will further broaden patient options and improve treatment compliance. The successful development of small molecule alternatives to peptides has the potential to reduce barriers to entry, increasing competition and potentially lowering cost.

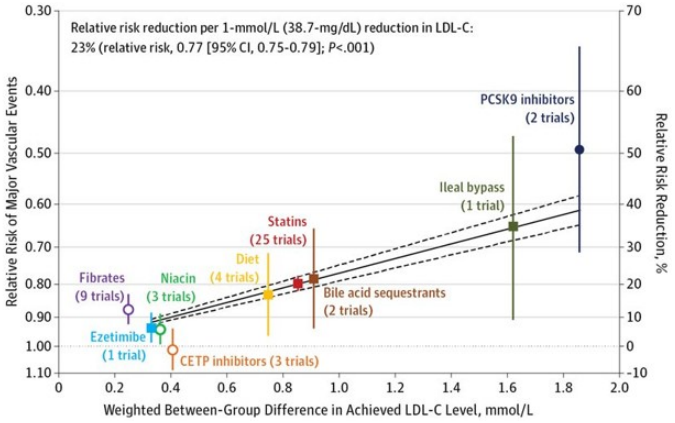
Exhibit 25: Weight loss heterogeneity - waterfall plots showing percent change in body weight at 72 weeks for tirzepatide 15mg versus placebo in the SURMOUNT-1 trial



Source: NEJM

Drivers of physician adoption, payer acceptance and commercial uptake for obesity medicines. We expect ongoing cardiovascular outcomes trials for Wegovy (SELECT) and tirzepatide (SURPASS-CVOT in T2D; Lilly is expected to initiate the SURMOUNT-MMO trial in obesity in 2022, alongside trials in co-morbidities associated with obesity including sleep apnea, heart failure, NASH and chronic kidney disease, which will help to identify different thresholds for treatment and weight loss targets. Whilst the "lower is better" message for LDL-C cholesterol lowering medicines could in parallel become an important driver of physician adoption, payer acceptance and commercial uptake for obesity medicines, we expect the heterogeneity of obesity and its associated co-morbidities to lead to more nuanced treatment guidelines. For example, if the dual-GLP-1/glucagon agonists continue to demonstrate differentiation on systolic blood pressure reduction (up to 11mmHg) and LDL-C reduction (20-25%), with these benefits alone implying a circa 35% reduction in cardiovascular events, it is possible that the morbidity/mortality benefits per percentage weight loss might vary significantly across different anti-obesity approaches.

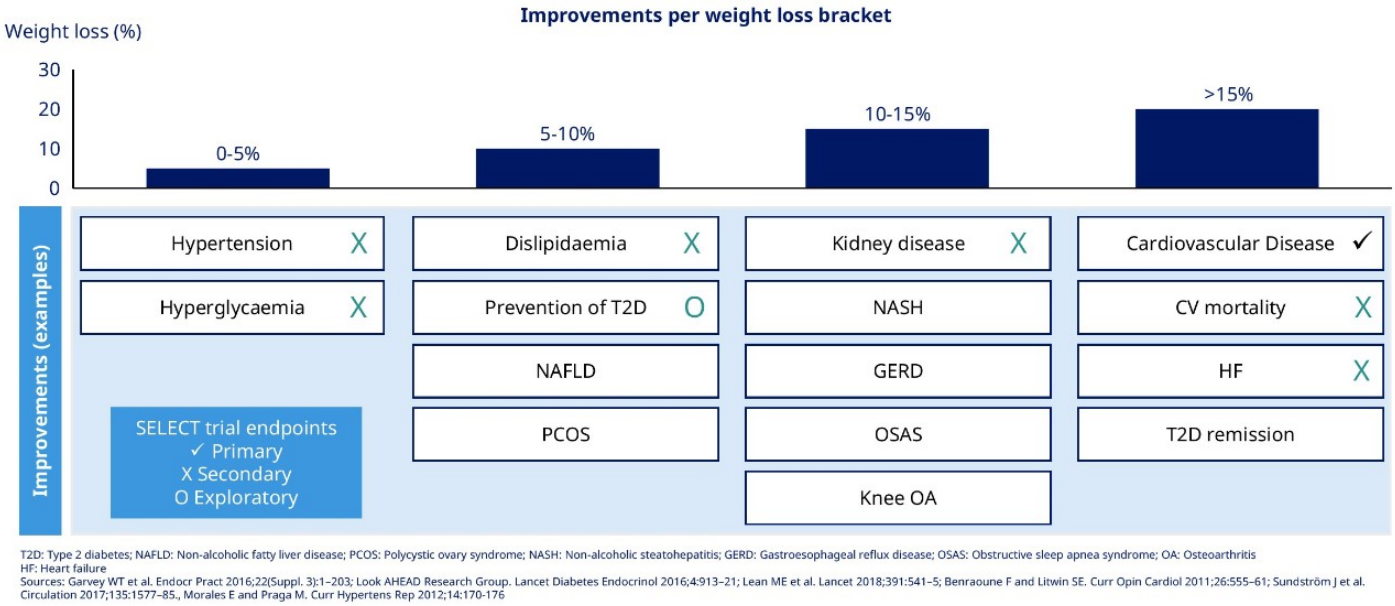
Exhibit 26: Association between LDL-C lowering and cardiovascular risk reduction



Source: JAMA. 2016;316(12):1289-1297

Both the treatment of hypertension and high cholesterol can be used as chronic medical care templates to educate the public, fund research and develop combination treatment strategies in obesity. Over time, we argue that once excess body weight/fat or a BMI reaches a certain threshold, or once the first sign of a co-morbidity such as pre-diabetes or a build-up in liver fat is identified, anti-obesity treatment will be initiated to target a threshold improvement in weight loss with the goal of preventing disease progression and reducing morbidity and mortality. To that end, and as discussed in the next section, we believe that obesity should be targeted upstream of diabetes, hypertension and high cholesterol in certain patient subgroups. As such, we expect morbidity outcomes trials will further support expansion into obesity-associated chronic conditions including obstructive sleep apnea, fatty liver disease (NAFLD) and heart failure.

Exhibit 27: The Wegovy SELECT trial will explore the impact of weight management on many co-morbidities



T2D: Type 2 diabetes; NAFLD: Non-alcoholic fatty liver disease; PCOS: Polycystic ovary syndrome; NASH: Non-alcoholic steatohepatitis; GERD: Gastroesophageal reflux disease; OSAS: Obstructive sleep apnea syndrome; OA: Osteoarthritis
HF: Heart failure
Sources: Garvey WT et al. Endocr Pract 2016;22(Suppl. 3):1–203; Look AHEAD Research Group. Lancet Diabetes Endocrinol 2016;4:913–21; Lean ME et al. Lancet 2018;391:541–5; Benraoune F and Litwin SE. Curr Opin Cardiol 2011;26:555–61; Sundström J et al. Circulation 2017;135:1577–85., Morales E and Praga M. Curr Hypertens Rep 2012;14:170-176

Source: Novo Nordisk Capital Markets Day 2022

Exhibit 28: Co-morbidity GLP-1 outcomes trials for semaglutide and tirzepatide

Drug	Mechanism	Dosing	Focus	Phase	Trial	Next data point
Ozempic	GLP-1 agonist	Subcut	PAD	3	STRIDE	4Q24
Ozempic	GLP-1 agonist	Subcut	CKD	3	FLOW	3Q24
Ozempic	GLP-1 agonist	Subcut	Diabetic retinopathy	3	FOCUS	3Q26
sema 2.4mg	GLP-1 agonist	Subcut	Obesity CV outcomes	3	SELECT	3Q22
semgalutide	GLP-1 agonist	Subcut	HFpEF	3	STEP HFpEF	2Q23
semgalutide	GLP-1 agonist	Subcut	NASH	3	ESSENCE	2024+
Rybelsus	GLP-1 agonist (high dose)	Oral	Diabetes	3	PIONEER PLUS	3Q22
Rybelsus	GLP-1 agonist	Oral	Diabetes outcomes	3	SOUL	3Q24
Rybelsus	GLP-1 agonist	Oral	Alzheimer's	3	EVOKE	3Q24
Rybelsus	GLP-1 agonist	Oral	Obesity	3	tbd	tbd / 2024
tirzepatide	GLP-1 agonist	Subcut	NASH	2	SYNERGY-NASH	4Q23
tirzepatide	GLP-1 agonist	Subcut	HFpEF	3	SUMMIT	4Q23
tirzepatide	GLP-1 agonist	Subcut	CKD	2	TREASURE-CKD	to initiate 2022
tirzepatide	GLP-1 agonist	Subcut	Obstrutive sleep apnea	3	SURMOUNT-OSA	1Q24
tirzepatide	GLP-1 agonist	Subcut	Obesity CV outcomes	3	SURMOUNT-MMO	to initiate 2022

Source: Morgan Stanley Research, clinicaltrial.gov

Putting obesity first in treatment guidelines

Obesity and Type 2 diabetes are interconnected, heterogeneous diseases. Adiposity (the abnormal accumulation of fat tissue) is a key underlying driver of obesity, Type 2 diabetes, cardiovascular complications and over 200 chronic conditions.

Treatment guidelines should be updated to target a substantial (>15%) reduction in weight as the principal target for the treatment of many (40-70%) patients with Type 2 diabetes, shifting the focus to the upstream cause as opposed to the downstream consequences of diabetes. The next American Diabetes Association (ADA) Treatment Guidelines update is anticipated at the end of 2022, with draft guidelines targeting obesity and weight management as key pillars.

If caught early enough, substantial weight reduction can reverse the progression of diabetes and achieve disease remission. In more advanced patients, weight reduction can improve diabetes control and prevent micro/macro-vascular complications.

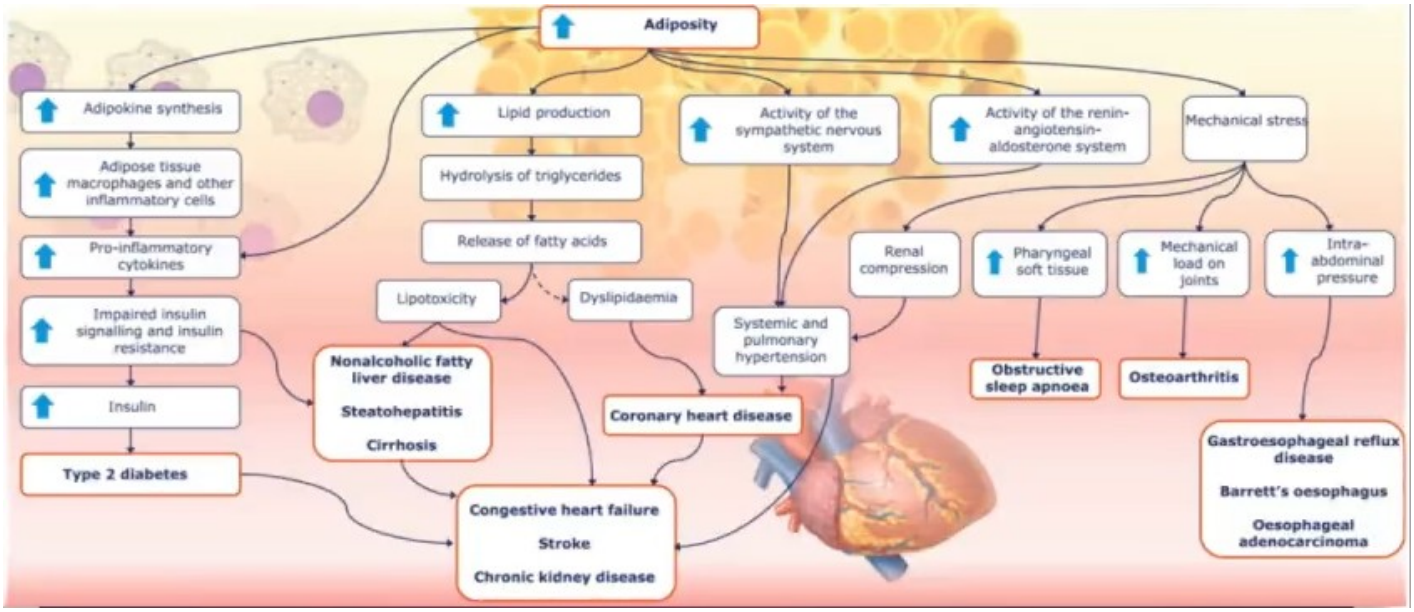
Outcomes studies including the Wegovy SELECT and SELECT-LIFE trials are expected to support updated treatment guidelines to promote weight loss as a principal target in non/pre-diabetics. A meta-analysis suggests a 27% reduction in cardiovascular events with Wegovy in the SELECT trial and we expect these data will be reflected in American Diabetes Association Treatment Guidelines no later than the end of 2023. Novo believes that Wegovy could reduce the risk of developing diabetes by circa 60% over 10 years.

The management of diabetes has undergone a major conceptual change recently with the focus on cardio-centric goals. Positive outcomes studies for GLP-1/SGLT2 medicines in 2015-19 led to updated diabetes treatment guidelines in 2019, promoting the use of these medicines in individuals with cardiovascular disease and accelerating their use. We expect positive outcomes studies promoting obesity as a disease with reversible complications will encourage a shift in clinical care to include weight-centric goals and support the uptake of obesity medicines.

Ildiko Lingvay et al have argued that weight loss should be the primary target for the treatment of Type 2 diabetes. More specifically, the authors propose that the primary focus for the treatment of diabetes should be adiposity, the accumulation of abnormal or excessive fat tissue, which is estimated to be the root cause behind over 200 chronic conditions including diabetes. There is an important distinction between adiposity and an individual being considered obese, defined as having a body mass index (BMI) of >30. The WHO defines obesity as "abnormal or excessive fat accumulation that presents a risk to health". However, many physicians still consider obesity to be a self-induced condition that can be cured simply by eating less and doing more physical activity, as opposed to a chronic disease caused by damage to appetite regulation mechanisms which then leads to weight gain. This highlights the educational challenge of understanding the science behind obesity.

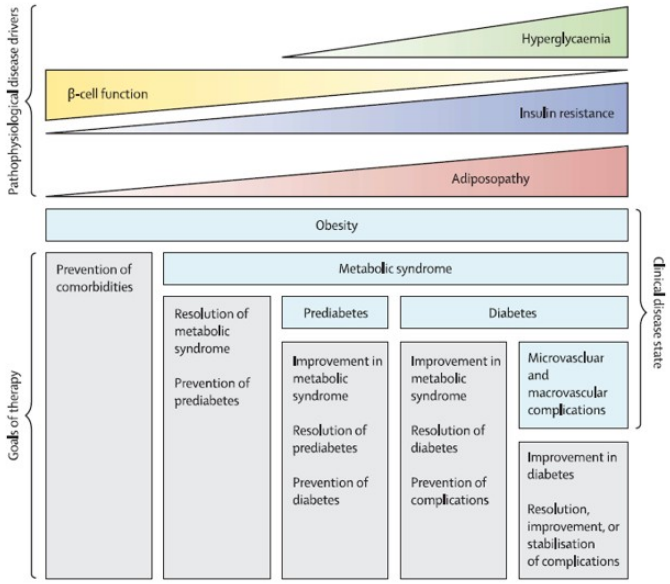
Obesity is a heterogeneous disease. Not all individuals who are categorised as obese (BMI>30) have excessive adiposity (fat accumulation) and some individuals with minimal adiposity develop metabolic complications such as diabetes. Adiposity is defined as the build-up of abnormal fat tissue due to excessive consumption of calories in genetically and environmentally (factors include poverty, high calorie affordable food options, sedentary lifestyles) susceptible individuals, with the (1) amount, (2) distribution and (3) function of the fat all important considerations. The accumulation of visceral fat inside the abdomen, wrapped around key organs including the liver and intestines, is believed to be the key factor that drives systemic inflammation and metabolic dysfunction. Not all Type 2 diabetics are obese, but most have abnormal adiposity.

Exhibit 29: Adiposity (the accumulation of abnormal fat tissue) is the key driver of over 200 chronic conditions



Source: Ildiko Lingway ADA 2022

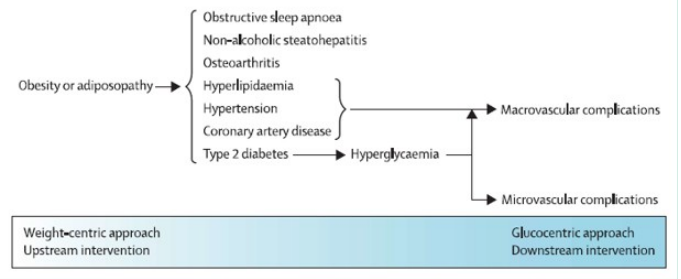
Exhibit 30: The disease continuum for weight-related Type 2 diabetes



Source: Lingvay et al Lancet 2022

Adiposity-based chronic disease (ABCD) typically takes decades to evolve into a diagnosis of Type 2 diabetes. The two core defects in the disease continuum are (1) insulin resistance and (2) declining beta cell function, as the ability of the pancreas to produce insulin in order to store excessive blood sugar diminishes, leading to pre-diabetes. Lifestyle intervention studies have shown that every kg of weight loss reduces the risk of diabetes by 16% (Diabetes Prevention Program (DPP) study) and that 70% of diabetics who lose >15kgs in weight go into diabetes remission (DiRECT trial follow-up). Following bariatric surgery, 37-51% of patients go into long-term diabetes remission and improvements in blood pressure, cholesterol, kidney function and glycemic control leads to a 56% reduction in microvascular events and a 32% reduction in macrovascular events such as heart attacks over 20 years of follow-up (study references here, here, here). Therefore the evidence supporting weight loss as a target is comparable to the cardiovascular outcomes data generated by the GLP-1/SGLT2 medicines which prompted a shift in the ADA treatment guidelines at the end of 2019.

Exhibit 31: Upstream weight-centric approach to treat the cause of diabetes instead of the downstream consequences



Source: Lingvay et al Lancet 2022

Treatment should focus on the upstream cause of Type 2 diabetes. For a significant proportion of Type 2 diabetics, the focus of treatment should shift towards the upstream cause, adiposity, as opposed to the downstream consequences of diabetes.Therefore it has been proposed that treatment guidelines should move from the current reactive glucocentric approach to treating diabetes towards a preventative weight-centric approachwhich targets a substantial (>15%) reduction in weight and disrupts the core disease pathology. It is argued that reducing adiposity irrespective of the starting quantity of adipose tissue will provide benefit, similar to the rationale for reducing LDL-C cholesterol with statins irrespective of baseline levels. Lingvay et al estimate that 40-70% of patients would fit the adiposity-related phenotype and that these individuals would tend to be younger, newly diagnosed patients.

Unfortunately there are no easy ways to characterise adipose tissue pathology in clinical practice, but common factors including increased waist circumference, hypertension, hypertriglyceridaemia, non-alcoholic fatty liver disease (NASH) and (if available) laboratory evidence of insulin resistance can be used. Likewise, there are no clinical trials in diabetes primarily focused on the benefits of weight loss on cardiovascular events and it is difficult to allocate the benefit of weight loss separated from other efficacy measures (glycemic control, direct cardiovascular benefits) in pre-approval safety trials for GLP-1 medicines (LEADER, SUSTAIN-6, PIONEER-6 and REWIND) where a 12-26% reduction in cardiovascular risk has been shown.

Exhibit 32: Proposed primary and secondary treatment goals for Type 2 diabetes by prevailing disease phenotype

Type 2 Diabetes Subtype	Adiposity-related Diabetes	Diabetes with Cardiovascular Disease	Isolated Hyperglycemia
Primary Pathophysiologic Driver	Insulin Resistance	Atherosclerosis, Inflammation	Beta-cell dysfunction
Approximate Prevalence*	40-70%	20-40%	10-20%
Primary Morbidity	Obesity	Cardiovascular Disease	Hyperglycemia
Foundational Diabetes Treatment Target	Weight-centric	Cardio-centric	Gluco-centric
Target	>15% BWL	Use of proven cardio-protective agents	HbA1c<7%
Examples of Foundational Diabetes Treatment	Anti-obesity agents or intervention, GLP-1RA, SGLT2inh, MET	SGLT2inh, GLP-1RA (TZD)	SU, INS, GLP-1RA
Secondary Treatment Targets	Glucose/BP/Lipids	Weight/Glucose/BP/ Lipids/Coag	NA

*Prevalence varies by definition and population.
BWL – body weight loss, GLP-1RA – glucagon like peptide 1 receptor agonist, SGLT2inh – sodium glucose co-transporter 2 inhibitor, MET – metformin, TZD – thiazolidinedione, SU – sulfonylurea, INS – insulin, NA – not applicable

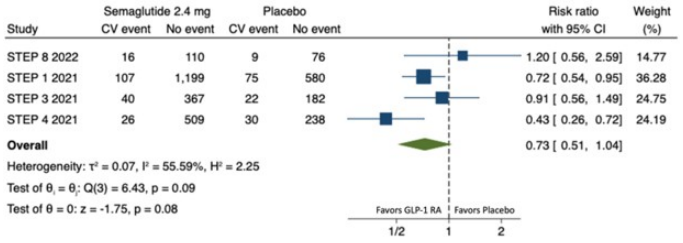
Lingvay et al. Lancet 2022: P394

Source: Lingvay et al Lancet 2022

SELECT trial will examine the impact of a weight-centric approach. The Wegovy SELECT trial and the continued follow-up of 5,000-10,000 individuals in the SELECT-LIFE 10-year extension study will examine the impact of a weight-centric approach to the treatment of adiposity-based chronic disease in non-diabetic patients at risk of cardiovascular events. A recent meta-analysis of placebo-controlled trials which enrolled a total of 11,430 patients without diabetes has suggested that the treatment of obesity with GLP-1 medicines reduces the risk of cardiovascular events by 19% (8.7% versus 11.2% event rate in the control group). Specifically across four Wegovy trials in non-diabetic patients, the meta-analysis suggested a 27% reduction in cardiovascular events, which is in-line with the 26% cardiovascular benefit seen with Ozempic in the SUSTAIN-6 trial in diabetic patients.

Meta-analysis suggests the interim analysis will be positive and the SELECT trial will close out before the end of 2022. For the Wegovy SELECT trial interim analysis in 3Q22, Novo has commented that the reduction in cardiovascular events would have to be quite substantially better than the 17% benefit targeted for the trial to stop early for overwhelming efficacy. SELECT LIFE will have a 10-year observation period and focus on Type 2 diabetes prevention (label claim opportunity, with Novo projecting a 60% reduction in the risk of developing Type 2 diabetes over 10 years), cardiovascular events and obesity related complications.

Exhibit 33: Meta-analysis of Wegovy trials suggests a 27% reduction in cardiovascular events in non-diabetic patients



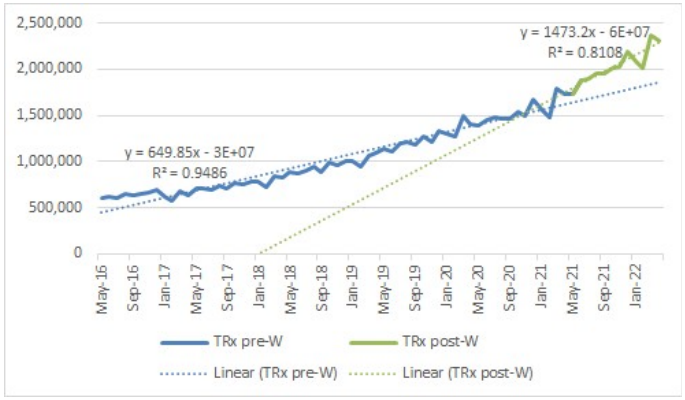
Source: Leite et al

Management of diabetes has already undergone a major conceptual change but more work is needed to promote a weight-centric focus. Treatment objectives are shifting to include cardio-centric goals in patients with high cardiovascular risk alongside the long-standing gluco-centric goals. The ADA and EASD (European Association for the Study of Diabetes) treatment guidelines were updated to prioritise the use of SGLT2 inhibitors and GLP-1 medicines in diabetes patients with the cardiovascular disease (the cardiovascular-centric phenotype). This change in treatment guidelines at the end of 2019 has led to an acceleration in prescription growth for these categories (potentially impacted by the COVID pandemic initially), with positive data for SGLT2 inhibitors in both heart failure and chronic kidney disease leading to the prioritisation of SGLT2 inhibitors in these patients.

The latest ADA treatment guidelines published January 2022 provide a Class A recommendation ("Clear Evidence") for SGLT2s/GLP-1s in targeting cardio-centric goals. In contrast with respect to obesity: (1) considering a diabetes medicine's effect on weight is a Class B recommendation ("Supportive Evidence"); (2) minimising medicines for comorbid conditions that cause weight gain is a Class E recommendation ("Expert consensus", the lowest level of recommendation). Whilst continuing treatment with weight loss medications in patients that achieve >5% weight loss receives a Class A recommendation, there is still considerable work required to elevate the importance of the weight-centric treatment focus.

The US launch of Wegovy in June 2021 elevated the dialogue surrounding effective treatment of obesity with GLP-1 medicines and the hope is that future combination approaches will achieve weight loss comparable to bariatric surgery. In the SURMOUNT-1 study, 57% of patients treated with tirzepatide reached >20% weight loss and up to 36% of patients achieved >25% weight loss. Combination approaches promise even greater and more consistent levels of weight loss, with pivotal data for cagrisema, LY3437943, LY3305677 (mazdutide), ALT-801 and AMG133 anticipated in 2025/26. Oral small molecule medicines, which can be combined with SGLT2 inhibitors, could further broaden treatment options. This has led to proposals that >15% weight loss should be adopted as a new target in Type 2 diabetes instead of the current 7% weight loss recommendation, with ADA treatment guidelines usually updated at year-end. Such a weight-centric approach would require a greater conceptual shift in the diabetes treatment framework than the cardio-centric update, with physicians having to focus on the underlying progression of adiposity-based disease as opposed to treating the downstream consequences including diabetes.

Exhibit 34: Acceleration in GLP-1 prescriptions following the launch of Wegovy mid-2021

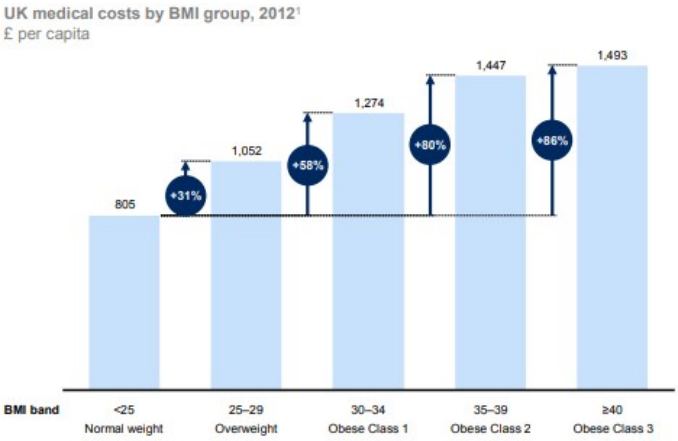


Source: IQVIA, Morgan Stanley Research

The increased focus on weight loss following positive data for Wegovy and tirzepatide has created a halo effect for the GLP-1 category. The rate of prescription growth has more than doubled since the launch of Wegovy in June 2021. Given the overlapping benefits of GLP-1 medicines for both the adiposity-related and cardiovascular-centric phenotypes of diabetes, we believe that positive SELECT trial data will ultimately lead to updated diabetes treatment guidelines targeting >15% weight loss. Increased engagement from payers and physicians in targeting weight loss as evidenced by the prescription data suggests the door to a weight-centric preventative approach to the treatment of diabetes is already ajar. After prioritising weight loss followed by cardiovascular complications, we believe that the control of blood sugar (glycemic control) might over time become the third factor of focus in diabetes. In this respect, we expect diabetes medicines which have a neutral impact on weight will be

favoured over insulins, as physicians seek to reduce the risk of micro-vascular complications (including retinopathy, nephropathy, and neuropathy) associated with diabetes.

Exhibit 35: Associated medical costs rise BMI increases



1 Includes primary care, general practitioner prescriptions, hospitalization, accident and emergency, and outpatient care. 2003 values taken from Tigbe et al. (2013) adjusted using 2012/13 Fédération Internationale de Médecine du Sport and Health Examination Survey data on per capita UK costs in each category.

SOURCE: W. W. Tigbe, A. H. Briggs, and M. E. J. Lean, "A patient-centred approach to estimate total annual healthcare cost by body mass index in the UK Counterweight programme," *International Journal of Obesity*, August 2013; Fédération Internationale de Médecine du Sport and Health Examination Survey, 2012/13; McKinsey Global Institute analysis

Source: McKinsey Global Institute 2014

When will healthcare systems shift to a weight-centric approach? It is not clear how long it is going to take for treatment guidelines and healthcare systems to evolve towards a weight-centric treatment approach following the completion of key outcomes studies including SELECT (2022/23) and SURMOUNT-MMO (timing TBD). However, we expect the Wegovy SELECT data will be reflected in Diabetes Treatment Guidelines no later than the end of 2023. Ultimately payers will need to appraise and allocate a value to treatment goals of 10%, 15% and >20% weight loss across different patient subcategories and invest in the long-term goal of minimising downstream metabolic complications and cardiovascular events. McKinsey Global Institute estimates that obesity accounts for >8% of healthcare budgets per country and circa 3% of global GDP, with survey data from the UK suggesting that reducing the average BMI of 39 in individuals suffering from obesity to a BMI <30 would reduce associated medical costs by circa 30%.

The development of combinations of medicines with complementary profiles should prompt more people to seek treatment and increase the number of prescribers. Obesity management requires education to support physicians and training to support patients. Once individuals are diagnosed with obesity and recommended for medical treatment, circa 40% are treated, which is similar to hypertension and slightly behind high cholesterol at circa 55%. The key problem is that only circa 7% of individuals suffering with obesity are diagnosed and recommended for medical treatment compared to circa 80-90% with downstream chronic complications including diabetes, high blood pressure and elevated cholesterol levels.

Targeting glucagon and market disruption

When adiposity drives an accumulation of fat in the liver, the function of glucagon receptors becomes impaired and this causes glucagon resistance. Decreased sensitivity to glucagon leads to increased glucose production by the liver, which leads to insulin resistance and drives the progression of Type 2 diabetes.

Targeting glucagon receptors has received relatively limited attention, with Novo Nordisk abandoning the target after three phase 1 trials due to safety concerns including heart rate increases, protein breakdown, increases in markers of inflammation and signals of liver/cardiac dysfunction. However, these safety issues have not been seen with other GLP-1R/GCGR dual agonists for which phase 2b data are expected to readout before the end of 2022 across >2,200 patients.

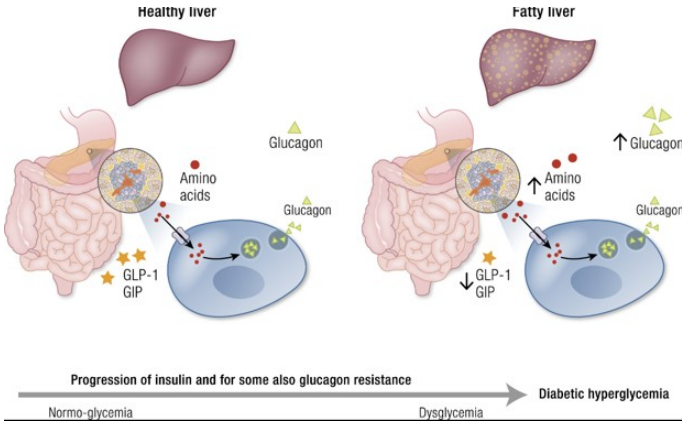
The extended release profile of Altimmune's GLP-1R/GCGR dual agonist ALT-801 reduces the risk of nausea/diarrhea such that no dose titration is required. After 12 weeks, ALT-801 has shown 10% weight loss (trending towards circa 20% at 24 weeks), 20-25% LDL-C reduction, >10mmHg systolic blood pressure reduction, no increase in heart rate and the near-complete removal of liver fat. The quality of the weight loss with ALT-801 may prove to be superior to other approaches, with the cholesterol and blood pressure benefits alone implying a circa 35% reduction in cardiovascular events.

Eli Lilly's glucagon agonist programs have shown positive changes in cardiometabolic parameters relative to Wegovy, albeit with significant increases in heart rate. Novo Nordisk's cagrilintide has shown -11% weight loss after 26 weeks and can be safely combined with semaglutide, but like Wegovy it shows limited impact on cholesterol and blood pressure parameters.

Despite glucagon being discovered in 1923 just two years after insulin, its full spectrum of actions is still not fully understood. Type 2 diabetes is characterised by glucose intolerance, caused by the development of insulin resistance, which in turns leads to Beta cells in the pancreas being unable to produce sufficient insulin to store glucose. The alpha cells in the pancreas produce glucagon, which is thought of as the counter-regulatory hormone of insulin and enhances glucose production from the liver. There is a feedback loop between glucagon receptors in the liver and the glucagon producing alpha cells in the pancreas (liver-alpha-cell axis), whereby glucagon regulates amino acid breakdown and in turn amino acids (such as alanine) regulate alpha-cell secretion of glucagon.

Glucagon resistance may play an underappreciated role in adiposity and diabetes. However, when fat accumulates in the liver (steatosis), the function of the glucagon receptors becomes impaired and the receptors are downregulated. This causes glucagon resistance. Decreased sensitivity to glucagon leads to an increase in amino acid levels, which then stimulate more glucagon to be released and this negative spiral leads to greater glucose production by the liver. Insulin sensitisers such as Avandia and Actos helped address insulin resistance and improve glycemic control. In the same way, GLP-1R/GCGR dual agonists hold the potential to address glucagon resistance and reset the liver-alpha-cell axis.

Exhibit 36: Fatty liver disease is believed to cause glucagon resistance, which leads to the over-production of glucagon, which results in excess blood glucose and then the development of insulin resistance, which drives the progression of Type 2 diabetes

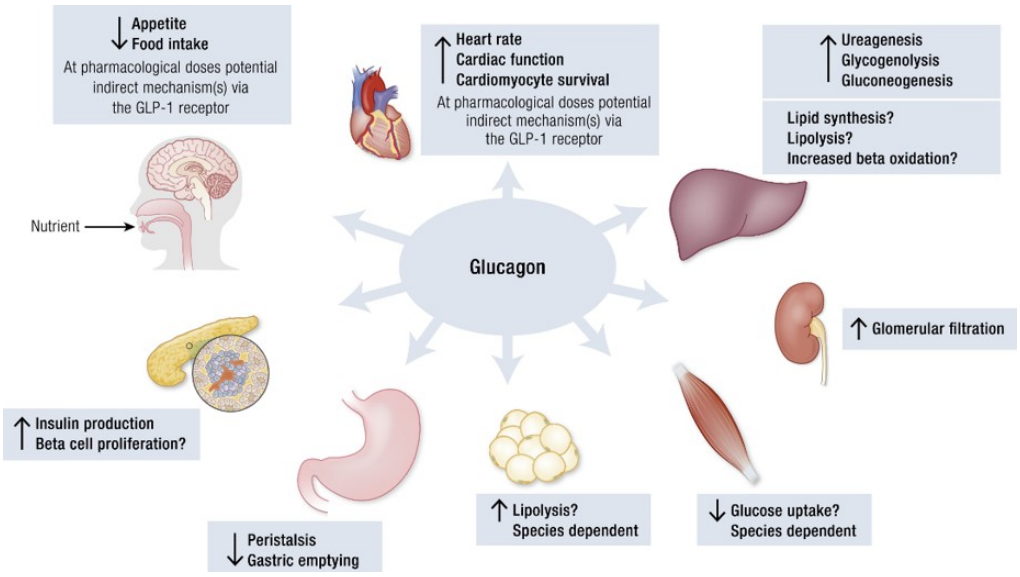


Source: Albrechtsen et al 2019

Targeting glucagon receptors has received relatively limited attention. After early phase 1 development, Novo abandoned the mechanism due to concerns surrounding increased heart rate, protein breakdown and liver enzyme changes. However, recent data for GLP-1R/GCGR dual agonists suggest a potential leading role in the treatment of adiposity with near-complete removal of fat from the liver, 20-25% LDL-C reduction, >10mmHg systolic blood pressure reduction and weight loss trending towards 20% at 24 weeks. Whilst there was a consistent relationship between LDL-C lowering and the reduction of cardiovascular events with different categories of LDL-C lowering medicines, the quality of weight loss with a GLP-1R/GCGR dual agonist might prove to be superior compared to a GLP-1R or GLP-1R/GIP medicine based on the differential benefits of liver fat, cholesterol and blood pressure.

Beyond its role in glucose regulation, at high pharmacological doses, glucagon binds both glucagon and GLP-1 receptors. This acute action leads to increased energy expenditure, decreased food intake, reduction in insulin resistance and an increase in insulin potentially caused by beta cell proliferation. Glucagon rapidly activates the conversion of liver fat into glucose, with this glucose taken up into functional brown adipose tissue and skeletal muscle. It has been postulated that the intake of too many calories might overcome these benefits of glucagon, hence the importance of the GLP-1R/GCGR dual binding. There is also speculation that the glucose released from the liver might stay more in the blood if an individual suffers from significant insulin resistance.

Exhibit 37: Summary of glucagon's actions

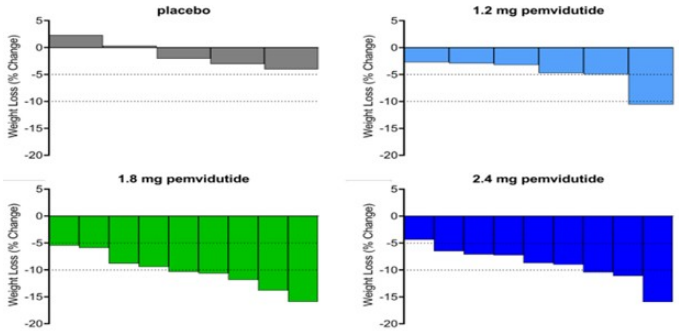


Source: Albrechtsen et al 2019

So can glucagon receptors be safely targeted and potentially disrupt the obesity market opportunity, which to this point has centred on GLP-1 medicines? Novo Nordisk conducted three phase 1 trials for a long-acting GLP-1R/GCGR dual agonist called NN1177. These studies enrolled just over 190 individuals with treatment for up to 12 weeks. A number of safety concerns were observed including an increase in heart rate (range 5-22 beats per minute), QTc prolongation of up to 18msec and decrease in reticulocyte count (immature red blood cells), which were dose dependent. The heart rate increases generally diminished over time to 1-15bpm at week 12, but a blunted nocturnal heart rate was observed (associated with cardiac damage) and the increase in heart with Wegovy was just 1-4bpm in the STEP1 study. The Novo group also reported increases in markers of inflammation (fibrinogen and C-reactive protein), liver abnormalities (including liver enzyme increases), impaired glucose tolerance (at the high doses) and reduced blood levels of some amino acids, whilst there was no reduction in systolic blood pressure. Reductions in weight were shown to be dose dependent up to 12.6% at 12 weeks, but the combination of safety concerns and the absence of cardiometabolic improvements led to the discontinuation of NN1177 development.

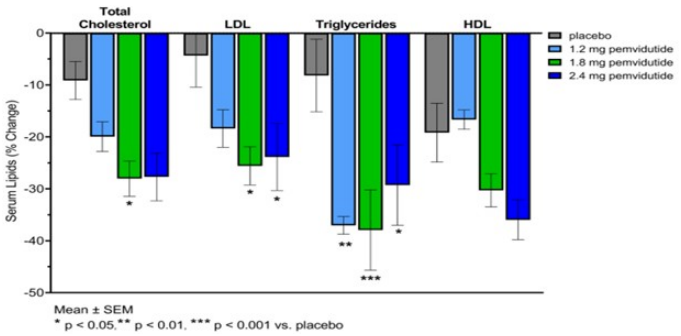
The safety issues seen with Novo's dual glucagon / GLP-1 medicine appear to be compound specific and not glucagon related. The Novo phase 1 data were published in a non-peer review preprint on 3 June 2022 and Ruth Gimeno, vice-president of Lilly's diabetes and metabolic research division, commented that "*none of the issues detailed with NN1177 had been seen with Eli Lilly's dual agonist mazdutide (LY3305677) or the GGG tri-agonist LY3437943*". We are not aware of the effects described with NN1177 being reported with other GLP-1R/GCGR dual or GLP-1R/GCGR/GIP tri-agonists in clinical development. Phase 2b data in obesity and diabetes for three glucagon agonist medicines are expected to readout before the end of the year across over 2,000 patients and will provide more visibility surrounding safety: (1) Boehringer Ingelheim / Zealand Pharma's BI-456906 (diabetes data at EASD meeting, 19 September); (2) Altimuune's pemvidutide ALT-801; (3) Lilly's GGG tri-agonist.

Exhibit 38: ALT-801 reductions in body weight (week 12)



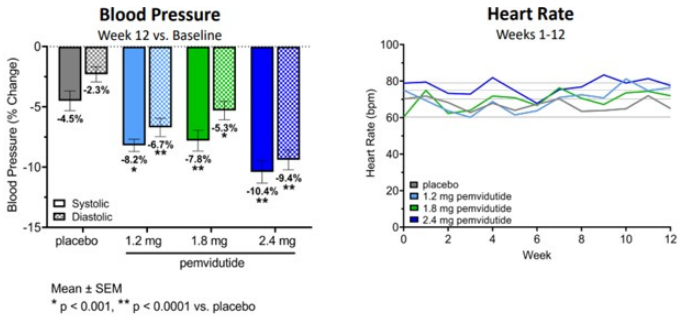
Source: Altimmune EASL 2022 presentation

Exhibit 39: ALT-801 impact on cholesterol and triglycerides (week 12)



Source: Altimmune ADA 2022 presentation

Exhibit 40: ALT-801 impact on blood pressure and heart rate (week 12)



Source: Altimmune ADA 2022 presentation

Exhibit 41: Reduction of liver fat >90% at 6 weeks

Individual Subjects with MRI-PDFF ≥ 5% at Baseline

Treatment Group	MRI-PDFF (%)			
	Baseline	Week 6	Relative Δ at Week 6	
			Individual	Mean
Placebo	5.2	3.7	28.8	28.8
Pemvidutide 1.2 mg	19.1	14.0	26.7	48.2
	11.2	3.4	69.6	
Pemvidutide 1.8 mg	12.4	< LOD	94.0	94.0
Pemvidutide 2.4 mg	17.0	< LOD	95.6	91.9
	5.5	< LOD	86.4	
	7.0	< LOD	89.3	
	19.5	< LOD	96.2	

For calculation of absolute and relative Δ, values < LOD is set at 0.75%

Source: Altimmune EASL 2022 presentation

Altimmune's ALT-801 is structurally designed to have a potentially best in class profile. Altimmune's GLP-1R/GCGR dual agonist ALT-801 (pemvidutide) has been engineered with a helix stabiliser and EuPort domain which together provide weekly dosing with a slower onset of action for improved tolerability. The extended release profile of ALT-801 results in a lower peak concentration (Cmax) / a long-term to peak concentration (Tmax 70 hours compared with circa 29 hours for semaglutide). The lower peak concentration (Cmax) of ALT-801 is believed to reduce the risk of: (1) nausea/diarrhea related to GLP-1 activation; (2) heart rate increases potentially correlated to glucagon receptor activation.

The lower risk of nausea/diarrhea means that ALT-801 does not require dose titration to achieve a therapeutic maintenance dose and no increase in heart rate has been observed. Altimmune retains the option to deploy dose titration, potentially in combination with other molecules, to achieve potentially greater efficacy with higher doses. In overweight/obese individuals (BMIs of 30-32) without diabetes, treatment with ALT-801 generated up to 10.3% weight loss at 12 weeks (versus 1.6% for placebo) and circa 20% weight loss is anticipated at 24 weeks based on the progressive linear reductions observed.

Slow onset of action and balanced GLP-1/glucagon agonism means that ALT-801 has shown profound cardiometabolic improvements, which were not observed with Novo's NN1177. LDL-C cholesterol is reduced by circa 20-25%, systolic blood pressure is lowered by up to 10mmHg and triglycerides are reduced by circa 30-38%. Liver fat is reduced by >90% after just 6 weeks with ALT-801, which implies a normalisation of glucagon resistance, which as discussed above, could be the initial step in the progression of adiposity to downstream metabolic complications including diabetes and cardiovascular disease.

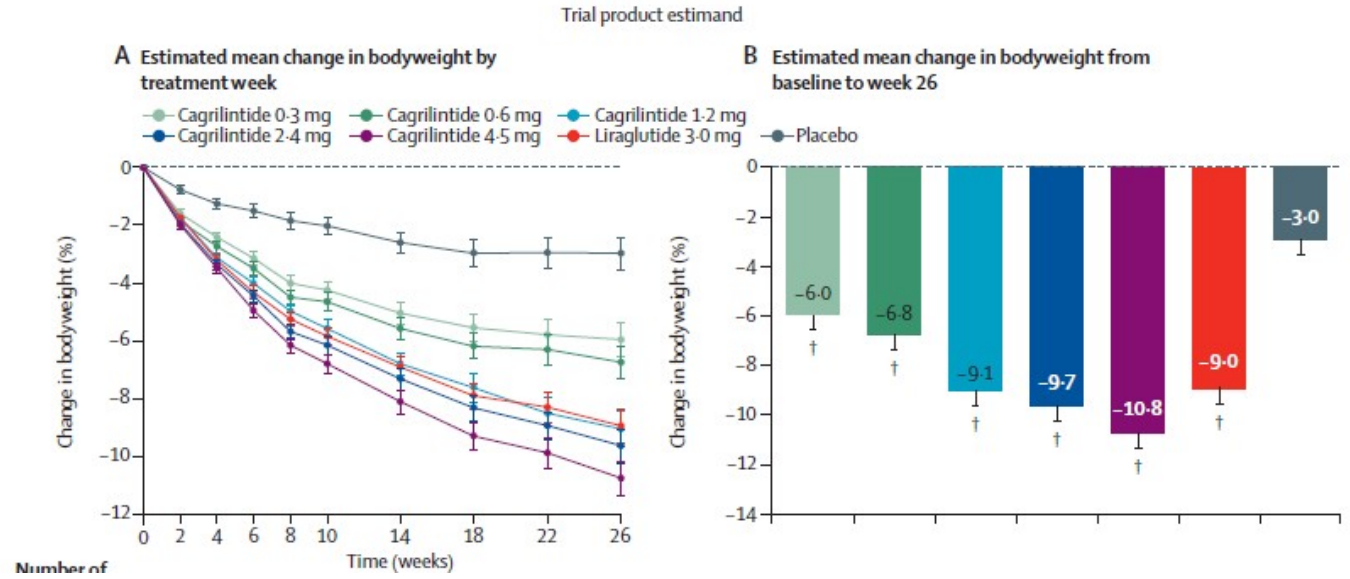
In comparison, treatment with Wegovy at 68 weeks resulted in up to 16.9% weight loss (versus -2.4% for placebo), a circa 3-6% reduction in LDL-C cholesterol, a circa 5% reduction in systolic blood pressure and a 1-4bpm increase in heart rate. Therefore from a cardiometabolic perspective, the ALT-801 might generate higher quality weight loss from a morbidity/mortality perspective with the LDL-C and SBP benefits alone implying a circa 35% reduction in cardiovascular events. The phase 2 MOMENTUM obesity trial has enrolled 320 subjects and an interim analysis at 24 weeks, anticipated at the end of 2022, should provide greater insight into the efficacy and safety profile (including the potential for liver enzyme elevations) of ALT-801.

Eli Lilly's glucagon agonist programs have shown positive changes in cardiometabolic parameters relative to Wegovy, albeit with significant increases in heart rate. Eli Lilly's GLP-1R/GCGR dual agonist LY3305677 (mazdutide) requires 3-4 week dose titration steps to manage the gastrointestinal side-effects, but has demonstrated weight reduction of up to 11.2kg (12.7% change from baseline) and HbA1c reduction of up to -1.72% (versus -0.7% for placebo) at 16 weeks in individuals with Type 2 diabetes. The GLP-1R/GCGR/GIP triple agonist LY3437943 also requires dose titration, but showed a 30bpm increase in heart rate which fell to 10bpm in the higher dose arm at 12 weeks (likely related to a Tmax of circa 24 hours). Dose-dependent weight reduction of up to 8.65kg (10.1% change from baseline), systolic blood pressure of up to 11mmHg and HbA1c reduction up to -1.9% (versus -0.3% for placebo) were seen with the triple agonist in Type 2 diabetics at 12 weeks.

What is Novo Nordisk's response to competition from Eli Lilly's GLP-1R/GCGR? Novo Nordisk's answer to competition from GLP-1R/GCGR dual agonist is to combine semaglutide with cagrilintide, but cagrilintide does not directly address adiposity or provide significant cardiometabolic benefits**.** Amylin is a hormone co-secreted with insulin after a meal which slows gastric emptying and reduces appetite by acting on the hindbrain as opposed to the hypothalamus. Cagrilintide is a long-acting amylin analogue which reduces food intake and body weight in a dose-dependent manner, with -10.8% weight loss after 26 weeks compared to -9.0% for Saxenda and -3.0% for placebo.

In contrast to Saxenda, no changes in HbA1c or fasting glucose were observed with cagrilintide, whilst reductions in triglycerides and other lipid parameters were similar to Saxenda. Mean concentrations of plasma renin and aldosterone showed a transient increase with cagrilintide, which normalised after 26 weeks with no change in blood pressure (despite the significant weight loss). Cagrilintide 2.4mg and 4.5mg in combination with semaglutide 2.4mg achieved -15.7% and -17.1% weight loss, respectively, at 20 weeks, with Novo Nordisk moving the 2.4mg+2.4mg combination into pivotal trials. The additive weight loss without worsening tolerability suggests complementary mechanisms of action. Whilst cagrisema is likely to achieve similar weight loss to the GLP-1R/GCGR dual agonists, it will not provide the same cardiometabolic benefits on LDL-C cholesterol, triglycerides, systolic blood pressure and liver fat.

Exhibit 42: Phase 2b weight loss data for Novo's cagrilintide - 2.4mg dose taken into pivotal trials



Source: Lau et al. Lancet 2021; 398: 2160-72

SELECT: a pivotal trial for the future of obesity medicines

Wegovy cardiovascular outcomes trial SELECT seen as "pivotal trial for the future of obesity medicine" and a conclusion that "weight management saves lives" could be an extremely powerful message for medical professionals, National Guideline policies and payers alike.

An interim analysis of the SELECT trial will be conducted in 3Q22 and a reduction in cardiovascular events would have to be quite substantially better than the targeted 17% benefit for the trial to stop early.

A meta-analysis of Wegovy trials in non-diabetics points to a 27% reduction in cardiovascular events in the SELECT trial, which is broadly in-line with the 26% cardiovascular benefit shown with Ozempic in the SUSTAIN-6 diabetes outcomes trial. Based on these data, we expect the SELECT trial to stop mid-3Q22 and for headline data to be released at the end of 2022 / early 2023.

The increased focus on weight loss following positive data for Wegovy and tirzepatide has already created a halo effect for the GLP-1 category in diabetes. We would expect positive SELECT trial data to be incorporated into treatment guidelines no later than the end of 2023 targeting >15% weight loss in diabetics. We expect this would support enactment of the Treat and Reduce Obesity Act in the US and expand government obesity management programs outside the US.

In a recent call, our diabesity expert was optimistic that the SELECT trial will show an anticipated 17% reduction in cardiovascular events, but noted that based on an estimated 2.2% annual event rate in the control arm, the absolute benefit might be modest from a health economic perspective. The SELECT trial target population (non-diabetic, secondary prevention) is also relatively narrow and our expert advocated starting a long-term primary prevention trial in obesity alongside subgroup trials (HFpEF, sleep apnea, CKD) to build a body of evidence supporting the medical treatment of obesity.

The Wegovy SELECT trial is the natural extension of seven outcomes trials conducted in diabetic patients. These trials have demonstrated up to a 26% reduction in major adverse cardiovascular events (observed with Ozempic in the SUSTAIN-6 trial). The SELECT trial is designed to demonstrate that Wegovy is superior to placebo when added to the standard of care for preventing cardiovascular events in non-diabetic overweight or obese patients (BMI >27kg/m2) with established cardiovascular disease (prior myocardial infarction and/or stroke and/or symptomatic PAD). GLP-1s have been shown to have beneficial effects on a number of cardiovascular risk factors including lowering blood pressure, promoting weight loss and reducing lipid levels in addition to lowering glucose levels.

The SELECT trial is an event-driven study which has enrolled circa 17,500 patients. It will have 90% power to detect a 17% reduction in the incidence of major cardiovascular events based on events observed in 1,225 patients. Recent cardiovascular outcomes trials conducted in patients without Type 2 diabetes include FOURIER (Repatha; 15% reduction in MACE at 2.2 years), SCOUT (Meridia; 16% increase in MACE at 3.4 years) and IRIS (Actos; 24% reduction in MACE at 4.8 years). Novo has announced that the independent Data Monitoring Committee (DMC) for the SELECT trial will perform an interim analysis in 3Q22 based on the primary endpoint, whilst taking into account the totality of data including key secondary endpoints: (1) cardiovascular death and (2) all-cause death.

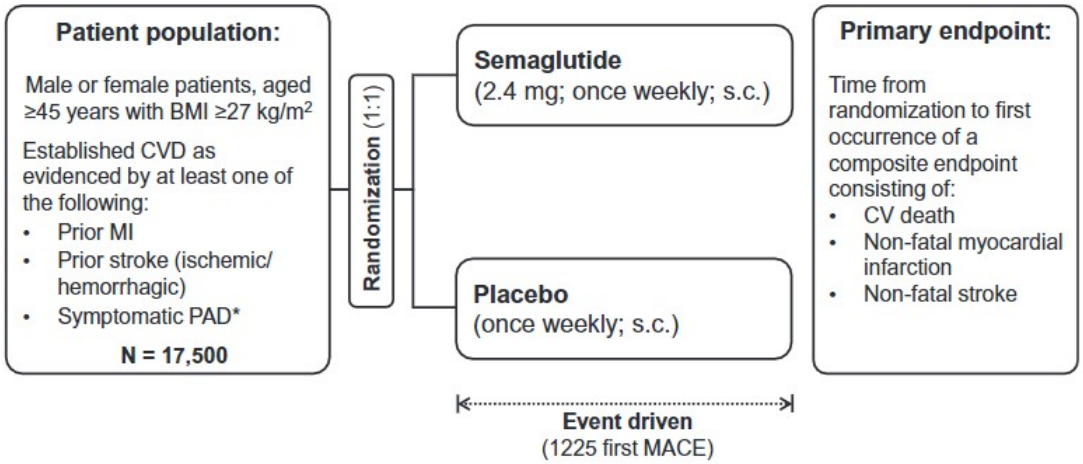
Exhibit 43: Summary of key cardiovascular outcomes trials for GLP-1s in diabetic patients

	ELIXA (n = 6068)[23]	LEADER (n = 9340)[24]	SUSTAIN-6 (n = 3297)[18]	EXSCEL (n = 14,752)[26]	HARMONY Outcomes (n = 9463)[25]	REWIND (n = 9901)[27]	PIONEER-6 (n = 3183)[30]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Dulaglutide	Semaglutide
Structural basis	Exendin-4	Human GLP-1	Human GLP-1	Exendin-4	Human GLP-1	Human GLP-1	Human GLP-1
Administration route	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Subcutaneous	Oral
Dose	20 µg/d	1.8 mg/d	0.5 or 1 mg/wk	2 mg/wk	30 or 50 mg/wk	1.5 mg/wk	14 mg/d
Mean age, y (SD)	60 (10)*	64 (7)	65 (7)	62 (9)	64 (9)	66 (7)	66 (7)
Sex, n (%)							
Male	4207 (69)	6003 (64)	2002 (61)	9149 (62)	6569 (69)	5312 (54)	2176 (68)
Female	1861 (31)	3337 (36)	1295 (39)	5603 (38)	2894 (31)	4589 (46)	1007 (32)
Ethnic origin, n (%)							
White	4576 (75)	7238 (77)	2736 (83)	11,175 (76)	6583 (70)	7498 (76)	2300 (72)
Other	1492 (25)	2102 (23)	561 (17)	3577 (24)	2880 (30)	2403 (24)	883 (28)
Mean BMI, kg/m^2 (SD)	30.1 (5.6)*	32.5 (6.3)	32.8 (6.2)	32.7 (6.4)	32.3 (5.9)	32.3 (5.7)*	32.3 (6.5)
Mean diabetes duration, y (SD)	9.2 (8.2)*	12.8 (8.0)*	13.9 (8.1)	12.0 (IQR 7.0-18.0)†	14.1 (8.6)*	10.5 (7.3)*	14.9 (8.5)
Mean HbA1c, % (SD)	7.7 (1.3)*	8.7 (1.6)*	8.7 (1.5)	8.0 (IQR 7.3-8.9)†	8.7 (1.5)	7.3 (1.1)*	8.2 (1.6)
Established CVD, n (%)	6068 (100)	7598 (81)	2382 (72)	10,782 (73)	9463 (100)	3114 (31)	2695 (85)‡
3-component MACE							
Hazard ratio	1.02	0.87	0.74	0.91	0.78	0.88	0.79
(95% CI)	(0.89-1.17)	(0.78-0.97)	(0.58-0.95)	(0.83-1.00)	(0.68-0.90)	(0.79-0.99)	(0.57-1.11)
P value	.81	.01	.016	.061	<.001	.026	.17
All-cause mortality							
Hazard ratio	0.94	0.85	1.05	0.86	0.95	0.90	0.51
(95% CI)	(0.78-1.13)	(0.74-0.97)	(0.74-1.50)	(0.77-0.97)	(0.79-1.16)	(0.80-1.01)	(0.31-0.84)
P value	.50	.02	.79	.016§*	.64	.067	.008

Adapted and reprinted from *The Lancet Diabetes & Endocrinology*, 7, SL Kristensen et al, Cardiovascular, Mortality, and Kidney Outcomes with GLP-1 Receptor Agonists in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Cardiovascular Outcome Trials, 776-785, Copyright (2019), with permission from Elsevier.[13]
Values are for the full population, where available; otherwise, they are from the intervention arm (denoted by *).
† SD unavailable from primary source reference.
‡ Includes CVD or chronic kidney disease.
§ Not regarded statistically significant due to hierarchical statistical testing plan.

Source: Ryan et al

Exhibit 44: Wegovy SELECT cardiovascular outcomes trial design



SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design. **Symptomatic PAD* defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

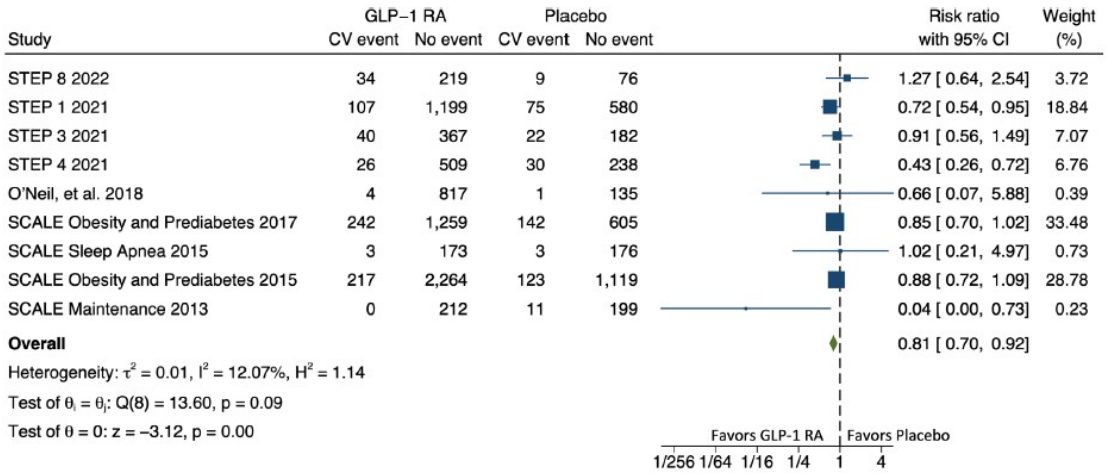
Source: Ryan et al

The SELECT trial could either: (1) be closed under conservative stopping criteria in 3Q22, with topline data released late 2021 / early 2022 or (2) continue to primary completion in September 2023. The first patient was enrolled in November 2018, with recruitment completed November 2021, suggesting an average duration of follow-up of circa 26 months at the point of the interim analysis and 40 months at the primary completion. In the UK Clinical Practice Research Datalink (CPRD) GOLD database study, over a four year observation period, individuals with a median weight loss of 13% from a BMI of 40kg/m2 at baseline demonstrated a risk reduction of 41% for Type 2 diabetes, 40% for sleep apnoea, 22% for hypertension, 19% for dyslipidaemia and 18% for asthma. However, the findings for cardiovascular outcomes (heart failure, atrial fibrillation, unstable angina/MO) were inconclusive, potentially reflecting imbalances in baseline characteristics and/or a relative lack of follow-up.

For the Wegovy SELECT trial interim analysis in 3Q22, Novo commented that the MACE benefit would have to be quite substantially better than 17% for the trial to stop. Leite et al conducted a meta-analysis of nine placebo controlled trials, which enrolled a total of 11,430 overweight or obese individuals without diabetes, and concluded that GLP-1 medicines reduced the risk of major cardiovascular events by 19%. However, when only taking into account Wegovy (semaglutide 2.4mg) trials in non-diabetics, the meta-analysis suggested a 27% reduction in major cardiovascular events which is broadly in line with Ozempic (semaglutide 1.0mg) in the SUSTAIN-6 trial diabetes outcomes trial which showed a 26% reduction in cardiovascular events.

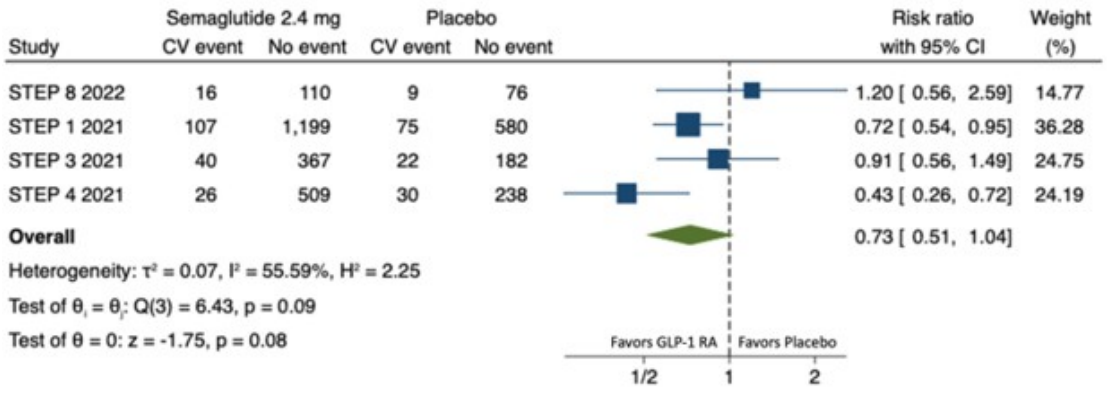
Therefore our base case scenario is that Novo will announce that the SELECT trial has been stopped in the middle of 3Q22. The extension phase of the SELECT trial (SELECT LIFE) will have a 10 year observation period and focus on diabetes prevention (label claim opportunity), cardiovascular events and obesity related complications.

Exhibit 45: Meta-analysis of GLP-1 trials in non-diabetic obese patients suggests a 19% reduction in cardiovascular events



Source: Leite et al

Exhibit 46: Meta-analysis of Wegovy trials suggests a 27% reduction in cardiovascular events in non-diabetic patients



Source: Leite et al

Ahead of the ADA 2022 meeting, our diabesity expert did not expect payers to lower reimbursement/access barriers for obesity medicines ahead of cardiovascular outcomes data. Our expert is optimistic that the SELECT trial will show an anticipated 17% reduction in cardiovascular events, but noted that based on an estimated 2.2% annual event rate in the control arm, the absolute benefit might be modest from a health economic perspective. The SELECT trial target population (non-diabetic, secondary prevention) is also relatively narrow and our expert advocated starting a long-term primary prevention trial in obesity alongside subgroup trials (heart failure (HFpEF), sleep apnea, and chronic kidney disease) to build a body of evidence supporting the medical treatment of obesity. However, the potential message from the SELECT trial (a "pivotal trial for the future of obesity medicine") that "weight management saves lives" could be extremely an powerful message for medical professionals, National Guideline policies and payers alike.

Increased focus on weight loss following positive data for Wegovy and tirzepatide has already created a halo effect for the GLP-1 category in diabetes. Increased engagement from physicians in targeting weight loss in Type 2 diabetics has seen the rate of prescription growth more than doubling since the launch of Wegovy in June 2021. Given the overlapping benefits of GLP-1 medicines for both the adiposity-related and cardiovascular-centric phenotypes of diabetes, we believe that positive SELECT trial data will ultimately lead to updated diabetes treatment guidelines targeting >15% weight loss no later than the end of 2023.

Bipartisan support to expand Medicare coverage to include the screening and treatment of obesity. The Treat and Reduce Obesity Act, or TROA, was reintroduced into the 117th Congress which convened on 3 January 2021, and is a bill with bipartisan support to expand Medicare coverage to include the screening and treatment of obesity with FDA-approved medicines from a diverse range of healthcare providers who specialize in obesity care. We expect positive outcomes studies including SELECT (2022/23) and SURPASS-CVOT (end-2024) will increase the probability that the TROA legislation passes Congress and that the bill is scored by the CBO before potentially being passed (potentially in 2024/25, coinciding with a wave of pivotal data for next-generation anti-obesity medicines in 2025).

Outside the US, we expect the approach taken by other governments to the treatment of obesity will vary. The UK government is engaged with a collaborative memorandum of agreement and other European governments are likely to take a more contractual approach. The UK NICE recommended Saxenda for the management of obesity in December 2020 alongside a reduced-calorie diet and increased physical activity in adults with a BMI of at least 35 kg/m2 (or at least 32.5 kg/m2 for higher risk groups), non-diabetic hyperglycemia and a high risk of cardiovascular disease, based on a 2-year treatment duration. Saxenda prescription volumes subsequently tripled through December 2021. The UK NICE has issued a positive final appraisal for Wegovy, with an estimated cost of £14,827-16,337 per QALY gained (versus £13,569 for Saxenda at a confidential price discount).

We expect as data emerge from the SELECT outcomes trial and from real-world studies emphasing the importance of remaining on treatment beyond 2-years, the collaborative agreement in the UK will evolve and expand to a broader target population. These data will help refine Novo Nordisk's risk equations in estimating the long-term risk reduction of cardiovascular events and the prevention of Type 2 diabetes from targeting adiposity and weight reduction.

Exhibit 47: Incidence of obesity in the US (million people) by co-morbidity status and BMI

	BMI				
	27-29.9	30-34.9	35-39.9	40+	Total
CV comorbidities	15.1	16	6.4	4.1	41.6
T2DM	2	5	3.6	2.3	12.9
Pre-diabetes	12	14.1	7.2	6.1	39.4
No CV co-morbidities	15.5	11	4.2	3	33.7
Total	**44.6**	**46.1**	**21.4**	**15.5**	**127.6**

Source: : Novo Nordisk FY2015 presentation

Tirzepatide - raising the efficacy bar in obesity

Weight loss from tirzepatide at the higher doses (10mg 19.5%/ 15mg 20.9%) approached bariatric surgery levels with a low discontinuation rate. The weight reduction was sustained over 72 weeks of treatment, with an estimated 60% of excess weight lost. As such, tirzepatide raises the efficacy bar in obesity relative to Wegovy (14.9% weight loss) with a comparable tolerability and safety profile.

The GIP activity of tirzepatide is believed to reduce nausea and expand the therapeutic window allowing higher dosing of the GLP-1 activity. Independent GIP benefits on glucose metabolism, kidney protection and body fat composition remain the subject of debate.

All pre-specified cardiometabolic parameters improved with tirzepatide, including a 0.5% reduction in HbA1c and for participants with pre-diabetes, >95% reverted to normoglycemia. There was a circa 5% reduction in LDL-C cholesterol, a circa 20% reduction in triglycerides and a 7.2mmHg reduction in systolic blood pressure (versus -1.0mmHg for placebo).

From a commercial perspective, key questions remain whether there is a fast route to market for tirzepatide in obesity (FDA filing of SURMOUNT-1 in 2H22 augmented by data in diabetics from the SURPASS trial program) and whether pricing will be the same in diabetes and obesity (which is what we model). The launch of tirzepatide (Mounjaro) in diabetes supported by a bridge-program remains strong (see our *Mounjaro Script Tracker* **here**).

Tirzepatide approaching bariatric surgery levels of efficacy in SURMOUNT-1 obesity trial (LLY PR, NEJM, NEJM discussant). The greater the weight loss achieved with a pharmacotherapy or bariatric surgery (c.30%), the greater the anticipated overall clinical benefit, with consistent weight loss of 10-20% across a broad population seen as a "sweet-spot" in terms of pharmacotherapy benefit. Just as with blood pressure and cholesterol, it is believed that (consistently) lower is better when it comes to weight loss for obesity.

In the SURMOUNT-1 trial, weight loss from treatment with tirzepatide at the higher doses (10mg 19.5%/ 15mg 20.9%) approached bariatric surgery levels with a low discontinuation rate. Up to 91% of patients treated with tirzepatide achieved >5% weight loss, up to 57% of patients reached >20% weight loss and up to 36% of patients achieved >25% weight loss. It is estimated that tirzepatide removed up to circa 60% excess weight. The weight reduction was sustained over 72 weeks of treatment and all pre-specified cardio-metabolic parameters improved with tirzepatide. The tolerability and safety profile of tirzepatide was consistent with the GLP-1 agonist category. Key points additionally made in the presentations:

Exhibit 48: Obesity data comparison SURMOUNT-1 vs. STEP-1

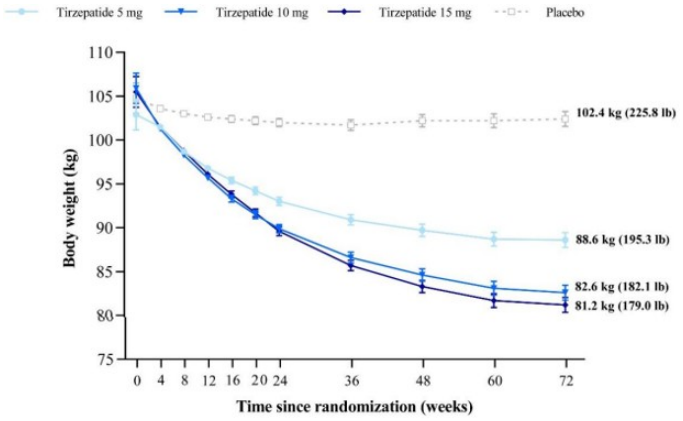
	SURMOUNT-1				STEP-1	
	5mg	10mg	15mg	placebo	Wegovy	placebo
efficacy / trial product estimand	16.0%	21.4%	22.5%	2.4%	16.9%	2.4%
	16kg	22kg	24kg	2kg	17.7kg	
% patients >5% weight loss	89%	96%	96%	28%		
% patients >20% weight loss	32%	55%	63%	1.30%		
treatment-regimen estimand	15.0%	19.5%	20.9%	3.1%	14.9%	2.4%
% patients >5% weight loss	85%	89%	91%	35%	84%	31%
% patients >20% weight loss	30%	50%	57%	3.10%		
nausea	24.6%	33.3%	31.0%	9.5%	44.2%	17.4%
diarrhea	18.7%	21.2%	23.0%	7.3%	31.5%	15.9%
vomiting	8.3%	10.7%	12.2%	1.7%	24.8%	6.6%
constipation	16.8%	17.1%	11.7%	5.8%	23.4%	9.5%
treatment discont AE	4.3%	7.1%	6.2%	2.6%	7.0%	3.1%
overall discont rates	14.3%	16.4%	15.1%	26.4%		

Source: Company data

1/ Tirzepatide's GIP receptor agonism is believed to reduce nausea and expand the therapeutic window allowing higher GLP-1 dosing, but there is still ongoing work to determine the exact mechanisms of action. GIP agonism might also enhance GLP-1 binding. It has also been proposed that GIP agonism might independently lead to a glucose-dependent increase in glucagon which raises energy expenditure and a positive effect on improving insulin sensitivity and preventing fat accumulation. It is not known how much GIP contributes to the weight loss of tirzepatide and whether tirzepatide is just a GLP-1 which has been dosed higher.

Phase 1 and 2 data for Novo's GIP agonist are anticipated in 3Q22 and 4Q22, respectively, and could provide incremental insights into this debate. It is possible that Novo's GIP agonist could expand the therapeutic window of semaglutide and allow higher doses >2.4mg of Wegovy to be explored (including in combination with cagrilintide). From an outcomes perspective, there remains some residual concerns that GIP agonism might not positively contribute to cardiovascular benefit, given the 26% MACE benefit in SURPASS-4 versus insulin glargine was below some expectations and reflecting observation real-world trials (here, here).

Exhibit 49: Weight loss curves out to 72 weeks in SURMOUNT-1: significant heterogeneity was observed, but nearly all patients on tirzepatide lost weight



Source: NEJM

2/ Tirzepatide's GIP activity could provide kidney protective benefits. Follow-on analysis exploring kidney outcomes in the SURPASS-4 trial suggests that treatment with tirzepatide resulted in a 32% improvement in albuminuria and a 2.2-fold improvement in the rate of eGFR decline compared to insulin glargine, with the pattern of improvement reminiscent of SGLT2 inhibitors. These effects were consistent across patient subgroups and background SGLT2 inhibitor use. These data suggest that Mounjaro may provide kidney protection and whilst the mechanism is not known, it is independent of blood pressure and could be related to Mounjaro's GIP-activity (ie independent of GLP-1 activity).

3/ In terms of cardiometabolic parameters, there was a 5-fold greater decrease in waist circumference with tirzepatide and a 3-fold greater percent reduction in fat mass versus lean mass resulting in an improvement in body composition. There was a 0.5% reduction in HbA1c and for participants with pre-diabetes, >95% reverted to normoglycemia. There was a circa 5% reduction in LDL-C cholesterol, a circa 20% reduction in triglycerides and a -7.2mmHg reduction in systolic blood pressure (versus -1.0mmHg for placebo) with the blood pressure improvements not appearing to be dependent on the magnitude of weight reduction. In the STEP-1 trial, treatment with Wegovy resulted in a circa 3% reduction in LDL-C cholesterol, a circa 22% reduction in triglycerides and a -6.2mmHg reduction in systolic blood pressure (versus -1.1mmHg for placebo).

4/ The most common adverse event was nausea, followed by diarrhea and constipation, which was transitory and mostly mild-to-moderate. The incidence of severe/serious gastrointestinal (GI) events was 1.7% 5mg, 3.1% 10mg, 3.3% 15mg versus 1.1% for the control arm. Overall discontinuations due to adverse events were 4.3% 5mg, 7.1% 10mg, 6.2% 15mg versus 2.6% for the control arm, with the difference driven by GI adverse events at 1.9% 5mg, 4.4% 10mg, 4.1% 15mg versus 0.5% for the control arm. Hair loss was transitory and has been seen in weight loss trials with bariatric surgery, an increase in dizziness occurred related to a reduction in fluid intake, there was no difference in gallbladder adverse events and increases in both pancreatic enzymes and heart rate were incretin-like.

Can Novo and Lilly's "duopoly" be challenged in obesity?

Novo Nordisk and Eli Lilly are set to strengthen their largely "duopoly" GLP-1 position with 12 obesity medicines in clinical development. Key readouts over the next 12 months include pivotal data for Novo's Rybelsus 50mg and proof-of-concept data for Lilly's weekly tri-agonist and oral small molecule GLP-1 medicines.

We expect large-cap biopharma companies with established commercial platforms in cardio-metabolic disease and research interests in obesity will be in competition to in-license innovative obesity medicines. We believe combination approaches will be required to improve the depth, consistency and quality of weight loss in obesity.

We believe that two to three credible challengers to Novo and Lilly will emerge based on the current crop of unpartnered obesity medicines in development: (1) weekly injectible foundational assets include Altimmune's ALT-801, Hamni's HM15211, Zealand Pharma's dapiglutide; (2) Zealand Pharma's weekly amylin analogue AP8396 offers a combination option; (3) oral GLP-1 assets from Regor Therapeutics, vTv Therapeutic and Sciwind Biosiences.

Novo Nordisk has enjoyed a monopoly position in the incretin obesity market since the launch of Saxenda at the end of 2014, followed by the roll-out of Wegovy in June 2021. Reflecting the overlap with Type 2 diabetes and the evolution of treatment guidelines to focus on cardiovascular risk reduction, the US launch of Wegovy has elevated the physician dialogue surrounding the effective treatment of obesity with GLP-1 medicines. This has created a halo effect for the GLP-1 category, with the rate of prescription growth more than doubling since the rollout of Wegovy.

The SURMOUNT-1 data for Eli Lilly's tirzepatide look set to raise the efficacy bar further in obesity, with up to 36% of patients achieving >25% weight loss equivalent to bariatric surgery. We expect the rollout of tirzepatide in obesity in 2024 (but this could be pulled into 2023 depending on FDA feedback) will be augmented by the ongoing strong launch of tirzepatide (Mounjaro) in diabetes.

Novo Nordisk and Eli Lilly are seeking to strengthen their largely "duopoly position" GLP-1 medicine position further. Both companies are seeking to launch new injectible higher-efficacy combination treatments in 2025/26, as well as launch oral options. Given their entrenched position, we have assessed whether large-cap biopharma companies, with established commercial platforms in cardio-metabolic disease, have the opportunity to import and develop innovation in obesity. We expect the obesity market to evolve into a treatment goal driven combination market similar to hypertension, focused on more consistent and greater weight loss benefits accompanied by excellent tolerability.

We have segmented the obesity market opportunity into five broad therapeutic categories. Each category is supported by the publication of positive proof-of-concept data. We have not included medicines targeting peptide YY ahead of phase 2 data anticipated for Novo's NNC0165 towards the end of 2022 in combination with semaglutide. Peptide YY is believed to reduce food intake leading to weight loss and improve insulin sensitivity through beta-cell proliferation and would be the sixth therapeutic category if proof-of-concept data support further development.

Exhibit 50: Leading approaches for the treatment of obesity

	GLP-1/GIP weekly inj.	Glucagon-focused weekly inj.	Amylin weekly inj.	Oral GLP-1 approaches	Long-acting GIPR inj.
Obesity focus	Weight & glycemic centric	Weight, cardio & glycemic centric	Weight centric	Weight & glycemic centric	Weight centric only?
Indications	Diabetes, obesity	NASH, obesity, diabetes	Obesity	Diabetes, obesity	Obesity
Weight loss	++	+++	++	++	+++
HbA1c	++	++	neutral	++	?
LDL-C	+	+++	+	+	?
SBP	+	++	neutral	+	?
Liver fat	na	+++	na	na	?
Safety	Nausea, diarrhea	Nausea, diarrhea, heart rate?	Nausea, diarrhea	Nausea, diarrhea	?
Companies	Novo Nordisk, Eli Lilly, Zealand Pharma, Sciwind Biosciences	Eli Lilly, Altimmune, Boehringer/Zealand Pharma, Hamni, Merck Inc	Novo Nordisk Zealand Pharma, Eli Lilly	Novo Nordisk, Eli Lilly, Pfizer, Regor Therapeutics, vTv Therapeutics, Sciwind Biosciences	Amgen

Source: Morgan Stanley Research

1/ GLP-1, GLP-1/GIP agonists. Wegovy and tirzepatide are likely to become the initial cornerstones of weight-centric and glycemic-centric obesity treatment, supported by key outcomes studies including SELECT (read-out 2022/23) / SELECT-LIFE and SURPASS-CVOT (read-out end-2024) / SURMOUNT-MMO (read-out >2024). It remains to be determined whether targeting GIP activity provides additional benefits beyond reducing nausea and expanding the therapeutic window allowing higher GLP-1 dosing, which translates into better HbA1c control and weight loss.

Novo's GIP-Sema co-formulated fixed dose combination is currently in a 495 patient phase 2b trial in diabetes which is expected to complete January 2023 (primary data October 2022), with phase 2 data for Novo's GIP (NNC0519-0130) alone and in combination with Wegovy anticipated in obesity 1H23 potentially providing additional visibility.

Zealand Pharma's dapiglutide, a once weekly GLP-1/GLP-2 dual agonist, has shown up to 4.5% weight loss after 4 weeks of treatment in healthy subjects and phase 2 trials are planned to commence early 2023. It remains to be seen what level of additional benefit the GLP-2 activity provides in terms of improving the tolerability of the GLP-1 activity, thereby broadening the therapeutic window of dapiglutide, and whether the theoretical proliferative effects of GLP-2 on the mucosal epithelial of the intestine lead to any safety concerns.

2/ GLP-1R/GCGR dual agonists / GLP-1R/GIP/GCGR tri-agonists. These medicines capitalise on the effect of both glucagon and GLP-1 on satiety, while counterbalancing glucagon's mobilisation of hepatic glucose with GLP-1s stimulation of insulin secretion. There are six weekly glucagon-focused medicines currently in phase 2 trials focussing on obesity, fatty liver disease (NASH) and diabetes. These medicines have the potential to address the earliest stages of metabolic syndrome by targeting glucagon resistance and adiposity, with Altimmune's ALT-801 showing >90% reduction in liver fat within 6 weeks. Reflecting 20-25% LDL-C reduction and>10mmHg systolic blood pressure reduction, glucagon-focused medicines could have the best efficacy profile amongst the leading obesity medicines in mid-stage development, targeting cardio-centric as well as weight-centric / glycemic-centric obesity.

The key question-mark with the glucagon-focused medicines revolves around safety, including heart-rate increases (initially as high as 30bpm), and the debate over lean body weight loss, i.e. whether there is a direct breakdown of protein which accompanies the increase in energy expenditure or whether the loss of excess (fat) weight indirectly leads to a loss of supportive musculature. Phase 2 data for five of the six weekly glucagon-focused medicines are anticipated before the end of the year and should provide greater visibility here. At this stage, the slow onset of action engineered into ALT-801 leads to no increase in heart rate and a potentially best in category profile. Phase 2 data for Boehringer Ingelheim / Zealand Pharma's BI 456906 will be presented at the EASD meeting 19-23 September 2022. Of note, Novo is not competing in the glucagon-focused category following termination of NN1177.

Exhibit 51: Obesity pipeline overview

Medicine	Company	Mechanism	Phase / data	Weight loss	HbA1c	LDL-C	SBP	Liver fat	Comments
GLP-1 based weekly injectibles									
Wegovy	Novo Nordisk	GLP-1	Marketed	-14.9%	-0.3%	-3%	c. -6mmHg vs -1mmHg	?	68wk data
tirzpatide	Eli Lilly	GLP-1/GIP dual agonist	Ph3; mid-23	-20.9%	-0.5%	-5%	c. -7mmHg vs -1mmHg	?	72wk data
NNC0480-0389	Novo Nordisk	GLP-1/GIP FDC	Ph2; data Jan-23	?	?	?	?	?	
XW003	Sciwind Biosciences	GLP-1	Ph2; data Oct-22	?	?	?	?	?	
Dapiglutide	Zealand Pharma	GLP-1/GLP-2	Ph2 ready	-5%	?	?	?	?	4wk data, healthy volunteers
HS-20004	Hansoh	GLP-1 (?)	Ph2; ?	?	?	?	?	?	
Glucagon-focused weekly injectibles									
LY3437943	Eli Lilly	GLP-1R/GIP/GCGR tri-agonist	Ph2; data Nov-22	8.65kg (-10.1%)	-1.9%	?	?	?	12wk data in diabetics; signif HR increase
LY3305677 (mazdutide)	Eli Lilly	GLP-1R/GCGR dual agonist	Ph1 complete	11.2kg (-12.7%)	-1.7%	?	?	?	16wk data in diabetics; signif HR increase
pemvidutide ALT-801	Altimmune	GLP-1R/GIP/GCGR tri-agonist	Ph2;data Dec-22	-10.30%	neutral	20-25% reduction	Up to -10mmHg	>90% reduction	12wk data
BI 456906	Boehringer/Zealand Pharma	GLP-1R/GIP/GCGR tri-agonist	Ph2;data Oct-22	?	?	?	?	?	Diabetes data at EASD 19 Sep-22
efinopegdutide / MK06024	Hamni/Merck	GLP/GRCG dual agonist	Ph2; data Oct-22	?	?	?	?	?	Primary focus NASH
HM15211	Hamni	GLP-1R/GIP/GCGR tri-agonist	Ph2; data Sep-22	?	?	?	?	?	Primary focus NASH
cotadutide (daily)	AstraZeneca	GLP/GRCG dual agonist	Ph2/3; data May-25	?	?	?	?	?	Primary focus NASH
Amylin weekly injectibles									
Cagrilintide (+sema)	Novo Nordisk	Amylin analogue	Ph3; Oct-24	-10.8%	neutral	circa -3%	neutral	neutral	26wk data obesity
ZP8396	Zealand Pharma	Amylin analogue	Ph1; Sep-22	?	?	?	?	?	
Amylin LA agonist	Eli Lilly	Amylin analogue	Ph1	?	?	?	?	?	
KBP-089	Nordic Bioscience	Amylin analogue	Ph1	?	?	?	?	?	
Oral GLP-1 approaches									
Rybelsus 50mg	Novo Nordisk	SNAC peptide	Ph3; May-23	?	?	?	?	?	
LY3502970	Eli Lilly	Small mol.	Ph2; data Nov-22	4.71kg	-1.77%	?	?	?	12 week data; no food restrictions
danuglipron	Pfizer	Small mol. (BID)	Ph2; data Dec-22	5.4kg	-1.60%	?	?	?	12 week data; no food restrictions
PF-07081532	Pfizer	Small mol.	Ph2; data mid-23	?	?	?	?	?	
TT273	vTv Therapeutics	Small mol.	Ph2 (diabetes)	?	?	?	?	?	
RGT-075	Regor Therapeutics	Small mol.	Ph2 (diabetes); Mar-23	?	?	?	?	?	
XW004	Sciwind Biosciences	Peptide	Ph1; data Feb-23	?	?	?	?	?	
GLP-1/GIP	Novo Nordisk	SNAC peptide	Ph1	?	?	?	?	?	
GLP-1/amylin	Novo Nordisk	SNAC peptide	Ph1	?	?	?	?	?	
Long-acting injectibles									
AMG 133	Amgen	GIPR Ab	Ph1b; data Nov-22	circa 11kg vs pbo	?	?	?	?	
Other									
PYY1875	Novo Nordisk	Peptide YY	Ph2; data Nov-22	?	?	?	?	?	
MBL949	Novartis	?	Ph2; Mar-23	?	?	?	?	?	
PYY analog agonist	Eli Lilly	Peptide YY	Ph1	?	?	?	?	?	
DACRA	Eli Lilly	DACRA	Ph1	?	?	?	?	?	
ZP6590	Zealand Pharma	GIP	Ph1	?	?	?	?	?	

Source: Morgan Stanley Research; clinicaltrials.gov; company data. Key assets highlighted in green text; Eli Lily assets shaded in orange, Novo Nordisk assets shaded in blue, partnership opportunity assets shaded in pink

3/ Long-acting amylin analogues. Amylin is a key appetite-regulating hormone which acts on the hindbrain as opposed to the hypothalamus which is targeted by GLP-1 activity. Phase 2 data for Novo's cagrilintide suggest that amylin analogues will have limited impact on key cardiometabolic parameters including glucose and blood pressure, but have good combinability with GLP-1 analogues in terms of tolerability. Therefore we see the amylin sub-category as being primarily focused on weight-centric obesity as an add-on strategy to GLP-1 medicines.

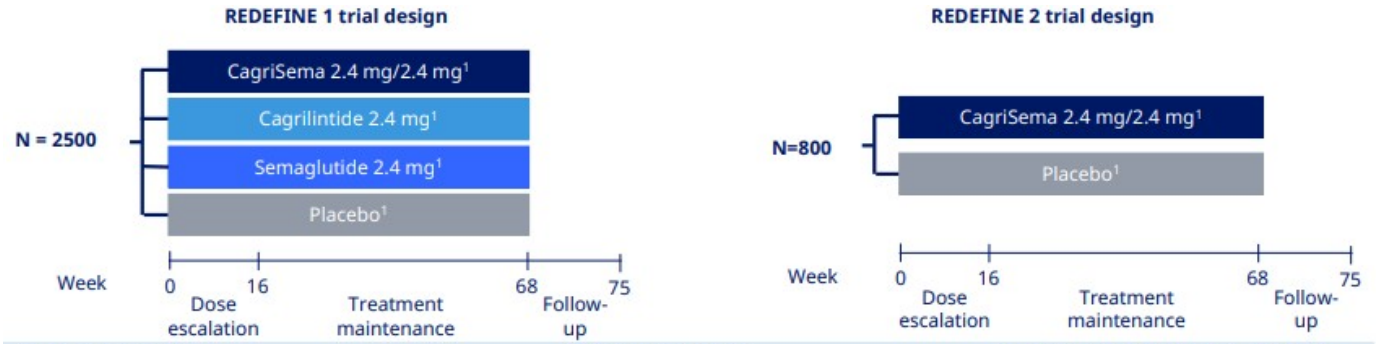
Cagrilintide is a cornerstone of Novo's obesity strategy beyond Wegovy, with two pivotal trials of cagrilintide 2.4mg in combination with semaglutide 2.4mg (cagrisema) anticipated to start before the end of 2022 (REDEFINE-1 & -2) after demonstrating -15.7% weight loss after 20 weeks. The additive weight loss is not accompanied by worsening tolerability, suggesting complementary mechanisms of action. Novo is planning to conduct a head-to-head trial with cagrisema versus tirzepatide, targeting superior weight reduction of >25%. Whilst cagrisema is likely to achieve similar weight loss to the GLP-1R/GCGR dual agonists, it will not provide the same cardiometabolic benefits on LDL-C cholesterol, triglycerides, systolic blood pressure and liver fat.

The downsides to cagrilintide are a blood pressure neutral profile despite the significant weight loss, potentially related to class-effect (transient) increases in plasma renin and aldosterone, and the need to use a dual chamber administration device with semaglutide. Zealand Pharma's amylin analogue ZP8396 appears to have a similar profile to cagrilintide, but is pH neutral which allows it to be combined directly with other molecules in a fixed-dose combination.

4/ Oral GLP-1 agonist approaches. There are two separate approaches to oral anti-obesity medicines: **(1) co-formulating peptides** within a protective, absorption enhancing carrier molecules - this approach has been pioneered by Novo Nordisk with Rybelsus, which uses Emisphere's SNAC technology (primarily gastric absorption), but other companies are working on similar concepts (e.g. Sciwind Biosciences with XW004; primarily intestinal absorption); **(2) small molecules GLP-1 agonists**, led by Eli Lilly and Pfizer, but given comparatively lower barriers to entry compared to peptide technology approaches, we expect a significant wave of additional competitors in addition to vTv Therapeutics and Regor Therapeutics. Greater competition suggests the potential for greater pricing pressure in the future.

Potential advantages of the small molecule approach include the lack of food restrictions (seen currently with Rybelsus), the potential to combine with other medicines including SGLT2 inhibitors or statins to target a broader cardiometabolic disease profile, potentially more localised interaction with GLP-1 receptors in the intestine and lower manufacturing cost considerations. Conversely, potential disadvantages of the small molecule approach include the possibility of greater nausea/diarrhea side-effects (seen with Pfizer's twice-daily danuglipron, although we await full presentation of the Ph2a data) and the potential off-target activity. Novo Nordisk is continually improving the SNAC technology behind Rybelsus to address the current food restriction and improve absorption properties to be competitive with small molecules when it comes to cost of manufacturing.

Exhibit 52: CagriSema pivotal trials planned in obesity



Inclusion criteria

REDEFINE 1:

- BMI: ≥ 30 kg/m² or ≥ 27 kg/m² and ≥1 comorbidity
- Excludes diabetes diagnosis or HbA_{1c} ≥ 6.5%

REDEFINE 2:

- BMI: ≥ 27 kg/m²
- Type 2 diabetes, HbA_{1c} < 10%

Primary endpoints:

- Change in body weight (%)
- Achieve ≥ 5% body weight reduction

Confirmatory secondary endpoints:

- Change in waist circumference
- HbA_{1c}
- Systolic blood pressure
- Patient reported outcomes²

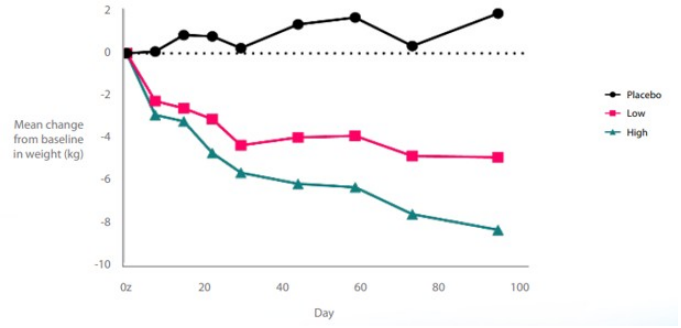
Source: Novo Nordisk Capital Markets Day 2022 (slide 83)

As with Wegovy and tirzepatide, oral GLP-1 approaches are likely to target the treatment of weight-centric and glycemic-centric obesity. Pivotal trials for Rybelsus 50mg in obesity are expected to readout in May 2023, which should deliver a clinical profile similar to Wegovy in a once daily oral format and will be supported by bridging to the SELECT outcomes trial. Novo has moved GLP-1/GIP and GLP-1/amylin molecules using the SNAC platform into phase 1. Novo is not pursuing small molecule GLP-1 research internally.

In terms of small molecule oral GLP-1 medicines, proof of concept data for Eli Lilly's LY3502970 are expected to read out for both diabetes (370 patients) and obesity (270 patients) in 4Q22. The early data for LY3502970 suggested a similar efficacy and tolerability profile to high-efficacy injectable GLP-1 medicines (HbA1c reduction -1.77% versus -0.45% for placebo; 4.71kg weight loss versus 0.48kg weight gain for placebo at 12 weeks), without food or water restrictions. Pfizer's once daily **PF-07081532** is expected to complete an initial phase 1b dose finding study in June 2022, before danuglipron and PF-07081532 are both moved into a phase 2 trial in diabetes with an optimised dose titration scheme which is expected to read out mid-2023. The phase 2 diabetes trial for Regor Therapeutics' RGT-075 is expected to complete in March 2023.

5/ Long-acting GIPR antibody. Amgen's AMG133 is a GIPR inhibitory antibody which has shown impressive early clinical data in obesity. A single dose of AMG133 demonstrated an impressive circa 8kg reduction in weight at a high dose (circa 5kg at a low dose) versus a 2kg weight gain for placebo after 90 days. Additional phase 1b data are anticipated in 100 obese patients after trial completion in May 2022.

Exhibit 54: Single dose of AMG133 demonstrates early clinical efficacy in obese patients



Source: Amgen Business Review Presentation February 2022

We believe that two to three credible challengers to Novo and Lilly will emerge based on the current crop of unpartnered obesity medicines in development.Based on our screen of the obesity R&D landscape, we believe that there are a handful of opportunities for large-cap biopharma companies, with commercial platforms in cardio-metabolicdisease, to import innovation and build an obesity pipeline. Giventhe significant resources required to conduct a pivotal trial program in obesity (>5,000 patients in the tirzepatide SURMOUNT trials), we expect positive phase 2 proof-of-concept data would likely trigger partnership discussions. We have highlighted potentially differentiated unpartnered obesity medicines in pink in Exhibit 51 : (1) weekly injectible foundational assets include Altimmune's ALT-801, Hamni's HM15211, Zealand Pharma's dapiglutide; (2) weekly injectible combination assets include Zealand Pharma's AP8396; (3) oral GLP-1 assets include Regor Therapeutics' RGT-085, vTv Therapeutic's TT273, Sciwind Biosiences' XW004. Large-cap biopharma companies with R&D interest in obesity and relevant commercial capabilities include AstraZeneca (OW), Novartis (EW), Pfizer (EW), Amgen (EW) and Merck Inc (EW). As discussed above, we believe combination approaches will be required in obesity to improve the consistency and deepen the reduction in weight loss whilst improving cardio-metabolic parameters.

Exhibit 53: Mid-stage obesity medicines with key proof-of-concept data over the next 12 months

Drug	Mechanism	Focus	Dosing	Phase	Patients	Next data point
BI 456906	GLP-1 / GR agonist	Subcut	Diabetes	2	413	mid-22
AMG 133	GIPR Ab	Subcut	Obesity	1b	100	mid-22
BI 456906	GLP-1 / GR agonist	Subcut	Obesity	2	387	4Q22
pemvidutide ALT-801	GLP-1 / GR agonist	Subcut	Obesity	2	320	4Q22
LY3437943	GGG tri-agonist	Subcut	Diabetes	2	300	4Q22
LY3437943	GGG tri-agonist	Subcut	Obesity	2	494	4Q22
LY3502970	GLP-1RA	Oral OD	Diabetes	2	370	4Q22
LY3502970	GLP-1RA	Oral OD	Obesity	2	270	4Q22
RGT-075	GLP-1RA	Oral OD	Diabetes	2	420	1Q23
danuglipron	GLP-1RA	Oral BID	Obesity	2	444	1Q23
danuglipron	GLP-1RA	Oral BID	Diabetes	2	tbd	mid-23
PF-07081532	GLP-1RA	Oral OD	Diabetes	2	tbd	mid-23

Source: Morgan Stanley Research; clinicaltrials.gov

Re-modelling the obesity market opportunity

We believe the treatment of obesity is on the cusp of moving into mainstream primary care and that obesity is where hypertension was in the mid-to-late 1980's from a market development perspective. 15 years after positive outcomes data and the introduction of next-generation medicines, the hypertension market evolved into a $30bn global sales category ($54bn, CPI adjusted to today).

Current day comparison to the cholesterol-lowering, anti-hypertensive and diabetes chronic treatment markets based on branded pricing points and comparably high treatment rates points to >$50bn obesity revenue bull-case opportunity in the US alone (Exhibit 56). Our analysis suggests that the key bottleneck remains the activation of patients to seek treatment and engagement with physicians.

Key inflection points ahead include the interim analysis of the Wegovy SELECT trial in 3Q22, treatment guideline updates at the end of 2022/23 and a wave of next-generation obesity medicines launching in 2025/26. Important "checkpoints" for investors include whether: (1) the relaunch of Wegovy drives obesity market expansion 2H22/2023; (2) Eli Lilly adopts a flat pricing strategy for tirzepatide across diabetes and obesity.

In our obesity market model we project that Novo Nordisk and Eli Lilly will each hold a circa 40% share of the obesity market in 2030, with new entrants including Altimmune capturing the remaining 20% share. On a global basis, we project combined Novo Nordisk obesity revenues of $20.9bn, Eli Lilly sales of $21.6bn and total global obesity sales of $54.0bn in 2030E. This illustrates that there is significant upside to the obesity estimates in both our Novo and Eli Lilly company models if the clinical data, regulatory pathway and commercialization strategies play out positively.

Historical comparison to the hypertension market supports a >$50bn global obesity revenue opportunity in 10-15 years. We believe that there are clear parallels between the historical evolution of the hypertension market and the ongoing development of the obesity market. In the 1960's, hypertension was considered to be a behavioural disorder caused by stress or an unavoidable consequence of ageing and was not recognised as a disease until the 1970's. The Hypertension Detection and Follow-Up (HDFP) trial published in 1979 was a key landmark outcomes trial for antihypertensive therapy, being the first study to demonstrate a mortality benefit of goal-directed, stepped care for blood pressure reduction. This was followed by positive outcomes trials including the MRC and EQHPE studies in the mid-1980's, which coincided with the emergence of the generation of medicines including ACE inhibitors and Calcium Channel Blockers. This was the point at which the treatment of hypertension moved into mainstream primary care. By the end of the 1990's, hypertension had evolved into a $30bn global sales category ($54bn, CPI adjusted to today) with four main treatment approaches.

Current day comparison to other chronic cardio-metabolic diseases points to >$50bn obesity revenue opportunity in the US alone based on more bullish treatment rates (Exhibit 56). Data from the US Centres for Disease Control and Prevention (CDC) suggest that a relative high proportion (79-91%) of individuals suffering from high blood pressure, elevated cholesterol levels or diabetes are diagnosed and actively managed. In contrast, just 7% of individuals with obesity are estimated to be diagnosed and actively managed. We see this as the key bottleneck for the development of the obesity market, with more efficacious and safe medicines integral to activating more people to seek treatment and increasing the number of prescribers.

Exhibit 55: Timeline of antihypertensive therapy 1967-2005

Study	Year	Primary question/issues	Conclusion of the study/impact
VA-1st	1967	Is severe hypertension (dias) 115–129 treatable	Yes, less stroke/CHF
VA-2nd	1970	Same question for moderate BP (90–115)	Treated group less stroke/CHF
HDFP	1979	Goal-oriented BP therapy better than usual therapy?	Yes. Targeting BP goal of dias 90 reduced CVA by 36% more
MRFIT	1982	Lowering BP and lipid and stopping smoking may reduce CHD mortality	No difference in CHD mortality 17.9 vs. 19.3% (per 1000)
MRC	1985	Hypertension treatment in younger patients (35–64) is beneficial also?	Yes. Total CV events 286 in treated group vs. 352 in control ($p < 0.05$)
EWHPE	1986	Hypertension treatment in exclusively older people (60) beneficial?	Yes. Mortality reduction 26% decrease in CV mortality 43%
SHEP	1991	Is treatment of systolic hypertension beneficial	Treating isolated systolic hypertension over 160 prevented stroke (ARR 3%), MI, and all CVD
TOMHS	1993	Outcome of 5 different classes BP meds vs. placebo	BP lowering similar among all classes CV events and death reduced (ARR 2.2%)
DASH	1997	Does Mediterranean diet with or without salt restriction lowers BP?	Compared to western diet it lowers bp and salt restriction adds to the effect
MRC	1997	Salt reduction in older people Lowers BP?	Reducing salt intake to 2 g Na lowered BP 7.2/3.2 mmHg
HOT	1998	Lowering Dias BP to 85 or 80 beneficial compared to standard 90 goal	No significant benefit in whole study but small benefit in diabetic
UKPDS	1998	Multiple studies 2 involved BP Tight BP control and agents (captopril vs. atenolol)	Group target <150/85 had 32, 44, and 34% less death, stroke, and retinopathy, respectively. No difference in ACEI group vs. BB
AASK	2002	To reduce progression of CKD BP goal mean 92 better than 105 ACEI, BB, or CCB better as drug?	No difference in mean BP goal of 92 vs. 105. ACEI use protected progression of CKD better than CCB
ALLHAT	2002	Compared to old thiazide (CTDN) new class of BP drugs CCB, ACEI, or AB has better outcome? AB gr closed for high incidence of CHF	No difference in MI, mortality, or CKD progression among 3 classes. CTDN vs. CCB for CHF RR 1.38. CTDN vs. ACEI for stroke and CHF RR 1.15 and 1.19
ANBP2	2003	ACEI vs. thiazide (HCTZ) for CV outcomes in Australian	In this study unlike ALLHAT, ACE was better all CV events RR was 0.88
ASCOT	2005	CCB and ACE inhibitor compared to BB and thiazide for BP control	CCB and ace inhibitor combination group showed better CV outcomes

Source: Saklayen and Deshpande; Front Cardiovasc Med. 2016; 3: 3.

Exhibit 56: Market dynamics for selected chronic cardio-metabolic diseases

	Obesity	Cholesterol	High blood pressure	Diabetes	Obesity (raised awareness)
Prevalence	142,228,850	94,000,000	116,000,000	37,300,000	142,228,850
Diagnosed/rec. medical treatment	9,800,000	85,923,218	91,700,000	29,314,956	56,891,540
% patients diag / rec. medical treatment	7%	91%	79%	79%	40%
Actual treated	3,920,000	47,000,000	33,600,003	24,243,469	31,290,347
% treated	40%	55%	37%	83%	55%
% patients treated, controlled	n/a	56%	70%	51%	na
Total prescriptions	10,240,782	249,039,740	636,660,671	218,856,941	250,322,777
Current gross sales ($m)	1,613	2,207	8,514	85,278	na
Revenues ($m) assuming $350/script	3,584	87,164	222,831	76,600	87,613

Source: IQVIA; CDC; Morgan Stanley Research

Obesity management requires education to support physicians and training to support patients, with positive outcomes data key to building payer support. Once actively managed, 37% of individuals with hypertension and 55% of those with high cholesterol are medically managed, which is broadly in-line with the proportion of actively managed obese patients who are treated with medicines (circa 40%). Increasing the proportion of obese patients actively managed to 40% and the percentage of those individuals receiving medicines to 55% would generate an estimated $88bn in US obesity revenues based on a $350/prescription net value. The same methodology would point to a fully branded ($350/script) cholesterol market of $87bn in revenues. We believe that the visible benefits of weight loss medicines relative to the asymptomatic benefits of cholesterol / hypertension medicines might support greater motivation for patients to seek treatment and stay on therapy.

The American Medical Association only classified obesity as a chronic disease in 2013, circa 20 years after the FDA published guidelines for the development of weight-loss drugs which stipulated a statistically significant weight reduction of at least 5% compared to placebo after 12 months. These FDA guidelines followed data showing that a combination of fenfluramine and low-dose phentermine (Fen-phen) achieved 15.9% weight loss over 34 weeks. Redux (a better tolerated alternative to fenfluramine) was approved by the FDA in July 1996 with weekly prescriptions reaching up to 85,000, before the medicine was withdrawn from the market in September 1997 due to heart valve damage risks. Safety concerns also led to the withdrawal of weight loss medicines Acomplia (2008) and Meridia (2010). Therefore with safety concerns impacting the historical development of the obesity market, phentermine has remained the most widely prescribed anti-obesity medicine despite only being recommended for short-term use.

The treatment of obesity is on the cusp of moving into mainstream primary care. We believe that obesity is where hypertension was in the mid-to-late 1980's from a market development perspective. Importantly, the safety of GLP-1 medicines has been established in the diabetes setting where cardiovascular outcomes trials have (1) demonstrated a 13-26% morbidity/mortality benefit and (2) supported the update of diabetes treatment guidelines late 2019 to prioritise the use of GLP-1 medicines in diabetes patients with the cardiovascular disease. Obesity and Type 2 diabetes are interconnected diseases, with an estimated 10% of obese patients suffering from diabetes and a further 31% of patients developing pre-diabetes (put another way, 80-85% of Type 2 diabetics are obese). Wegovy and tirzepatide have both extended the amount of weight loss that is achievable and demonstrated important cardiometabolic benefits, with a convenient weekly injection device. The increased focus on weight loss following the launch of Wegovy in June 2021 has created a halo effect for the GLP-1 category, with the rate of prescription growth more than doubling as physician and patient engagement increases.

The key revenue acceleration period for investors to monitor starts in 2023. We have identified a series of checkpoints behind our assumptions that the high efficacy obesity medicine market in the US will increase from revenues of $0.8bn in 2021 to $13.8bn in 2026E and onto $31.5bn in 2030E.

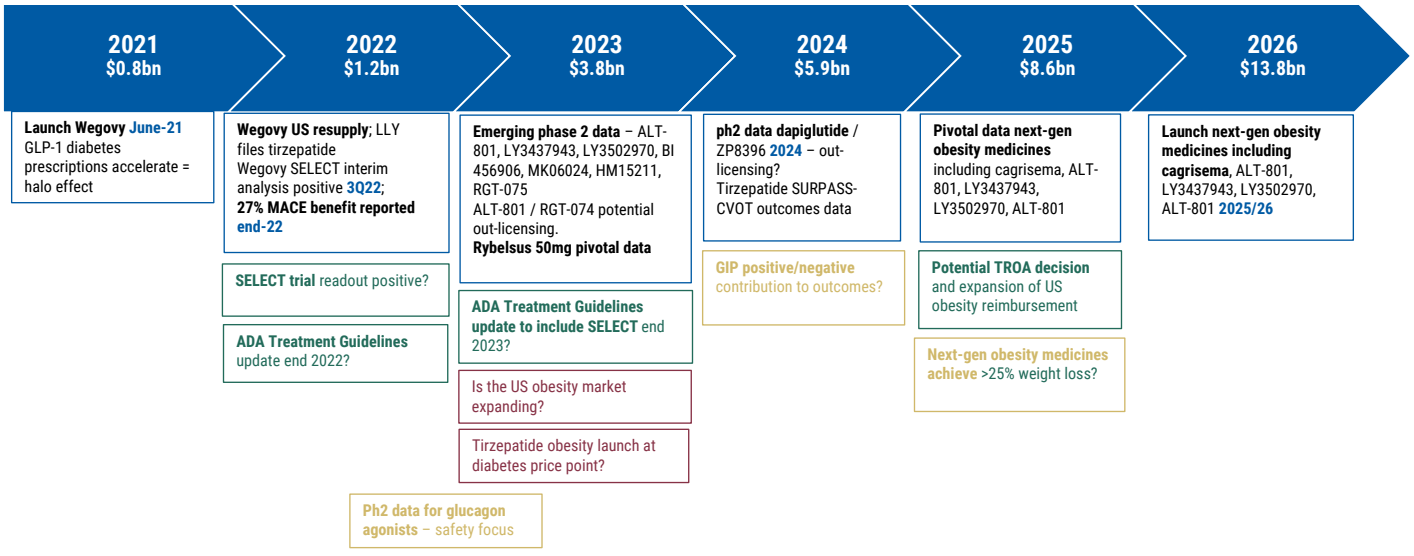
2H22. The near-term focus is on prescription dynamics following the progressive removal of Wegovy supply constraints starting in 3Q22. We project total obesity prescriptions to increase by circa 35% in 2023 as Wegovy drives market expansion and this remains a key "reality-check" checkpoint for investors.

Exhibit 57: Obesity medicine overview

	>5% weight loss	>10% weight loss	Discont. Due to AEs	US TRx share (Dec-21)
Xenical	45%	20%	8%	<1%
Belviq	49%	25%	6%	<1%
Contrave	55%	30%	12%	4%
Saxenda	63%	34%	13%	5%
Qysymia	74%	54%	10%	2%
Wegovy	84%	66%	7%	10%
tirzepatide	85-91%	69-84%	4-7%	n/a

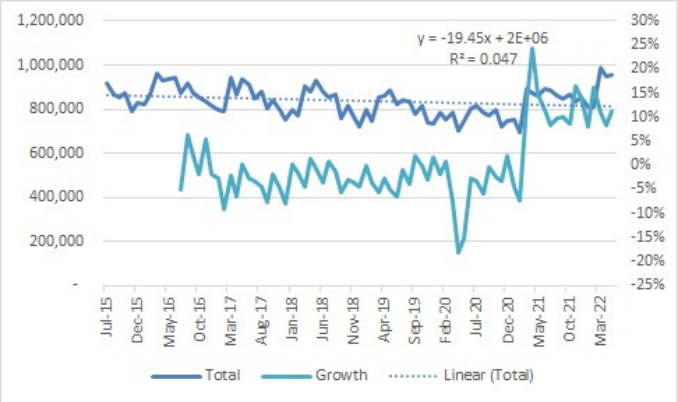
Source: Silverman et al; Jastreboff et al; www.wegovy.com; IQVIA; Morgan Stanley Research

Exhibit 58: US obesity market expansion checkpoints; 2023-25 represent key transition years



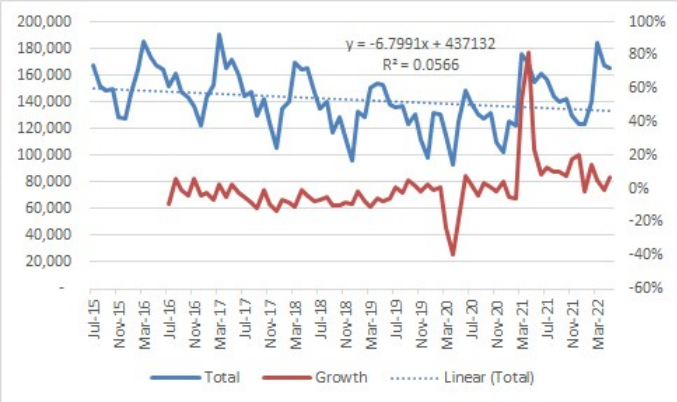
Source: Morgan Stanley Research

Exhibit 59: US obesity market dynamics: TRx prescriptions and YoY growth



Source: Morgan Stanley Research, IQVIA

Exhibit 60: US obesity market dynamics: NTS prescriptions and YoY growth



Source: Morgan Stanley Research, IQVIA

2H22. We expect the interim analysis of the Wegovy SELECT trial in 3Q22 to lead to the study being stopped early for overwhelming efficacy. A recent meta-analysis of Weogvy trials in non-diabetics patients suggests a circa 27% reduction in the risk of major cardiovascular events. We see the SELECT study as a "pivotal trial for the future of obesity medicine" and we expect a conclusion that "weight management saves lives" to be a powerful message for medical professionals, National Guideline policies and payers alike.

End-2022. We believe that ADA diabetes treatment guidelines might be updated at the end of 2022 to recommend a >15% weight loss target for Type 2 diabetics versus the current 7% weight loss recommended. ADA diabetes treatment guidelines changed at the end of 2019 to promote the use of SGLT2 inhibitors and GLP-1 medicines in patients with high cardiovascular risk.

2H23/2024. Eli Lilly is exploring the potential for an early filing of tirzepatide for obesity based on the SURMOUNT-1 trial and supportive data in diabetic patients from the SURPASS clinical trial program. Assuming FDA acceptance and the approval of tirzepatide 2H23 onwards, a key focus will be whether Eli Lilly adopts a flat pricing strategy for tirzepatide across diabetes and obesity (which is what we model). We expect the net price of GLP-1 medicines in obesity to fall from circa $950/prescription towards $450/prescription in 2025E and $350/prescription in 2030E. This is a key checkpoint for investors.

End-2023. We expect the Wegovy SELECT trial to establish a proven link between weight loss and important health outcomes, with treatment guidelines updated accordingly at the end of 2023.

2024-25. A wave of next-generation high efficacy obesity medicines are expected to report pivotal data during 2024-25, expanding treatment options for patients and promising deeper / more consistent / higher quality weight loss (25%-plus) compared to current treatments. Weekly injectibles with dual/triple-mechanisms of action including Novo's cagrisema and glucagon-targeting medicines from Eli Lilly, Altimmune and Hamni will report pivotal data. Phase 3 data for more convenient, higher efficacy oral medicines from Eli Lilly, Pfizer and Regor Therapeutics will also read out.

2025(?). We expect positive outcomes studies including SELECT (2022/23) and SURPASS-CVOT (end-2024) will increase the probability that the Treat and Reduce Obesity Act (TROA) legislation passes Congress and that the bill is scored by the CBO before potentially being passed, expanding Medicare coverage to include the screening and treatment of obesity.

Obesity model considerations

Patient dynamics

We assess the impact of broadening reimbursement and physician willingness to prescribe. In 2021, we estimate that 91% of US patients actively managed with anti-obesity medicines (AOMs) were treated with generics such as phentermine for just over 2 months per annum. This is the key target category for Wegovy and new high efficacy anti-obesity medicines when assessing the impact of broadening reimbursement and physician willingness to prescribe. Saxenda has captured 70% commercial managed care coverage but taking into account employee opt-in dynamics, effective commercial coverage is closer to 40%. Wegovy commercial coverage has exceeded this level ahead of the anticipated removal of supply constraints from 3Q22 onwards (Novo currently has stopped the shipment of lower doses of Wegovy).

Exhibit 61: US obesity market - patient projections

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US population	327,716,245	331,026,510	334,336,775	337,680,143	341,056,944	344,467,514	347,912,189	351,391,311	354,905,224	358,454,276	362,038,819
	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%	1%
Obesity prevalence	43%	44%	44%	45%	45%	46%	46%	47%	47%	48%	48%
Severe obesity	10%	10%	10%	10%	10%	11%	11%	11%	11%	11%	12%
Obese patient pool	142,228,850	145,320,638	148,445,528	151,618,384	154,839,853	158,110,589	161,431,256	164,802,525	168,225,076	171,699,598	175,226,788
Severe obesity patient pool	31,460,760	32,440,598	33,433,678	34,443,375	35,469,922	36,513,556	37,574,516	38,653,044	39,749,385	40,863,787	41,996,503
Target population											
Obese patients	**98,000,000**	**100,000,000**	**102,150,342**	**104,333,690**	**106,550,491**	**108,801,194**	**111,086,256**	**113,406,139**	**115,761,311**	**118,152,246**	**120,579,424**
Actively managed	9,800,000	10,000,000	10,419,335	11,163,705	12,466,407	14,361,758	16,329,680	18,938,825	21,647,365	24,457,515	27,371,529
% actively managed		10%	10%	11%	12%	13%	15%	17%	19%	21%	23%
Treated with AOM	3,920,000	4,000,000	4,167,734	4,688,756	5,734,547	6,893,644	8,001,543	9,469,413	11,040,156	12,717,908	14,506,911
% actively managed treated with AOM	40%	40%	40%	42%	46%	48%	49%	50%	51%	52%	53%
Total prescriptions	9,213,535	9,286,187	10,403,848	13,897,807	20,241,718	28,812,631	40,833,558	54,524,858	69,111,626	82,649,512	97,516,863
Total patients	3,920,000	4,000,000	4,167,734	4,688,756	5,734,547	6,893,644	8,001,543	9,469,413	11,040,156	12,717,908	14,506,911
Implied scripts per patient	2.4	2.3	2.5	3.0	3.5	4.2	5.1	5.8	6.3	6.5	6.7
Implied stay time (months/year)	2.4	2.3	2.5	3.0	3.5	4.2	5.1	5.8	6.3	6.5	6.7
Generic AOM scripts	8,118,533	7,710,385	7,811,710	8,091,091	8,861,218	9,144,467	8,034,924	7,352,171	6,638,781	6,604,864	6,411,162
Implied patients	3,646,250	3,652,959	3,700,964	3,833,327	4,198,191	4,332,386	3,806,717	3,483,248	3,145,264	3,129,195	3,037,425
Implied scripts per patient	2.2	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Implied stay time (months/year)	2.2	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Branded AOM prescriptions	1,095,002	1,575,802	466,770	855,429	1,536,356	2,561,257	4,194,826	5,986,165	7,894,892	9,588,713	11,469,486
Implied patients	273,751	347,041	466,770	855,429	1,536,356	2,561,257	4,194,826	5,986,165	7,894,892	9,588,713	11,469,486
Existing AOMs prescriptions	1,095,002	1,200,523	1,142,020	1,036,716	910,350	821,894	759,975	716,632	686,291	665,053	650,186
Implied patients existing AOMs	273,751	300,131	285,505	259,179	227,588	205,474	189,994	179,158	171,573	166,263	162,547
Stay time (months/year)	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
High efficacy prescriptions	-	375,279	1,450,118	4,770,000	10,470,150	18,846,270	32,038,659	46,456,056	61,786,554	75,379,596	90,455,515
Implied patients high efficacy	-	46,910	181,265	596,250	1,308,769	2,355,784	4,004,832	5,807,007	7,723,319	9,422,449	11,306,939
Stay time (months/year)		8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
% prescription share											
High efficacy		**4%**	**14%**	**34%**	**52%**	**65%**	**78%**	**85%**	**89%**	**91%**	**93%**
Saxenda		13%	11%	7%	4%	3%	2%	1%	1%	1%	1%
Generics		83%	75%	58%	44%	32%	20%	13%	10%	8%	7%
% patient share											
High efficacy		**1%**	**4%**	**13%**	**23%**	**34%**	**50%**	**61%**	**70%**	**74%**	**78%**
Saxenda		8%	7%	6%	4%	3%	2%	2%	2%	1%	1%
Generics		91%	89%	82%	73%	63%	48%	37%	28%	25%	21%
High efficacy branded patient share		14%	39%	70%	85%	92%	95%	97%	98%	98%	99%

Source: Morgan Stanley Research estimates

We have assumed that patients remain on Wegovy treatment for an average of 8 months each year. This compares to 4 months for Saxenda and just over 2 months for generic AOMs. This is a key assumption for Wegovy and other high efficacy treatments in development, including Eli Lilly's tirzepatide and Novo's cargri-sema. We have assumed that the SELECT trial stops early due to overwhelming efficacy with top-line data released at the end of 2022. We expect the rollout of high efficacy anti-obesity medicines supported by positive outcomes data, updated treatment guidelines and increasingly supportive payer dynamics will drive increased physician / patient engagement.

We have assumed the percentage of the obese patient target population which is actively managed increases from 10% to 25% in 2035E. This is equivalent to two-thirds of the severely obese target population being actively managed. However, we have assumed a more modest increase in the proportion of actively managed patients who receive an anti-obesity medicine, rising from 40% to 55% in 2035E. These assumptions mirror treatment dynamics observed in the high blood pressure and elevated cholesterol markets. Given the longer stay-times on the high efficacy anti-obesity medicines, we assume a 78% patient share drives a 93% prescription share in 2030.

Revenue dynamics

We expect increased competition to drive obesity medicine prices down. We have applied a blended average prescription net price of $741/scrips in 2023 reflecting co-pay patient support programs (underlying net price of $950/script) and increasing competition. We have assumed that Eli Lilly adopts a flat pricing strategy for tirzepatide across diabetes and obesity such that pricing converges, with Novo forced to match tirzepatide on price to maintain formulary access and Rybelsus 50mg rolling out in both indicators. We expect the net price of GLP-1 medicines in obesity to fall to $450/script in 2025E and $350/script in 2030E. The entry of new commercial players into the obesity market, including Pfizer, Merck and Novartis, especially in the small molecule space, has the potential to further potentiate pricing pressure.

Exhibit 62: US obesity revenues projected to reach $31.5bn in 2030, with the share of weekly injectible medicines falling towards 70%

REVENUES											
	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Saxenda $m sales	494	560	321	312	161	93	62	41	27	18	12
High efficacy market $m sales		**220**	**885**	**3,537**	**5,714**	**8,481**	**13,697**	**18,867**	**23,838**	**27,629**	**31,497**
INJECTIBLE WEEKLY											
Market share		**100%**	**100%**	**100%**	**100%**	**99%**	**98%**	**94%**	**90%**	**85%**	**82%**
Category revenues		**220**	**885**	**3,537**	**5,702**	**8,396**	**13,423**	**17,716**	**21,335**	**23,484**	**25,827**
Sales											
Wegovy		220	885	3,537	5,497	7,288	9,624	9,195	6,305	4,227	2,324
Cagrisema		-	-	-	-	168	1,074	2,480	3,840	4,697	5,165
Sema-GIP		-	-	-	-	-	134	354	853	1,409	2,066
PYY 1875 combo		-	-	-	-	-	-	89	213	352	517
LA-GDF15 combo		-	-	-	-	-	-	-	53	117	258
Novo injectible		220	885	3,537	5,497	7,456	10,832	12,118	11,265	10,803	10,331
tirzepatide		-	-	-	171	840	1,879	3,189	4,694	5,167	5,424
LY3437943 (GGG)		-	-	-	-	-	268	886	2,134	2,818	3,616
LY3305677(GCR/GLP-1; mazdutide; oxyntomodulin)		-	-	-	-	-	134	531	853	939	1,291
Lilly injectible		-	-	-	171	840	2,282	4,606	7,681	8,924	10,331
BI 456906 (dual GCR/GLP-1)		-	-	-	11	34	81	142	213	235	258
ALT-801 (pemvidutide; dual GCR/GLP-1)		-	-	-	-	-	67	531	1,493	2,348	3,099
MBL949 (Novartis)		-	-	-	11	34	81	142	213	235	258
Hamni portfolio (efinopegdutide GRA/GLP MK06024)		-	-	-	11	34	81	142	213	235	258
Dapiglutide (GLP-1/GLP-2)		-	-	-	-	-	-	35	213	470	775
ZP8396 (amylin analogue combo)		-	-	-	-	-	-	-	43	117	258
ZP6590 (GIP combo)		-	-	-	-	-	-	-	-	117	258
Volume share											
Wegovy		100%	100%	100%	96%	87%	72%	52%	30%	18%	9%
Cagrisema						2%	8%	14%	18%	20%	20%
Sema-GIP							1%	2%	4%	6%	8%
PYY 1875 combo								1%	1%	1.50%	2%
LA-GDF15 combo									0%	0.50%	1%
Novo injectible		100%	100%	100%	96%	89%	81%	68%	53%	46%	40%
tirzepatide					3%	10%	14%	18%	22%	22%	21%
LY3437943 (GGG)							2%	5%	10%	12%	14%
LY3305677(GCR/GLP-1; mazdutide; oxyntomodulin)							1%	3%	4%	4%	5%
Lilly injectible					3%	10%	17%	26%	36%	38%	40%
BI 456906 (dual GCR/GLP-1)					0%	0%	1%	1%	1%	1%	1%
ALT-801 (pemvidutide; dual GCR/GLP-1)							1%	3%	7%	10%	12%
MBL949 (Novartis)					0%	0%	1%	1%	1%	1%	1%
Hamni portfolio (efinopegdutide GRA/GLP MK06024)					0%	0%	1%	1%	1%	1%	1%
Dapiglutide (GLP-1/GLP-2)								0%	1%	2%	3%
ZP8396 (amylin analogue combo)									0%	1%	1%
ZP6590 (GIP combo)										1%	1%

Source: Morgan Stanley Research estimates

We have assumed that weekly injectible high efficacy obesity medicines continue to dominant the category ahead of phase 2 data year-end and pivotal data 2024/25 for the new small molecule oral medicines. This is split 40% for Novo's portfolio of products, 40% Eli Lilly and 20% new entrants. In our view, glucagon-targeting medicines could over time establish a higher quality weight loss (significant reductions in LDL-C cholesterol, blood pressure and clearance of liver fat) and gain significantly greater category share. Novo has abandoned glucagon as a target and so the safety profile of these glucagon-targeting medicines with respect to heart rate, protein breakdown and signals of liver damage will be an important focus over the next 12 months. Key glucagon-focused companies include Eli Lilly, Altimmune, Boehringer Ingelheim/Zealand Pharma and Hamni/Merck Inc. The estimates in Exhibit 63 below are ahead of the pipeline estimates in our Eli Lilly and Pfizer models and represent theoretical market share if the clinical data, regulatory pathway and commercialization strategy play out positively.

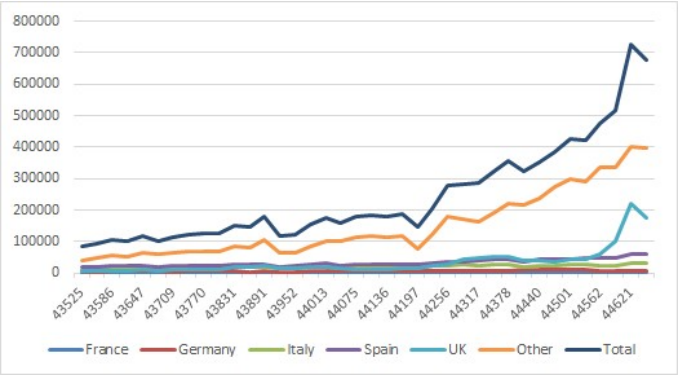
Exhibit 63: We expect oral and ultra long-acting injectible obesity medicines to capture a 30% volume share by 2035E

REVENUES											
	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Saxenda $m sales	494	560	321	312	161	93	62	41	27	18	12
High efficacy market $m sales		**220**	**885**	**3,537**	**5,714**	**8,481**	**13,697**	**18,867**	**23,838**	**27,629**	**31,497**
ORAL											
Market share					**0%**	**1%**	**2%**	**6%**	**10%**	**14%**	**16%**
Category revenues					**11**	**85**	**274**	**1,132**	**2,384**	**3,868**	**5,039**
Sales											
Rybelsus 50mg					11	83	248	826	1,192	1,044	1,260
GLP-1+amylin					-	-	-	11	72	309	605
LY3502970 (oral small mol - mono & combo)					-	2	22	226	834	1,934	2,268
danuglipron (oral small mol)					-	-	-	-	-	-	-
PF-07081532 (oral small mol)					-	-	3	45	191	387	605
Regor RGT0975 (oral small mol GLP-1)					-	-	1	23	95	193	302
vTv Therapeutics TT273 (oral small mol GLP-1)					-	-	-	-	-	-	-
Volume share											
Rybelsus 50mg					100%	98%	91%	73%	50%	27%	25%
GLP-1+amylin								1%	3%	8%	12%
LY3502970 (oral small mol - mono & combo)						2%	8%	20%	35%	50%	45%
danuglipron (oral small mol)							0%	0%	0%	0%	0%
PF-07081532 (oral small mol)							1%	4%	8%	10%	12%
Regor RGT0975 (oral small mol GLP-1)							1%	2%	4%	5%	6%
vTv Therapeutics TT273 (oral small mol GLP-1)							0%	0%	0%	0%	0%
LONG-ACTING ANTIBODY											
Market share								**0.1%**	**1%**	**1%**	**2%**
Category revenues								**19**	**119**	**276**	**630**
Sales											
AMG133 (GIPR Mab)								19	119	276	630
Volume share											
AMG133 (GIPR Mab)								100%	100%	100%	100%

Source: Morgan Stanley Research estimates

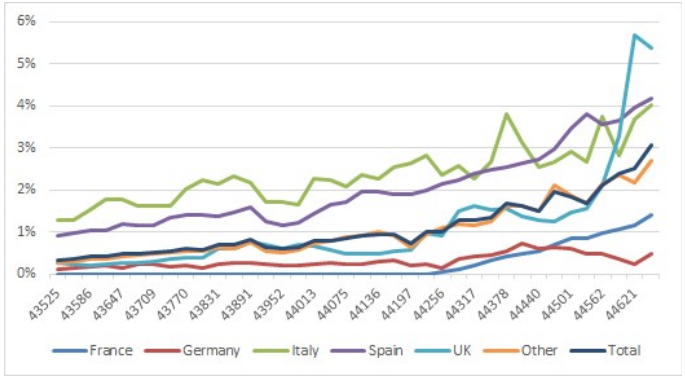
We have assumed that oral GLP-1R agonist approaches a 25% volume share by 2035E. Small molecules GLP-1 agonists, led by Eli Lilly, Pfizer and Regor Therapeutics, are expected to benefit from a lack of food restrictions, lower manufacturing cost considerations and the potential to be combined with other medicines including SGLT2 inhibitors or statins to target a broader cardiometabolic disease profile. Proof-of-concept data are anticipated over the next 12 months and we will be closely following these data given that oral medicines over time could capture a higher proportion of patients. Another disruptive wild-card asset is Amgen's GIPR inhibitory antibody, which could demonstrate bariatric surgery-like efficacy with every 3-month dosing; ahead of the presentation of phase 1 data, we assume ultra-long acting obesity medicines capture just 5% volume share in 2035E.

Exhibit 64: Saxenda prescription volumes in Europe: UK and EU other key regions



Source: IQVIA MIDAS; Morgan Stanley Research

Exhibit 65: Saxenda prescription volume share in Europe



Source: QVIA MIDAS; Morgan Stanley Research

We project that Novo Nordisk and Eli Lilly will each capture a circa 40% share of the $31.5bn US obesity market in 2030E. We assume Altimmune captures a circa 10% share and other market participants capture a further circa 10% share. We have used IQVIA MIDAS prescription data to understand obesity market dynamics in Europe where reimbursement agreements (e.g. UK NICE recommendation for Saxenda in December 2020) have historically resulted in a step-change in uptake. Using Saxenda as a proxy for other international markets, we forecast the anti-obesity market outside the US to expand to $22.5bn in 2030. On a global basis, we forecast Novo Nordisk revenues of $20.9bn, Eli Lilly sales of $21.6bn and total global obesity sales of $54.0bn in 2030E. This illustrates that there is significant upside to the obesity estimates in our Eli Lilly model if the clinical data, regulatory pathway and commercialization strategy play out positively.

Exhibit 66: Global anti-obesity medicines revenue projections

$m	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
US revenues											
Novo		780	1,206	3,849	5,669	7,632	11,142	12,997	12,556	12,175	12,208
Lilly		-	-	-	171	841	2,304	4,833	8,515	10,858	12,599
Altimmune		-	-	-	-	-	67	531	1,493	2,348	3,099
Amgen		-	-	-	-	-	-	19	119	276	630
Other		-	-	-	34	101	246	529	1,182	1,989	2,973
Total		**780**	**1,206**	**3,849**	**5,875**	**8,574**	**13,758**	**18,908**	**23,866**	**27,647**	**31,509**
Ex-US revenues											
Novo		554	736	1,407	2,793	4,577	6,732	8,667	8,692	8,722	8,722
Lilly		-	-	-	84	505	1,392	3,223	5,895	7,779	9,001
Altimmune		-	-	-	-	-	41	354	1,034	1,682	2,214
Amgen		-	-	-	-	-	-	13	83	198	450
Other		-	-	-	17	60	148	352	818	1,425	2,124
Total		**554**	**736**	**1,407**	**2,894**	**5,143**	**8,314**	**12,610**	**16,522**	**19,806**	**22,512**
Global revenues											
Novo		1,335	1,941	5,255	8,462	12,209	17,874	21,664	21,248	20,897	20,930
Lilly		-	-	-	255	1,346	3,696	8,055	14,410	18,637	21,600
Altimmune		-	-	-	-	-	108	886	2,527	4,031	5,314
Amgen		-	-	-	-	-	-	31	202	474	1,080
Other		-	-	-	51	161	394	881	2,001	3,414	5,098
Total		**1,335**	**1,941**	**5,255**	**8,769**	**13,716**	**22,072**	**31,518**	**40,388**	**47,453**	**54,021**

Source: Morgan Stanley Research

Social media and obesity: from linear to exponential demand

Whilst the availability of more medicines for obesity is an exciting prospect, only when obesity treatment is understood and more widely accepted can it catalyse a step-change in demand. In this section, we argue that social media is already creating a recursive cycle of education, word of mouth and heightened demand for weight-loss drugs even before they are available to the public. Simply put, if calorie counting apps are the linear growth route to obesity management, social media combined with medicines like Wegovy is already showing the early signs of an exponential virtuous cycle.

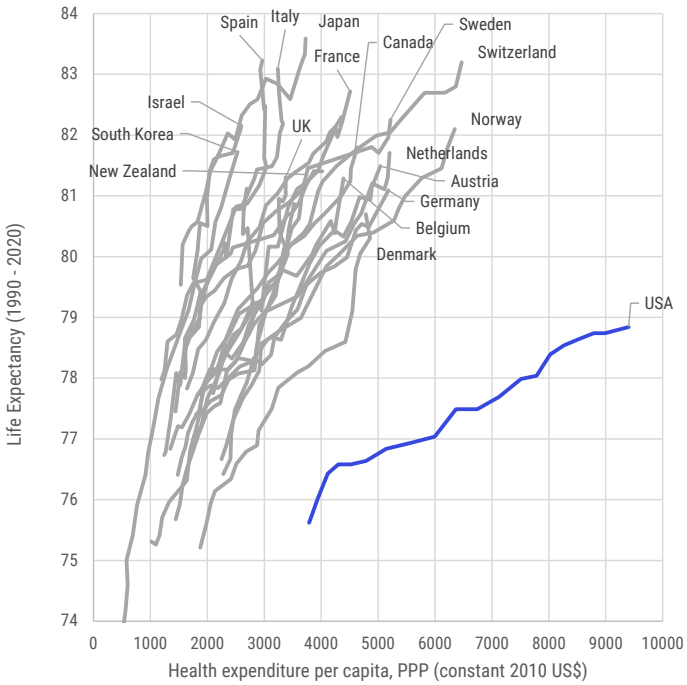
History shows the challenges of moving from linear to exponential

Demographic trends are akin to turning cargo ships; policy changes and cultural habits take an extraordinarily long time to deviate course. Even then, when inflection points are reached, it can take many years more for anomalous patterns to re-converge with nations of comparable socio-economic "norms". For example, simply spending more money on improving the health of the world's richest economy - and in turn re-converging the US's anomolously low life expectancy to a developed market norm - has proven to be fallacious (Exhibit 67).

Moreover, given all major developed economies have seen the prevalence of obesity rising concurrently with life expectancy, we clearly cannot infer that obesity is the most important variable in driving life expectancy. However, what can be deduced is that nations which have seen slower increases in the rate of obesity have simultaneously experienced the fastest increases in life expectancy; Japan most notably.

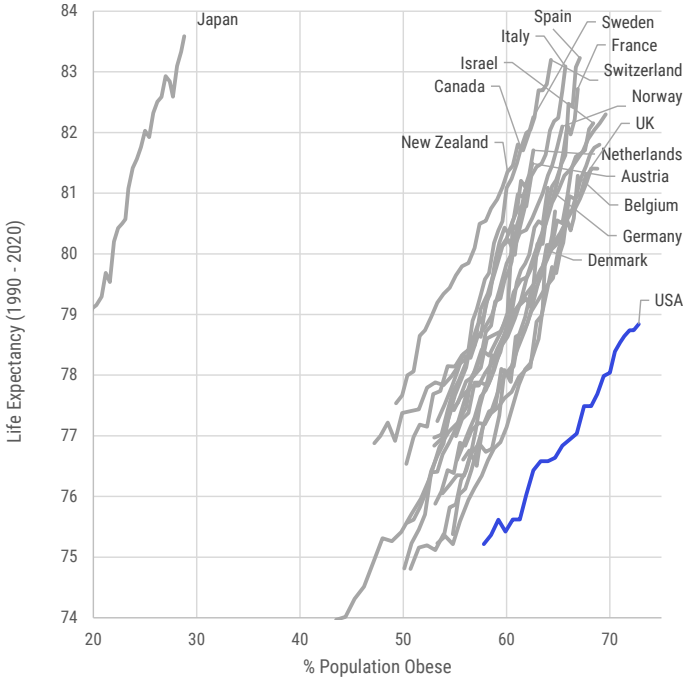
Either way though change has been slow, linear and tends to move in one direction over the long-run. We do not expect immediate change. However, speed of knowledge proliferation through social media has never been so powerful, and the US has a particularly captive audience with high rates of obesity. This combination, we believe, can shift behaviour from linear to exponential.

Exhibit 67: Life expectancy versus per capita spend on Healthcare (1990 - 2020) - developed nations



Source: United Nations, OECD, World Bank, Morgan Stanley Research

Exhibit 68: Life expectancy versus obese portion of population (1990 to 2020) - developed nations



Source: United Nations, OECD, World Bank, NCD Risk Factor Collaboration (NCD-RisC) Database, Morgan Stanley Research

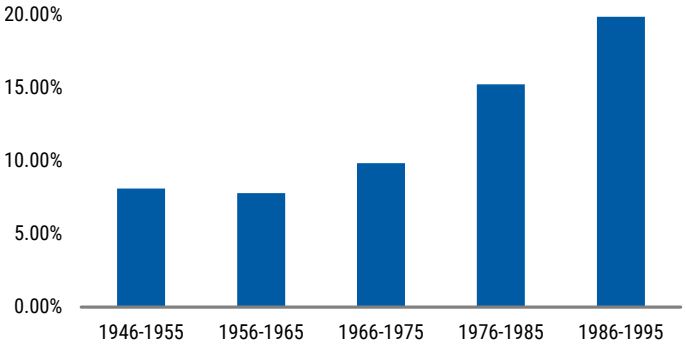
Gen Z to Propel a Virtuous Cycle

A particularly important element to this debate is that people are getting heavier quicker and younger than ever. Gen Z is not the largest cohort of obese people in absolute count - either in the US or globally - however the acceleration in obesity rates amongst the young is more pronounced than in older age groups. Teenagers in the US who were born between 1986-1995 (i.e. Millennials) were twice as likely to be obese than teenagers who had been four decades earlier (i.e. Boomers).

The importance of early onset obesity has been recognised by Novo Nordisk, with the STEP TEENS trial (average age 15.4yrs) showing a BMI reduction of 16% in adolescents and improvements in diabetic and cardiovascular risk factors.

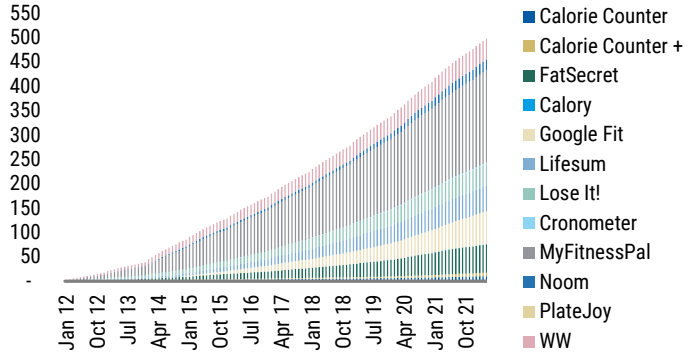
500 million app downloads globally over the past decade for the 12 most popular Western calorie-counting and fitness apps imply a strong and steady growth in demand for weight-loss solutions. This is particularly true in younger age groups. However, via social media and the rise of influencing, we believe medical weight-loss solutions have the potential to grow exponentially rather than linearly.

Exhibit 69: Obesity rates in the US during the age of 10-19 years old by decade of birth



Source: Tulane University, Morgan Stanley Research

Exhibit 70: Fitness and weight-loss app downloads since 2012 globally



Source: SensorTower, Morgan Stanley Research

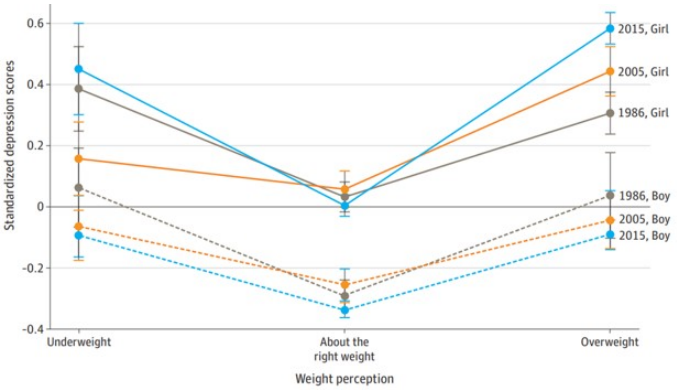
Social Media - The Problem and The Solution

Across a number of studies, Social Media has been shown to have causal links to depression and anxiety. More specifically there is a growing body of research which associates social media in either facilitating or exacerbating obesity, particularly in younger users of platforms.

Research from UCL recently provided further quantification of the relationship between an individual's weight **perception** and their likelihood to see higher prevalence of depression. This causality, they demonstrate, is most pronounced in girls rather than boys. Furthermore, while it holds for heightened depression risk as a result of the perception of being underweight, it is more pronounced for those perceiving themselves to be overweight. Most striking of all is the change over time. Taking just girls perceiving themselves to be overweight in the study, the standardised depression scores monitored in the study increased threefold between 1986 and 2015. Body consciousness and associated depression has been steadily rising in this particularly vulnerable portion of society.

Rising use of social media over this time cannot reasonably be ascribed all the blame for this secular shift; there are a number of other causal factors. However, when one third of the users on TikTok, for example, fall into the 10-19 year-old category (the cohort shown above to be experiencing the most rapid rise in obesity rates), it is reasonable to suggest that while social media may have perpetuated the issue it could equally hold a solution.

Exhibit 71: Changes in association between weight perception and depressive symptoms by cohort and sex



Source: University College London

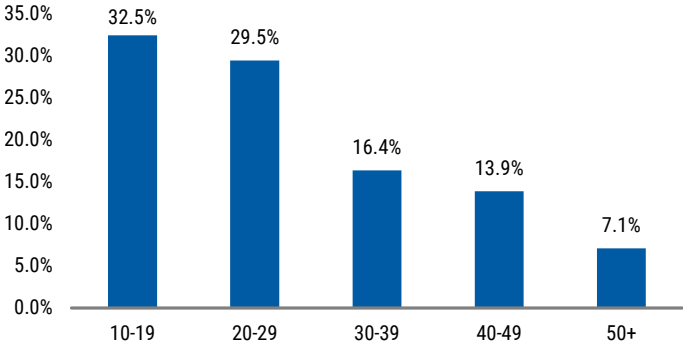
We have analysed hashtag trends on TikTok over time for a number of health, weight and wellness categories; 15bn individual hashtags in total. Given TikTok's algorithm is notable for its ability to find and show content that users will find engaging and thus sticky, it is notable that #Wegovy and #Semaglutide are frequently and increasingly found interspersed with videos relating to mentions of #weightloss and #calories.

In fact - and admittedly partially as a result of their recency as hashtag terms - Wegovy (indicated for obesity), Ozempic (indicated for diabetes) and semaglutide (the active molecule in both medicines) are seeing incredibly high YoY growth in the use of these hashtags in TikTok videos and comments. The result, we argue, is the potential for (1) knowledge of and thus (2) demand for drugs to spread exponentially rather than linearly in future. Particularly given the studies above about social media and the link between depression, anxiety and obesity, we believe those drugs catering to personal appearance are most likely to spread virally.

Given Wegovy's relatively short history in public media and consciousness, there is not enough data to track these social media patterns back further than 18 months. However, we also note a second reinforcing pattern emerging through Google Trends activity. There has been low-level search activity on Google for many years by consumers trying to find both "Drugs for weight loss" and "Diabetes drugs for weight loss". However, in the past 13 months since Wegovy first appeared in the media and created a halo effect around Ozempic and active molecule semaglutide, these terms have since permeated into social media hashtag use and finally resulted in an exponential rise in activity for consumers searching Google for details on "drugs for weight loss". This feedback loop sets up the Wegovy market to potentially have powerful exponential demand drivers in the future.

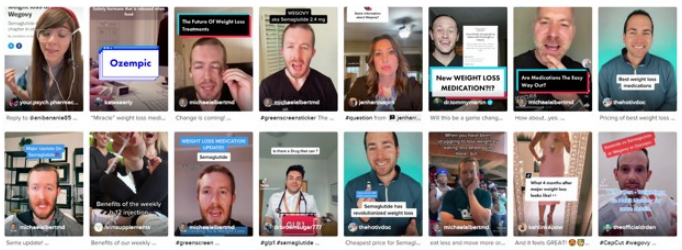
It should be said, there are clearly social risks - amongst others - associated with the knowledge and popularity of weight loss drugs spreading virally. We are not in a position to opine on those risks. We simply note that this type of behaviour has reached an inflection point and comes ahead of a material increase in the supply of Wegovy for the US market in 2H22 and the roll-out globally.

Exhibit 72: TikTok user age distribution



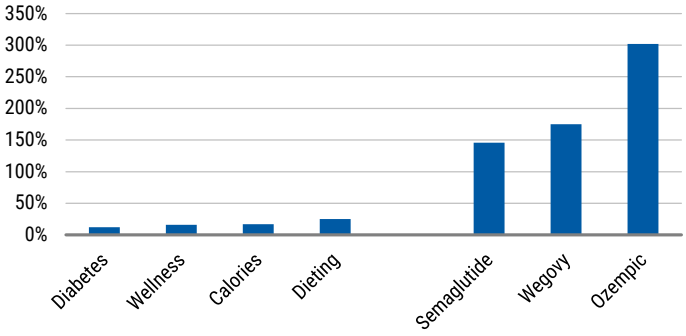
Source: App Ape, Morgan Stanley Research

Exhibit 73: TikTok uses of the hashtag: #Wegovy



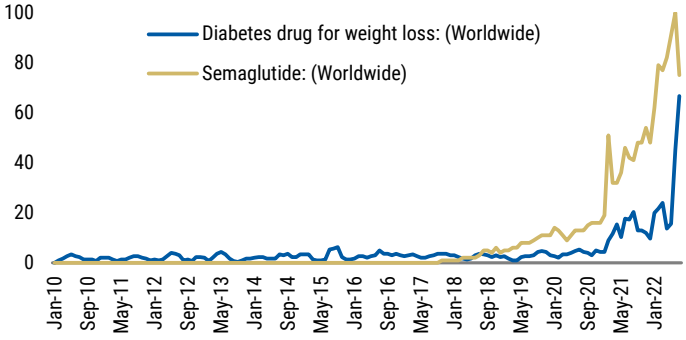
Source: TikTok

Exhibit 74: YoY growth in frequency of usage for certain health-related hashtags



Source: TikTok, Morgan Stanley Research

Exhibit 75: Google search activity globally for the terms "semaglutide" and "Drug for Weight Loss"



Source: Google Trends, Morgan Stanley Research

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INDUSTRY COVERAGE: Pharmaceuticals

COMPANY (TICKER)	RATING (AS OF)	PRICE* (07/14/2022)
James P Quigley		
Bayer AG (BAYGn.DE)	O (12/14/2018)	€54.42
Evotec SE (EVTG.DE)	O (12/06/2021)	€24.58
Evotec SE (EVO.O)	O (12/06/2021)	US$12.42
Lonza Group AG (LONN.S)	E (09/17/2021)	SFr 549.00
Merck KGaA (MRCG.DE)	E (05/17/2019)	€171.15
MorphoSys AG (MOR.O)	E (01/14/2022)	US$5.19
MorphoSys AG (MORG.DE)	E (01/14/2022)	€20.36
PolyPeptide Group AG (PPGN.S)	O (06/09/2021)	SFr 43.60
Sartorius AG (SATG_p.DE)	O (03/31/2022)	€373.90
Sartorius AG (SATG.DE)	O (03/31/2022)	€359.50
Sartorius Stedim Biotech SA (STDM.PA)	E (03/31/2022)	€332.80
Mark D Purcell		
AstraZeneca Plc (AZN.L)	O (08/09/2021)	10,776p
GlaxoSmithKline Plc (GSK.L)	++	1,680p
Novartis AG (NOVN.S)	E (01/14/2022)	SFr 81.02
Novo Nordisk A/S (NOVOb.CO)	E (04/12/2022)	DKr 808.70
Roche Holding AG (ROG.S)	E (01/08/2021)	SFr 323.70
Sanofi SA (SASY.PA)	O (09/20/2019)	€98.47
Roy D Campbell		
Aspen Holdings (APNJ.J)	E (02/22/2022)	ZAc 14,237
Sarita Kapila		
Grifols SA (GRLS.MC)	E (04/08/2022)	€15.44

Vifor Pharma AG (VIFN.S)	E (12/13/2021)	SFr 178.10
Thibault Boutherin		
Almirall (ALM.MC)	O (09/08/2021)	€10.89
Hikma Pharmaceuticals Plc (HIK.L)	E (03/03/2022)	1,664p
Idorsia Ltd (IDIA.S)	E (07/27/2020)	SFr 12.21
Indivior Plc (INDV.L)	E (03/25/2022)	298p
Ipsen SA (IPN.PA)	U (11/05/2021)	€92.25
UCB S.A. (UCB.BR)	E (05/19/2022)	€81.74

Stock Ratings are subject to change. Please see latest research for each company.
* Historical prices are not split adjusted.

INDUSTRY COVERAGE: Major Pharmaceuticals

COMPANY (TICKER)	RATING (AS OF)	PRICE* (07/13/2022)
Terence C Flynn, Ph.D.		
Abbvie Inc. (ABBV.N)	O (05/11/2020)	US$152.15
Arvinas Inc (ARVN.O)	E (04/06/2022)	US$49.23
Bristol Myers Squibb Co (BMY.N)	U (04/06/2022)	US$74.53
Eli Lilly & Co. (LLY.N)	O (09/03/2020)	US$322.46
Johnson & Johnson (JNJ.N)	E (09/07/2021)	US$175.44
Merck & Co., Inc. (MRK.N)	E (09/07/2021)	US$93.77
Organon & Co. (OGN.N)	E (06/11/2021)	US$32.28
Pfizer Inc (PFE.N)	E (07/30/2019)	US$51.79
Royalty Pharma Plc (RPRX.O)	O (04/06/2022)	US$42.39

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Morgan Stanley

The Americas
1585 Broadway
New York, NY 10036-8293
United States
Tel: +1 (1) 212 761 4000

Europe
20 Bank Street, Canary Wharf
London E14 4AD
United Kingdom
Tel: +44 (0) 20 7 425 8000

Japan
1-9-7 Otemachi, Chiyoda-ku
Tokyo 100-8104
Japan
Tel: +81 (0) 3 6836 5000

Asia/Pacific
1 Austin Road West
Kowloon
Hong Kong
Tel: +852 2848 5200