

GLP-1: Winners and Losers

April 2024

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**RISE OF GLP-1
RECEPTOR
AGONISTS FOR
OBESITY**

02

**BEYOND
OBESITY**

03

**WINNING AND
LOSING**

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Obesity prevalence is high and rising, affects >1 billion people globally and directly costs the U.S. ~\$173 B each year



1B+

Obese People
Worldwide



50%

U.S. Population
Obese by 2030



9%

U.S. GDP
Total Cost of Chronic
Diseases due to Obesity



\$173 B

Direct U.S. Annual Costs
in Prevention, Diagnosis
and Treatment of Obesity

RISK FACTOR
for Many Chronic Diseases



Worse Health
Outcomes






Reduced
Quality of Life



Premature
Death



Current treatments for obesity are based primarily on lifestyle interventions and, where appropriate, bariatric surgery

1	 72 M Making Lifestyle Changes	<ul style="list-style-type: none">• Behavioral change (i.e., diet, exercise) always encouraged• Variable efficacy and durability
2	 >3.2 M Taking Anti-obesity Medications	<ul style="list-style-type: none">• Low prescription rate, despite >50% patients eligible, given lack of insurance coverage• GLP-1RAs preferred 1L given efficacy (15 – 20% weight loss)
3	 250 K Undergone Bariatric Surgery	<ul style="list-style-type: none">• Not scalable; reserved for severely obese• Efficacious and durable (≥30% sustained for 5 years)¹



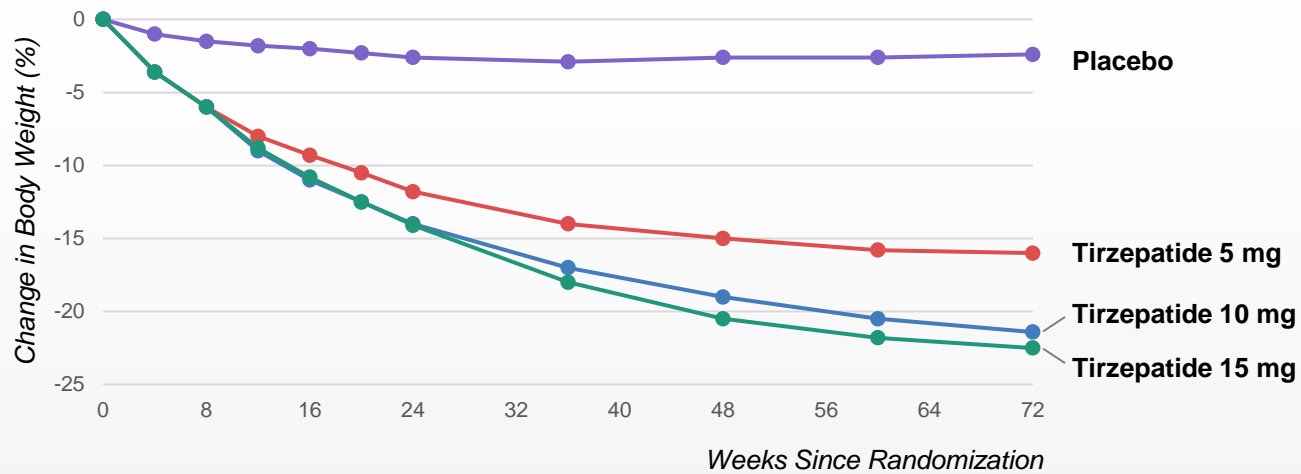
TREATMENT RATE

- ▶ 176 M obese people in the U.S.
- ▶ 94% not actively managed
- ▶ Poor insurance coverage (e.g., Medicare does not cover Wegovy)
- ▶ Potential for increased insurance coverage, given increasing willingness to view obesity as a disease with high likelihood Medicaid removing restrictions on weight loss drugs

GLP-1 receptor agonists are changing the game; weight loss and improvement in co-morbidities achievable for obese patients without T2DM

GLP-1 RECEPTOR AGONISTS EFFECT ON CO-MORBIDITIES

Effect of Once Weekly Tirzepatide on Body Weight



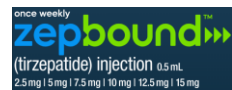
GLP-1 RECEPTOR AGONISTS EFFECT ON CO-MORBIDITIES

19% Decrease in cardiovascular events (death, myocardial infarction, or stroke)

13% Decrease in risk of stroke in obese patients

25% Improvement in preventing worsening of fibrosis in metabolic (dysfunction)-associated fatty liver disease

50% Reduction in apnea-hypopnea index in moderate or severe obstructive sleep apnea



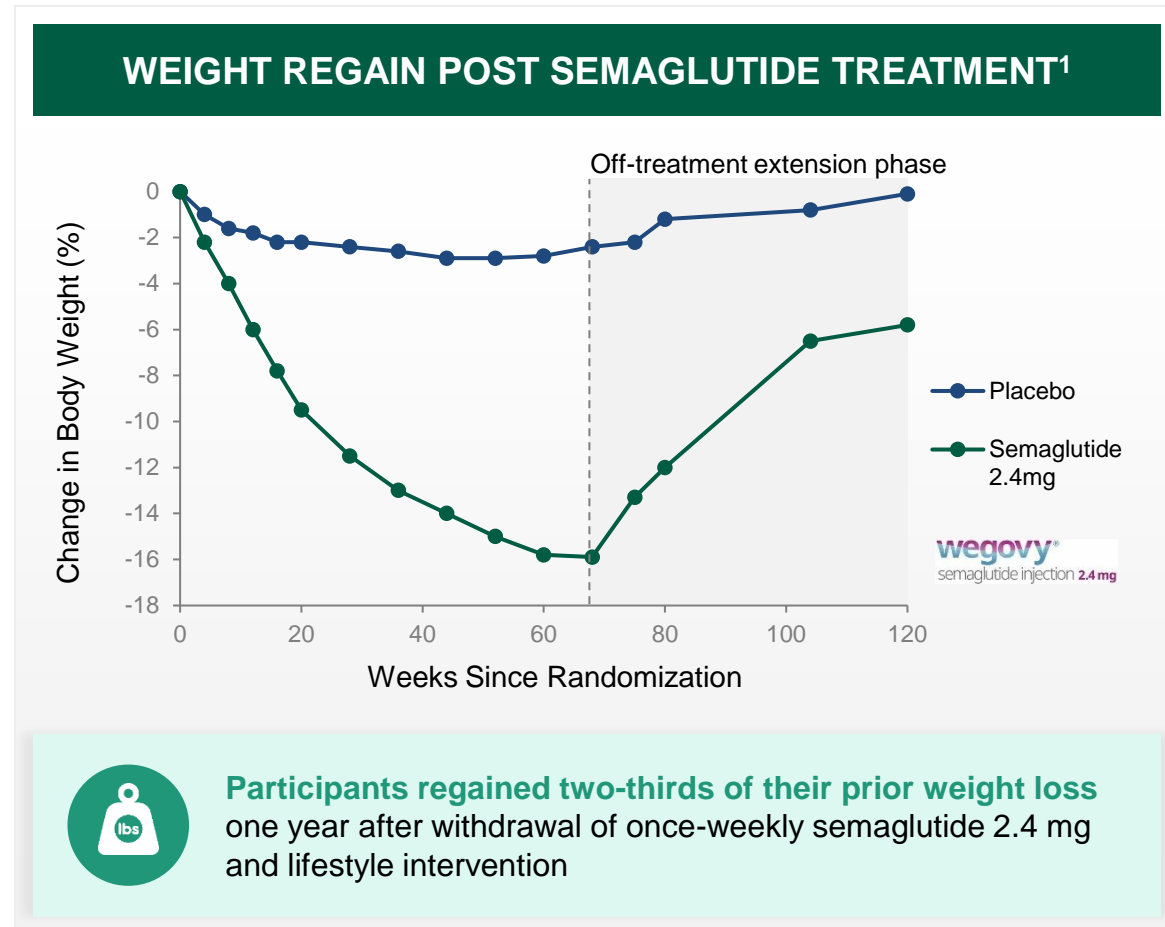
Tirzepatide, showed a **19% decrease in body weight** over 72 weeks



Semaglutide showed a **12.4% decrease in body weight** over 68 weeks

Current GLP-1 based AOM have several issues including muscle loss, increased cancer risk, gastrointestinal issues, and significant weight regain

Issues with current anti-obesity medication



MUSCLE LOSS



- AOM may result in **significant muscle loss** and put patients at risk of sarcopenic obesity
- Especially **high risk in patients rebounding** after stopping AOM

CANCER RISK



- GLP-1 agonists have been shown to **increase the risk of thyroid cancer** by over 50%
- However, decreasing obesity may have a **protective effect against other cancers**

GASTROINTESTINAL ISSUES

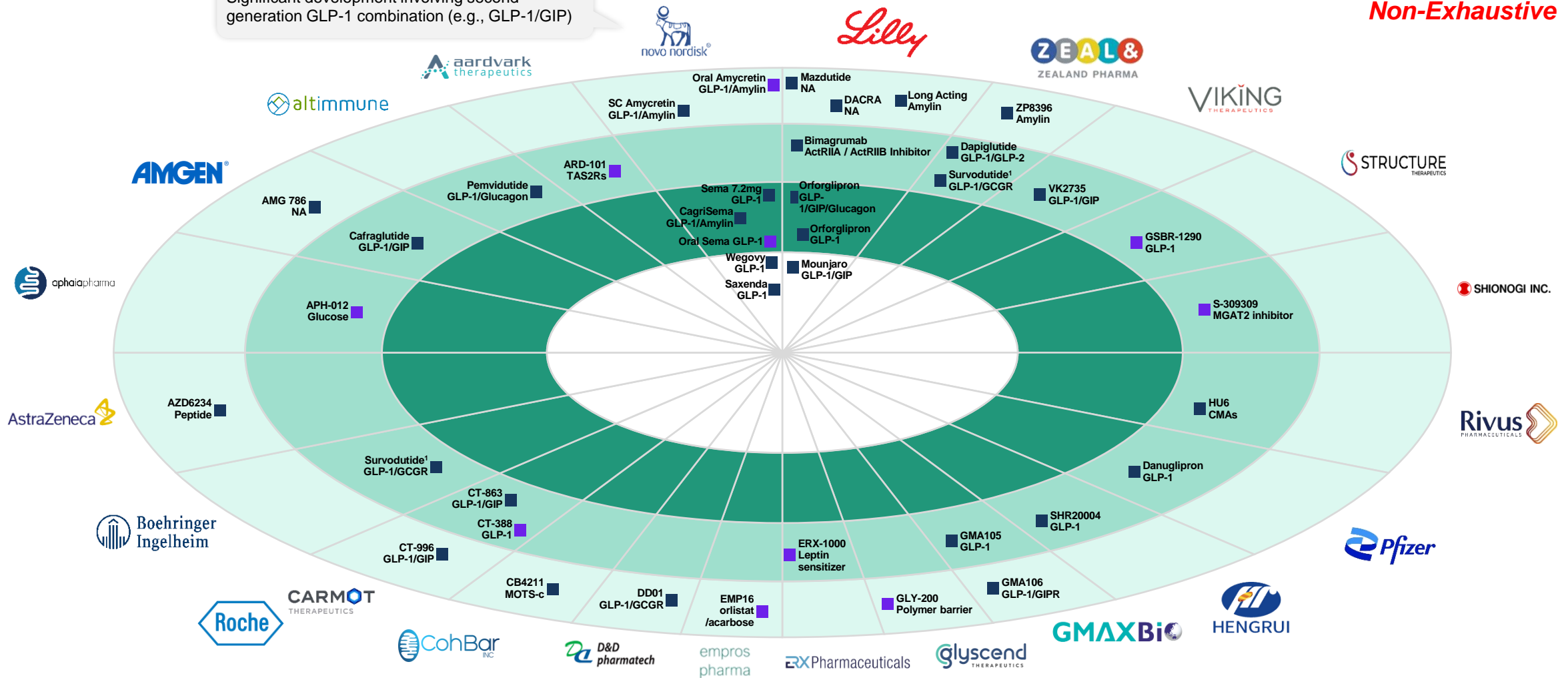


- Frequent side effects of GLP-1RAs include nausea, abdominal pain and diarrhoea
- **More serious side effects e.g., intestinal obstruction and gallstones** may require surgery

Only Novo Nordisk and Lilly have assets in P3 development; cementing their position as market leaders for anti-obesity medication

Significant development involving second generation GLP-1 combination (e.g., GLP-1/GIP)

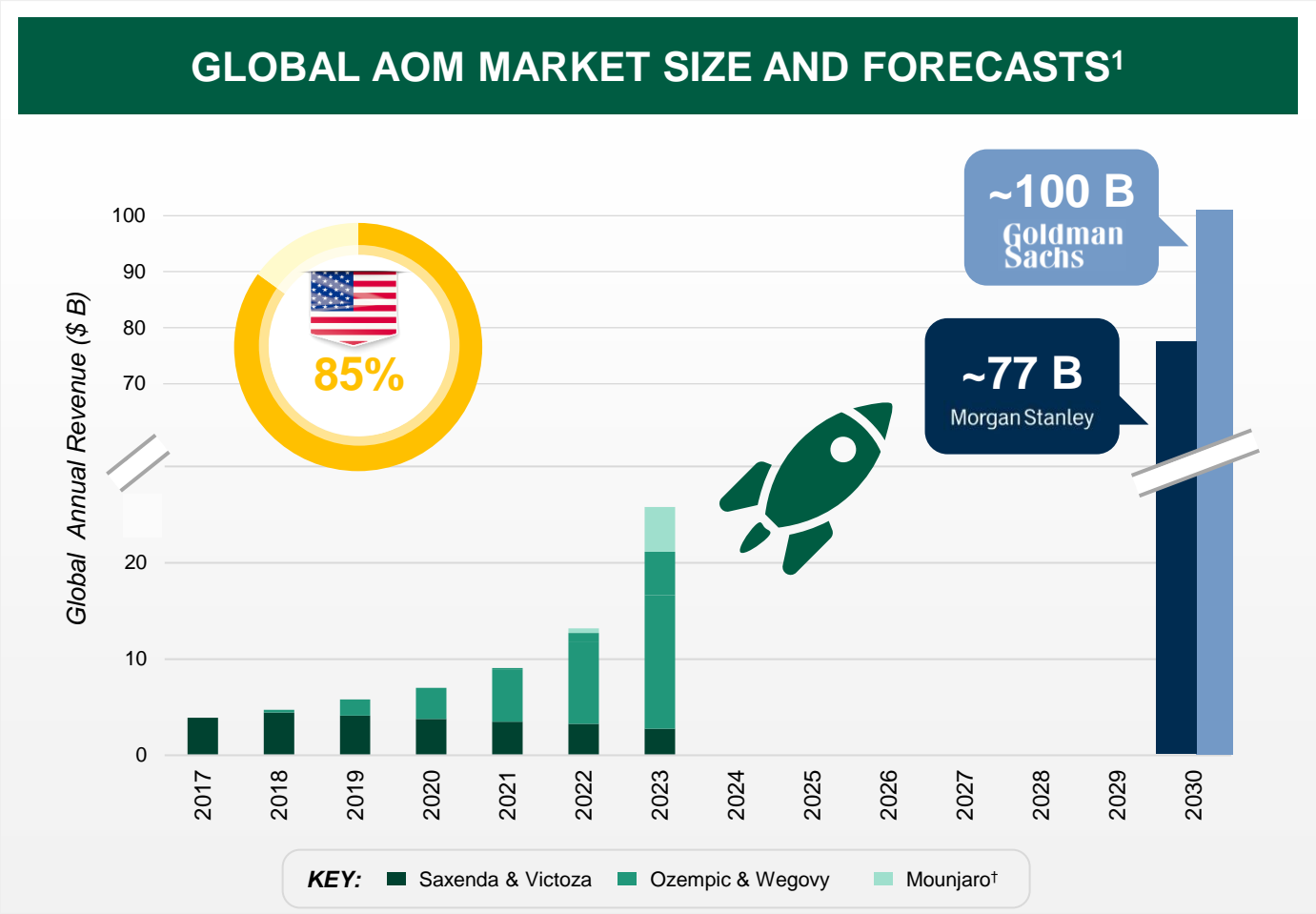
Non-Exhaustive



¹ Survodutide developed in partnership with Boehringer Ingelheim and Zealand Pharma. AOM: Anti-Obesity Medication. Source: Company Websites; Clearview Analysis

Key: ■ Subcutaneous ■ Oral ■ P1 ■ P2 ■ P3 □ Approved

Global anti-obesity medication market generated ~\$2.4 B in 2022, it is forecast to grow to up to ~\$100 B in 2030



GROWTH DRIVERS

- Addressable patient population:**
 Over half of the global population will be overweight or obese by 2035
- Improved rate of insurance reimbursement:**
 Medicare coverage for the treatment of obesity continues to make progress
- Duration of use among patients:**
 STEP 1 extension trial showed patients regained most of the weight they lost after stopping Wegovy
- Drug pricing:**
 AOM expected to cost ~\$5.5 K/year per patient in 2030²

† 2023 sales based on YTD forecast
¹ Represents revenue that is publicly available or available via analyst reports and may not include revenue from generics. ² Based on Goldman Sachs assumptions. AOM: Anti-Obesity Medication. Source: Evaluate Pharma; Goldman Sachs; Morgan Stanley; ClearView Analysis.

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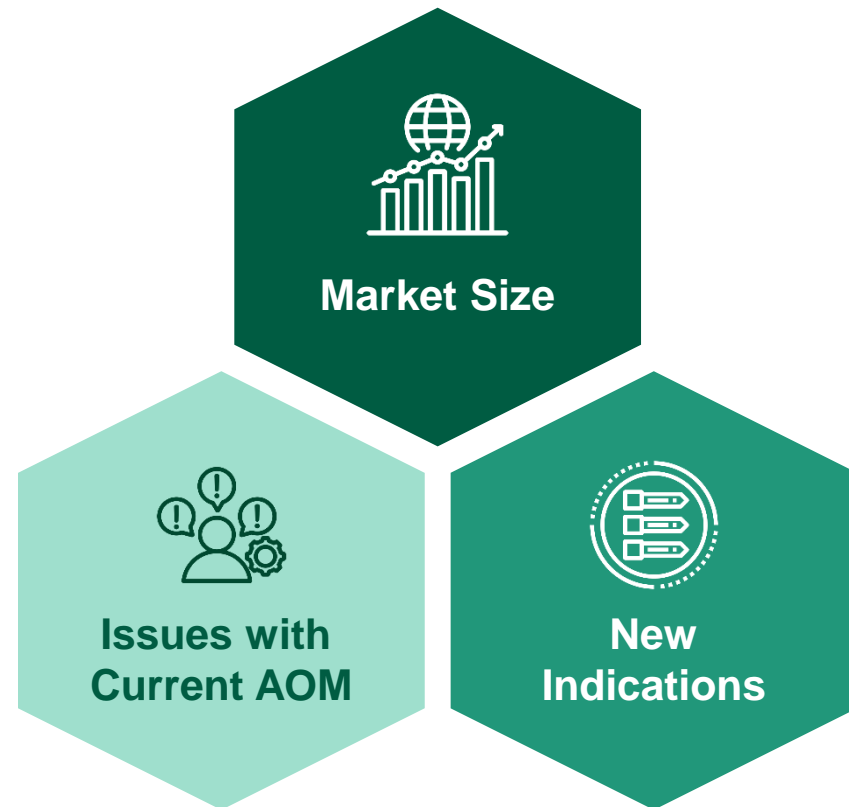
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Significant pipeline development AOMs is driven by the growth potential of the AOM market, new indication and current AOM side effects

Factors driving pipeline development



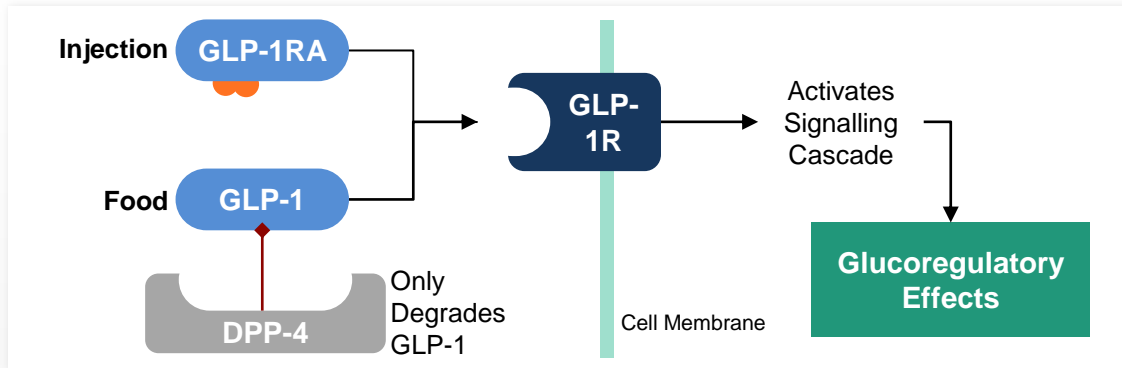
- The anti-obesity market is forecast to reach up to **\$100 B in 2030**; driven by a large addressable patient population, duration of use, pricing, and improved reimbursement

- GLP-1s and other AOM have the potential to expand **into several large indications with high unmet need**
- For example, Alzheimer's disease, cardiovascular disease, obstructive sleep apnea, and addiction

- Many next generation products are targeting **oral routes of administration to negate the need for subcutaneous injection**
- **New modalities** being pursued due to **ongoing manufacturing challenges**
- May have greater tolerability, efficacy and durability

GLP-1 receptor agonists work by activating receptors found in the pancreas and the brain triggering a variety of glucoregulatory effects

GLP-1 RECEPTOR AGONISTS MOA



- ▶ **GLP-1** is a gluco-regulatory hormone primarily produced in the small intestine (to a lesser degree in the brain) in response to food consumption
- ▶ **GLP-1** receptor agonists work by mimicking the GLP-1 hormone, binding to and activating GLP-1 receptors in cells to trigger a variety of glucoregulatory effects
- ▶ **GLP1** is degraded by DPP-4; GLP-1R agonists resist breakdown by DPP4, prolonging half-life

EFFECTS OF GLP-1 RECEPTOR AGONISTS

STOMACH

- ↓ Gastric emptying
- ↓ Acid secretion



BRAIN

- ↓ Food intake
- ↓ Water intake
- ↑ Neuroprotection
- ↑ Neurogenesis



SKELETAL MUSCLE

- ↑ Perfusion
- ↑ Glucose uptake



PANCREAS

- ↑ Insulin secretion
- ↑ Somatostatin secretion
- ↑ β-cell proliferation
- ↓ Glucagon secretion
- ↓ β-cell apoptosis



KIDNEY

- Diuresis
- Natriuresis



INTESTINES

- ↑ Growth
- ↑ Motility
- ↓ Lipoprotein secretion



IMMUNE SYSTEM

- ↓ Inflammation



LIVER

- ↓ Glucose production
- ↓ VLDL (ApoB100)
- ↓ Steatosis



HEART AND VESSELS

- ↑ Glucose utilization
- ↑ Cardio protection
- ↑ Cardiac output
- ↑ Vasodilation
- ↓ Fatty acid metabolism



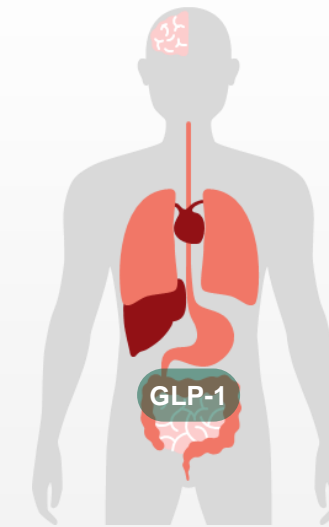
WHITE ADIPOSE

- ↑ Perfusion
- ↑ Glucose uptake
- ↑ Lipolysis



















BROWN ADIPOSE

- ↑ Thermogenesis



GLP-1RAs may influence indications such as cardiovascular disease that may lead to significant cost savings for healthcare systems

	U.S. Patient Population (~110 M obese patients)	Development Timeline	Unmet Need	Key Points	Overall Potential Impact of GLP-1RAs
Obstructive Sleep Apnea 	~30 M (~6 M dx)	Tirzepatide P3 PCD: Mar '24	Unmet need around diagnosis	Low dx rates limits GLP-1 opportunity	
Alzheimer's Disease 	~6 M	Semaglutide P3 PCD: Sept '25	No meaningfully effective tx	GLP-1RA benefits in non-metabolic pts unclear	
Cardiovascular Disease 	~36 M	CagriSema P3 PCD: Sep '27	¼ Americans die of heart disease	CVD to cost U.S. ~\$1 trillion by 2035	
Non-alcoholic Fatty Liver Disease 	~80 M	Semaglutide P3 PCD: Apr '28	Limited approved treatment options	High burden due to transplant demand	
Polycystic Ovary Syndrome 	~5M	No Clinical Trials Off-label use	Limited approved treatment options	GLP-1RA benefits in non-metabolic pts unclear	
Depression 	~21 M	No Clinical Trials Off-label use	More options for TRD needed	GLP-1RAs may prevent antipsychotic weight gain	
Off-label/Cosmetic Use 	~36 M	Liraglutide Binge Eating P3 '22	Limited pharma treatment options	GLP-1RAs may suppress addictive substance use	
Reward System Disorders 	~150 M1	Significant off-label cosmetic use	Few lasting weight loss tx	GLP-1s may enter >200 B weight mgmt. market	

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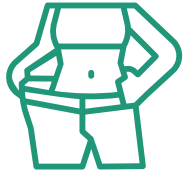
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Market trends due to GLP-1 success are likely dependent on the long-term effects on obesity trends in the general population



SCENARIO 1 GLP-1s Cause Lasting Weight Loss

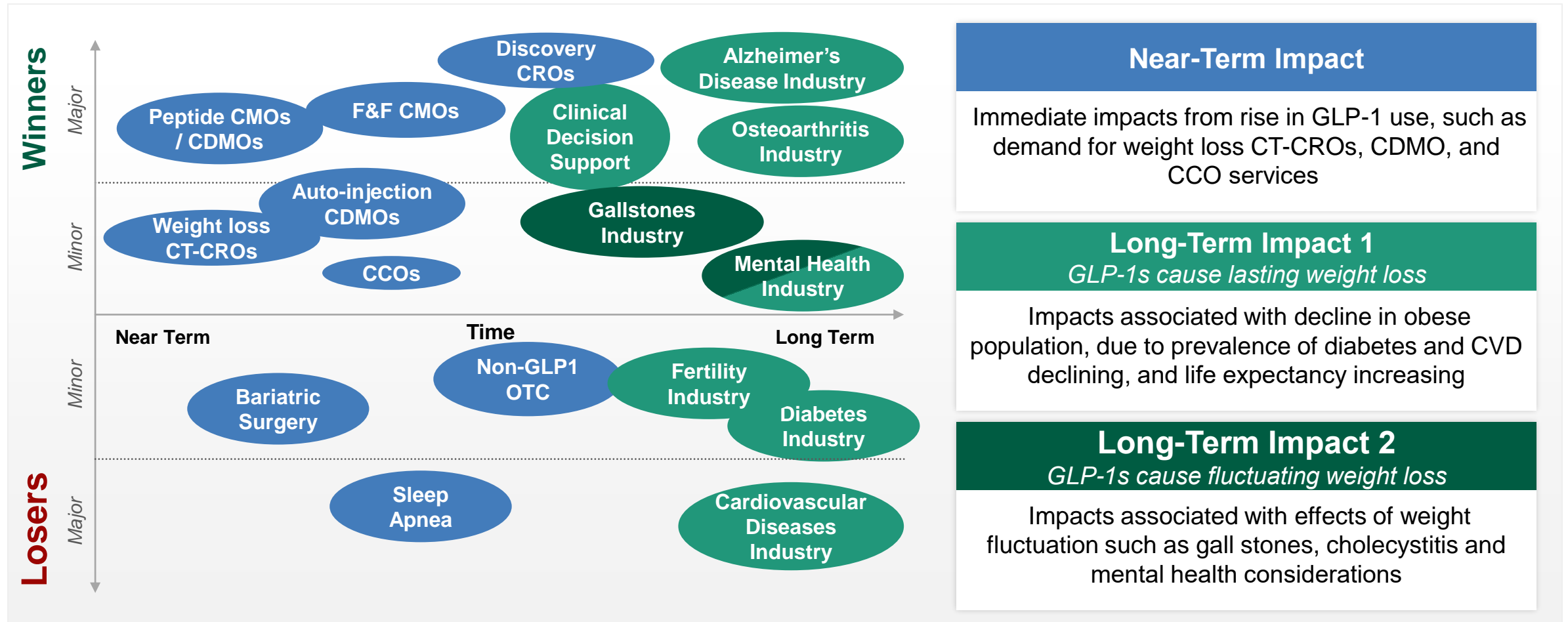
Markets may be impacted by long term weight loss of obese population shifting dynamics in other indications



SCENARIO 2 GLP-1s Leads to Fluctuating Weight

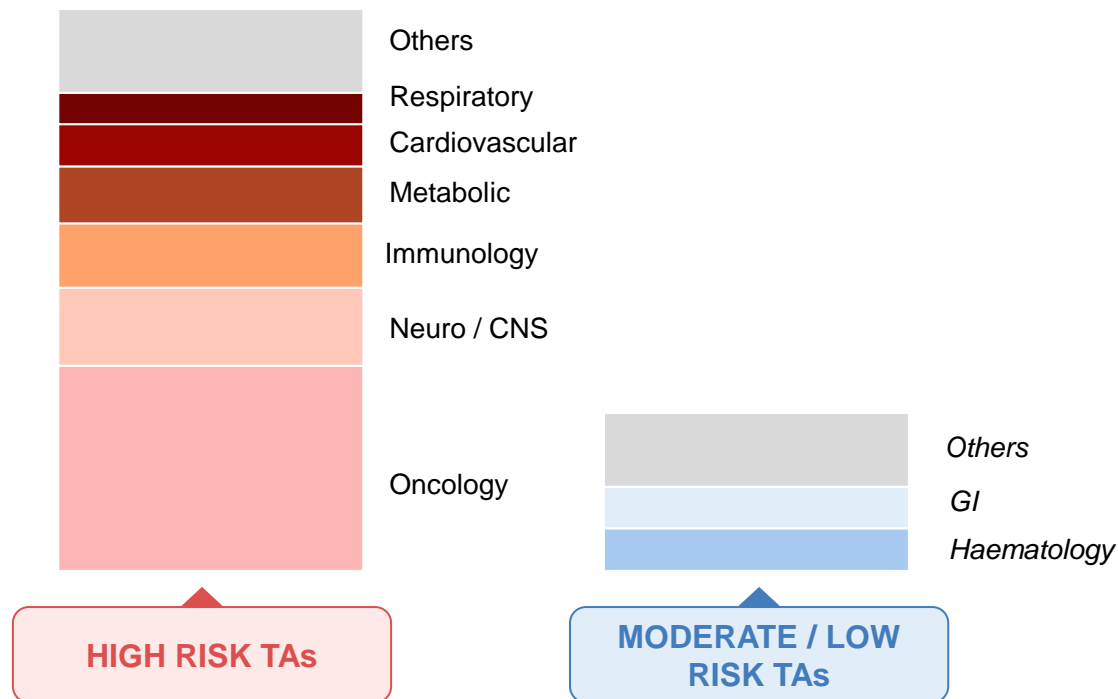
Fluctuating weight caused by inconsistent use of GLP-1s likely to shift market trends based on side-effects and lack of long-term weight loss

Service providers and multiple therapy areas will be impacted by GLP-1 success but nuances exist depending on long term weight loss effects



Should GLP-1s cause long term weight loss, ~66% of Top 25 Pharma pipeline assets associated with obesity are at risk of shrinking opportunities

NUMBER OF PIPELINE (PC – P3) ASSETS



HIGH RISK – Causal link with obesity

- Obesity directly or indirectly linked to ~2/3 of 'Top 25 Pharma' pipeline therapy areas
 - Oncology, neurology and immunology ~1/3 of assets
 - Obesity crucial to asset value proposition
- Size of opportunities shrinking if obesity rates decrease

MODERATE / LOW RISK – Correlation with obesity

- ~1/3 Top 25 Pharma pipeline assets in TAs where:
 - Mix of diseases that do and do not have association with obesity (e.g., UC and NASH)
 - Diseases have moderate link / association with obesity (e.g., atopic dermatitis)
 - No known link with obesity / conflicting evidence (e.g., infectious diseases)

While the impact that anti-obesity medicines will is becoming clearer, there are multiple open questions about how the market will evolve

Key remaining questions and uncertainties

NON-EXHAUSTIVE



CLINICAL DATA EVOLUTION

Outcomes data?

Safety data?

Real-world impact?

Economic value?



MARKET DYNAMICS

Reimbursement types?

Reimbursement duration?

Out-of-pocket demand?

Commercial models?



MANUFACTURING /SUPPLY

Supply chain for current products?

Supply chain for new modalities?

New supply chain models?



BEYOND OBESITY

Evidence outside of obesity?

Magnitude of impact?

Indication expansion and pricing?

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