



Society of Actuaries in Ireland

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# Prospects for Obesity Medicines

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6 November 2024

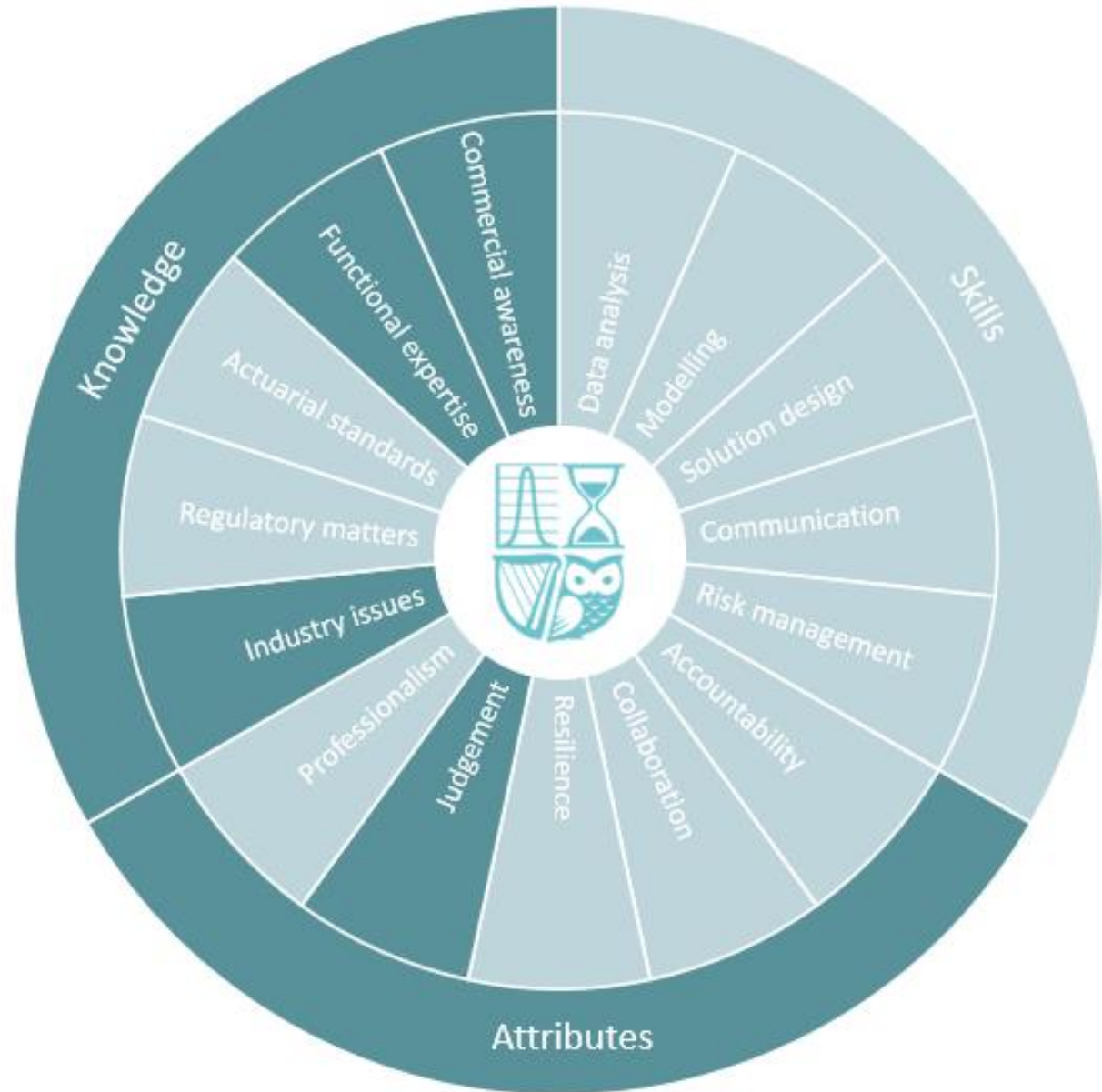
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# Disclaimer

*The views expressed in this presentation are my own and not necessarily those of the Society of Actuaries in Ireland. For the avoidance of doubt, I have no employer or clients. While I am an experienced biotech investor, I have no medical qualifications. I have held investment positions in biotech companies referenced in this presentation (and may do so again after 6 November 2024).*

# Competency Framework Wheel



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# Agenda

- Development of new obesity medicines
- Superb efficacy & commercial success
- Only minor public health impact
- Prospects for further obesity medicines

# Major & Complicated Public Health Burden

## Obesity Rates (BMI > 30)

Country	Obesity Rate (c.2020)
USA	43%
Mexico	36%
Australia	30%
UK	28%
Canada	24%
Ireland	23%
France	16%
South Korea	7%
Japan	5%

## Mortality Impact (Baseline Age 46)<sup>1</sup>

BMI Range	Probability Surviving to Age 70
22.5 – 25.0 (Normal)	c.80%
35.0 – 40.0	c.60%
40.0 – 50.0	c.50%

<sup>1</sup> Prospective Studies Collaboration, Whitlock G, Lewington S, et al. Body-mass index and cause-specific mortality in 900,000 adults: collaborative analyses of 57 prospective studies. Lancet. 2009

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# Pharma Industry Previously Avoided Obesity

- USA Scandal = Fen-Phen
  - Combo of 2 known obesity medicines launched in early 90's
  - Effective & captured public attention
  - Withdrawn 1997 = heart-valve damage
  - Manufacturer (Wyeth) paid \$22+ billion in lawsuits
- EU Scandal = Acomplia
  - Approved 2006
  - Decent efficacy by influencing brain activity
  - Withdrawn 2008 = psychiatric side effects (inc. suicidality)
  - No US approval due to side effect concerns

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# Diabetes a Parallel Public Health Burden

- c.6% of Irish population has Type 2 Diabetes (T2D)
- Huge & growing market requiring more effective medicines
- Key goal to improve on natural insulin
  - Has a short half-life when injected
  - Over dosing problematic/dangerous
  - Causes weight gain (exacerbates T2D)

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# Glucagon Like Peptide-1 (GLP-1)

- Hormone produced mainly in the gut
- Discovered in 1986-87 & not yet fully understood
- Multiple GLP-1 properties relevant to T2D
  - Significantly ups insulin production
  - Inhibits glucagon hormone (which ups blood sugar levels)
  - Inhibits appetite
  - Slows down food digestion
  - Body relatively tolerant to over-dosing



# GLP-1 Innovation for T2D

Launch Year	Medicine Name	Medicine Brand	Manufacturer	Dosing (Injections)	Standalone Efficacy (HbA1c%)	Peak Sales
2005	Exenatide	Byetta	AstraZeneca	2 * daily	-0.9% (6 months)	\$0.9bn
2010	Liraglutide	Victoza	Novo Nordisk	1 * daily	-1.1% (12 months)	\$3.9bn
2014	Dulaglutide	Trulicity	Eli Lilly	1 * weekly	-0.8% (6 months)	\$7.4bn
2017	Semaglutide	Ozempic	Novo Nordisk	1 * weekly	-1.6% (7 months)	\$16.7bn (so far)
2022	Tirzepatide	Mounjaro	Eli Lilly	1 * weekly	-1.7% (9 months)	\$12.4bn (so far)

- Byetta sales limited by side effects!
- Advances in genetic engineering
  - Longer half-life (i.e. less injections)
  - Improved potency



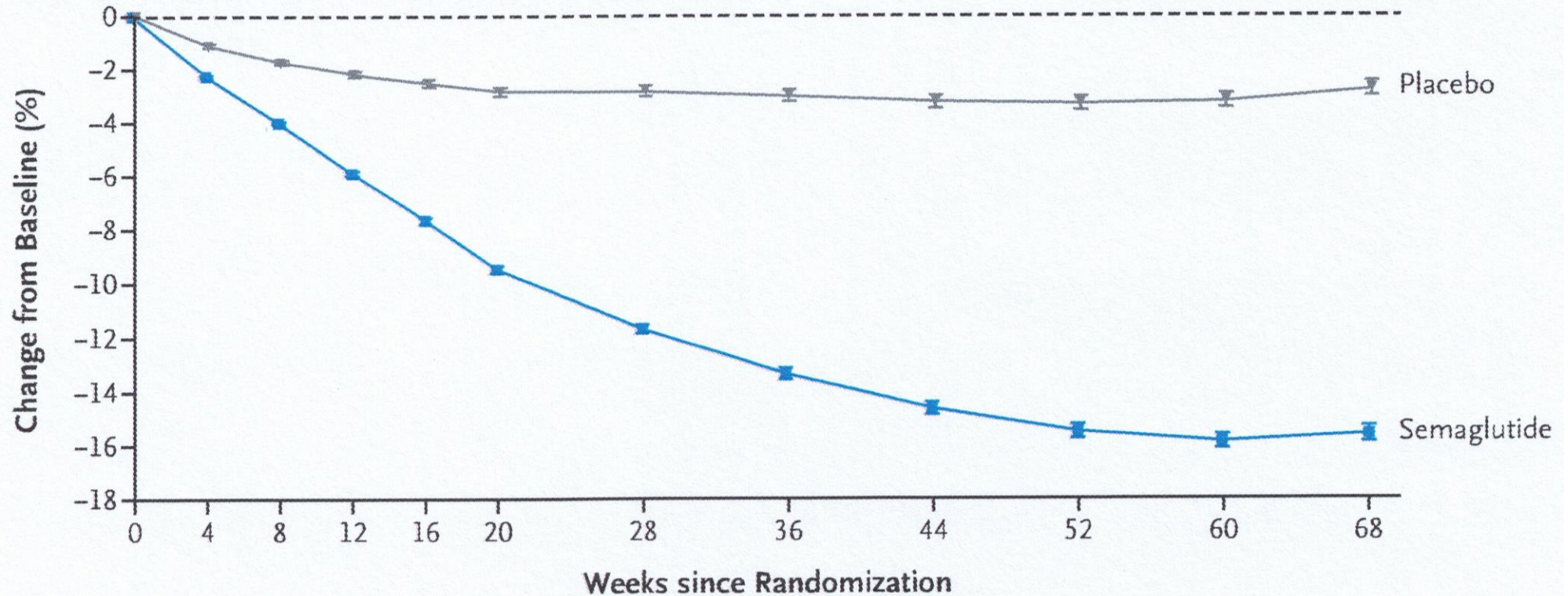
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# Liraglutide = 1st GLP-1 Obesity Medicine

- Novo Nordisk realised could repurpose Liraglutide
  - GLP-1 inhibits appetite & slows down digestion
  - Body tolerates higher GLP-1 dosing = more efficacy
- Novo Nordisk developed Saxenda
  - Dose upped to 3mg (Victoza=1.8mg)
  - 7.4% weight loss at 56 weeks (4.5% placebo adjusted)
- Reasonable commercial success
  - Launched 2015
  - Peak sales \$1.5bn in 2022

# Semaglutide = 2<sup>nd</sup> GLP-1 Obesity Medicine

Body Weight Change from Baseline by Week, Observed In-Trial Data



Example : 5 ft 4 woman weighing 14 st 9 lb (i.e. BMI=35) => expected 2 st 3 lb loss after c.1 year

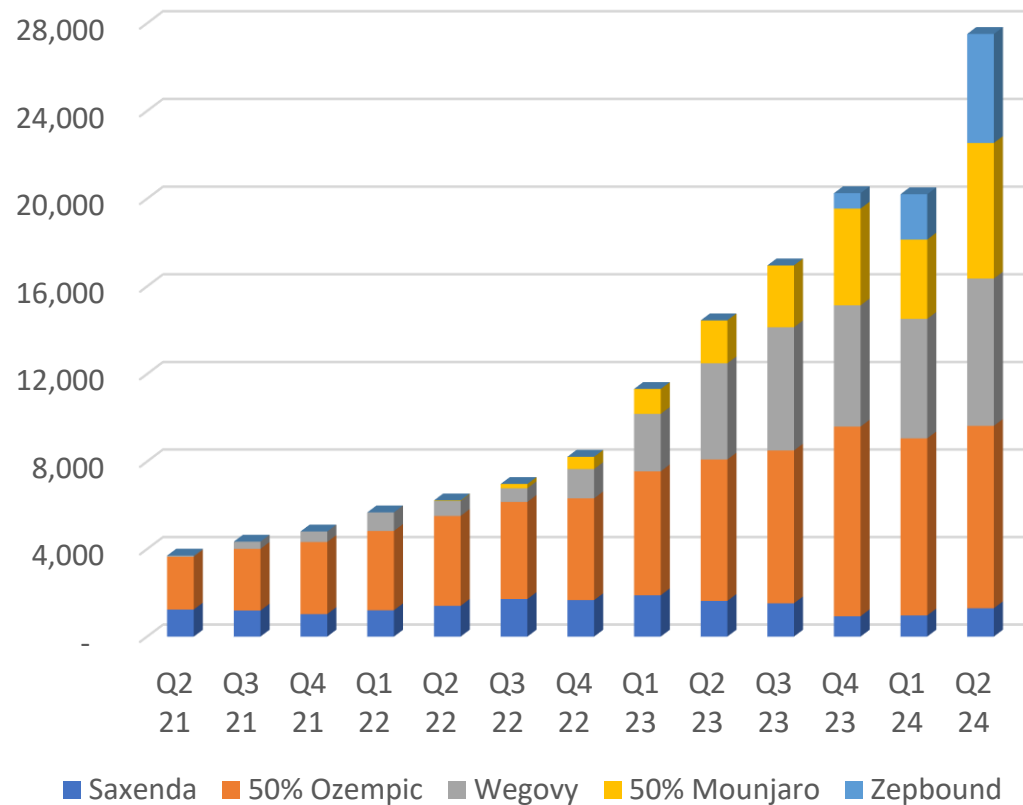
# Tirzepatide = 3<sup>rd</sup> GLP-1 Obesity Medicine

Medicine Name	Medicine Brand	Injection Dose	Medicine & Lifestyle (Weight%)	Lifestyle Only (Weight%)	Year Launched
Semaglutide	Wegovy	2.4mg	-14.9% (68 weeks)	-2.4% (68 weeks)	2021
Tirzepatide	Zepbound	5.0mg	-15.0% (72 weeks)	-3.1% (72 weeks)	2023
Tirzepatide	Zepbound	10.0mg	-19.5% (72 weeks)	-3.1% (72 weeks)	2023
Tirzepatide	Zepbound	15.0mg	-20.9% (72 weeks)	-3.1% (72 weeks)	2023

- Parallel lifestyle changes for full benefit
- Zepbound better?
  - Higher doses improve efficacy
  - Zepbound (15.0mg dose) = 3<sup>rd</sup> 1 lb weight loss in prior example
  - Tirzepatide also affects a 2<sup>nd</sup> weight-altering hormone (GIP)

# Blistering Sales Ramp-Up

Illustrative Annualised Quarterly  
WW Obesity Sales (\$m)



- Manufacturing constraints
- Assumes 50% Ozempic & Mounjaro sales diverted to obesity
- Analysts projecting \$130bn+ peak sales (all indications)

# Markets Validating Future Growth

Europe – Top 10 Listed	Cap. (€bn)
<b>Novo Nordisk</b>	<b>458</b>
LVMH	309
SAP	258
ASML	253
Roche	235
Nestle	227
Hermes	221
AstraZeneca	211
Novartis	203
Linde	203

US – Top 10 Listed	Cap. (€bn)
Apple	3,118
NVIDIA	3,074
Microsoft	2,838
Alphabet (ex Google)	1,950
Amazon	1,922
Meta (ex Facebook)	1.333
Berkshire Hathaway	899
Broadcom	733
Tesla	732
<b>Eli Lilly</b>	<b>724</b>

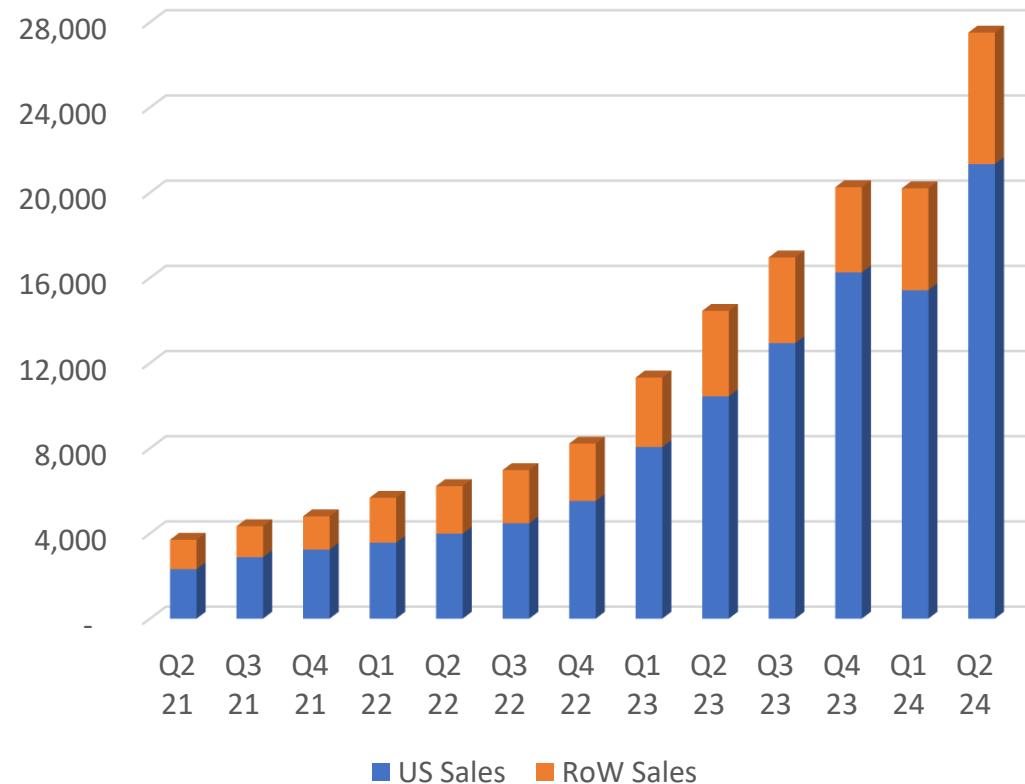
# Mission Accomplished?

Time Period	US Population Obesity Survey (Age 20+)	Absolute Change
2013 – 2014	37.7%	
2015 – 2016	39.6%	+1.9%
2017 - 2020	41.9%	+2.3%
2021 - 2023	40.3%	-1.7%

- First clear reversal in upwards trend originating from early 1970's!
- Perhaps 3.5%-4.0% net reduction (adjusting for trend)

# US Dominating Sales - But Mediocre ROI?

Illustrative Annualised Quarterly  
US & RoW Obesity Sales (\$m)



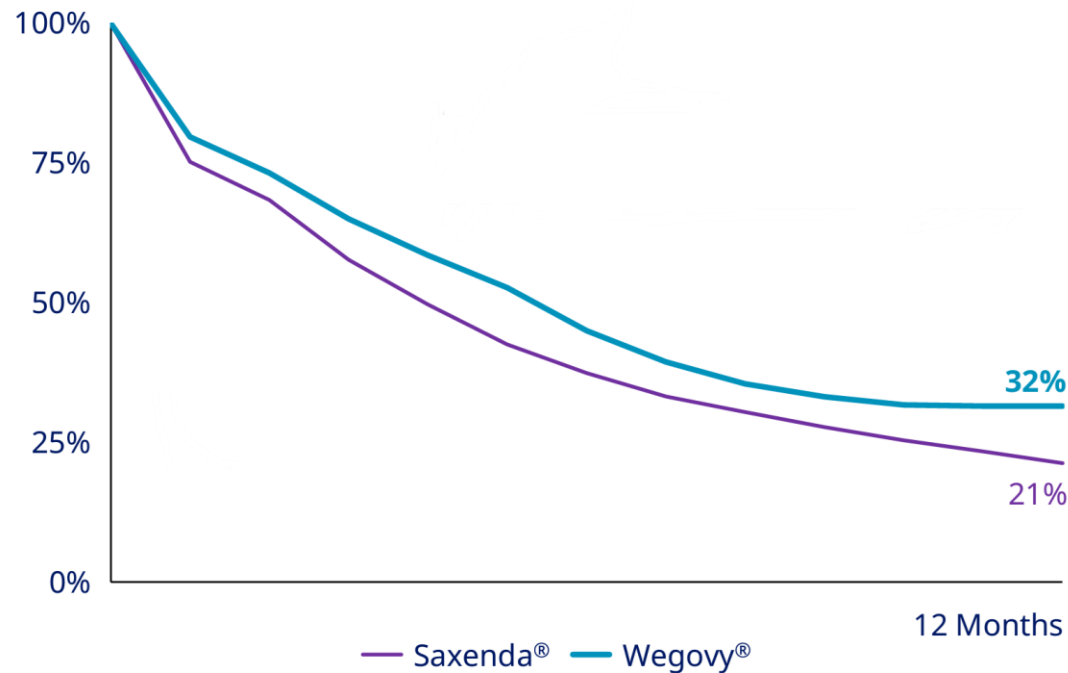
- Higher US price points
- US prioritised (constrained supply)
- Yearly US sales c.\$6.5bn average during '21-'23 obesity survey



# So, What's The Problem? ... Lapse Rates!

## Novo Nordisk Q2 24 Investor Presentation (7 August 2024)

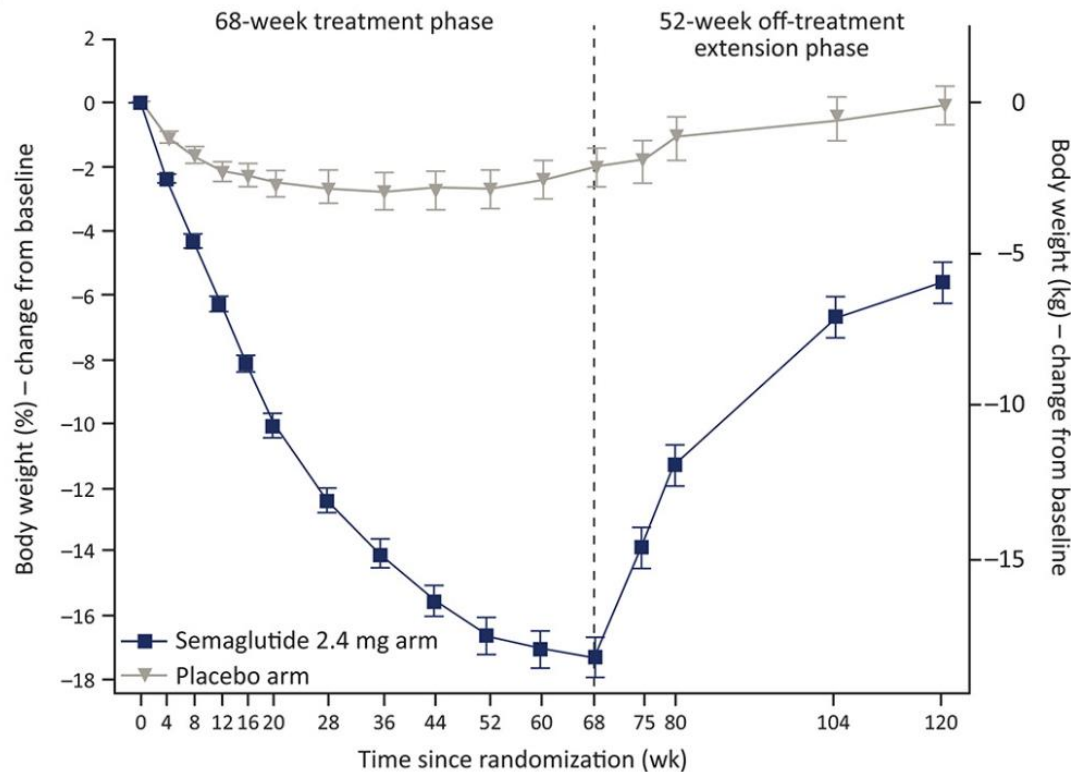
Patients remaining on treatment (%)



## Prime Therapeutics/Magellan Rx Abstract (10 July 2024)

*“Conclusions: At the end of two years, GLP-1 obesity treatment persistency and adherence were poor with only 1 in 7 members remaining on therapy...”*

# GLP-1 Withdrawal = Weight Regained



- Nominal c.6% retained weight loss after withdrawal
- BUT...
  - Not yet at plateau after (arbitrary) 52 weeks?
  - Trial volunteers unrepresentative
- 0%-5% long-term retained weight loss plausible for general population

# Lapse Issue #1 - GLP-1 Side Effects

Side Effect from Wegovy Pivotal Trial	Wegovy Patients – Annualised Event Rate	Placebo Patients – Annualised Event Rate	Wegovy Patients – Event Rate (Moderate/Severe)
Nausea	63%	18%	c.15%
Diarrhoea	45%	17%	c.15%
Vomiting	37%	6%	c.15%
Constipation	23%	9%	c.5%
Headache	23%	13%	N/A
Combined GI Disorders	253%	89%	N/A

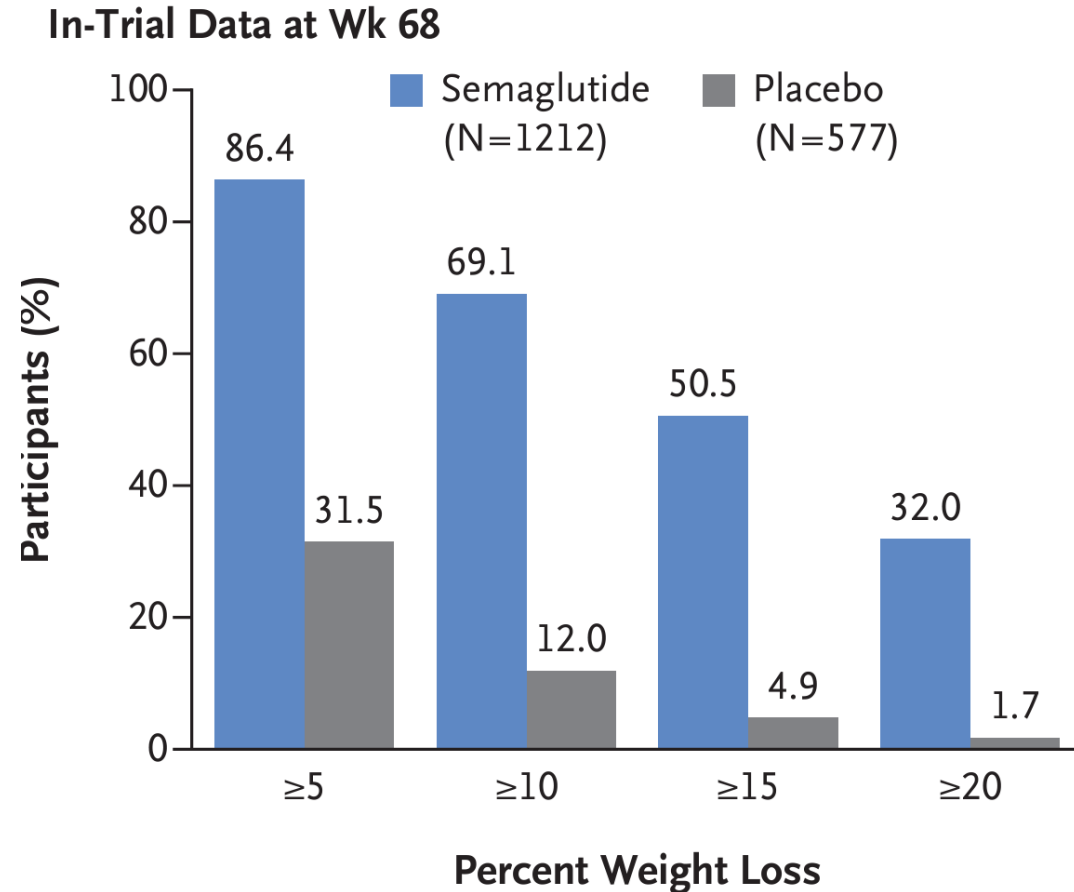
- GI Disorder side effects are features – not bugs – of GLP-1 class
  - Mechanisms used by GLP-1 to enforce appetite inhibition
  - Exacerbated by permanent super-normal dosing
- Significant lapses an inevitable outcome

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# Lapse Issue #2 - Cost

- Currently patented medicines
  - Novo Nordisk : c.80% sales are out-of-pocket
  - High Direct Cost : Wegovy (US) = \$16.2k yearly list price
  - High Indirect Restrictions : Wegovy (UK NHS) = 1\*Obesity Co-Morbidity & BMI>35
- Patent expirations key to start lowering costs
  - Semaglutide (inc. Wegovy) = Likely 2032
  - Tirzepatide (inc. Zepbound) = Possibly 2039

# Lapse Issue #3 - GLP-1 Can Be Ineffective



- 5% weight loss is floor for clinical meaningfulness
- Many more than 13.6% patients below 5% floor earlier in trial
- Lapses exacerbated for patients with parallel side effect/cost concerns

# Hypertension – System of Medicine Example

Medicine Class	Example Medicine	Oral Pill?	Dosing	Year Launched
Diuretic	Hydrochlorothiazide	Yes	1 * Daily	1959
ACE Inhibitor	Enalapril	Yes	1 * Daily	1984
Calcium Channel Blocker	Amlodipine	Yes	1 * Daily	1990
ARB	Losartan	Yes	1 * Daily	1995

- Leading mortality risk factor (c.60% aged 65+ affected)
- c.90% patients can now be controlled
  - 4 front-line classes to pick from
  - Switch to alleviate side effects
  - Combine classes & up dosing to bolster efficacy
  - Cheap generics
- Half century journey to create genericised system of medicine

# Obesity – Coming System of Medicine

Medicine Class	GLP-1	GIP	Amylin	Glucagon
Main Obesity Mechanism	Inhibits Appetite	Complements GLP-1	Boosts 'Fullness'	Burns Energy
Mechanism Proven?	In Obesity	In Obesity	In T2D	In T2D
Currently Launched	3	1	0	0
Obesity Efficacy	High	Medium	High?	Medium?
GI Side Effects	High	Low	Medium	Medium
Currently in Trials – Mono	13	0	3	0
Currently in Trials - Combo	18	9	3	5
Currently in Pivotal Trials	6	1	1	2
Oral Medicines in Trials?	Yes	Yes	Yes	Not Yet
First Generic	2032	2039	2040-2045	2040-2045

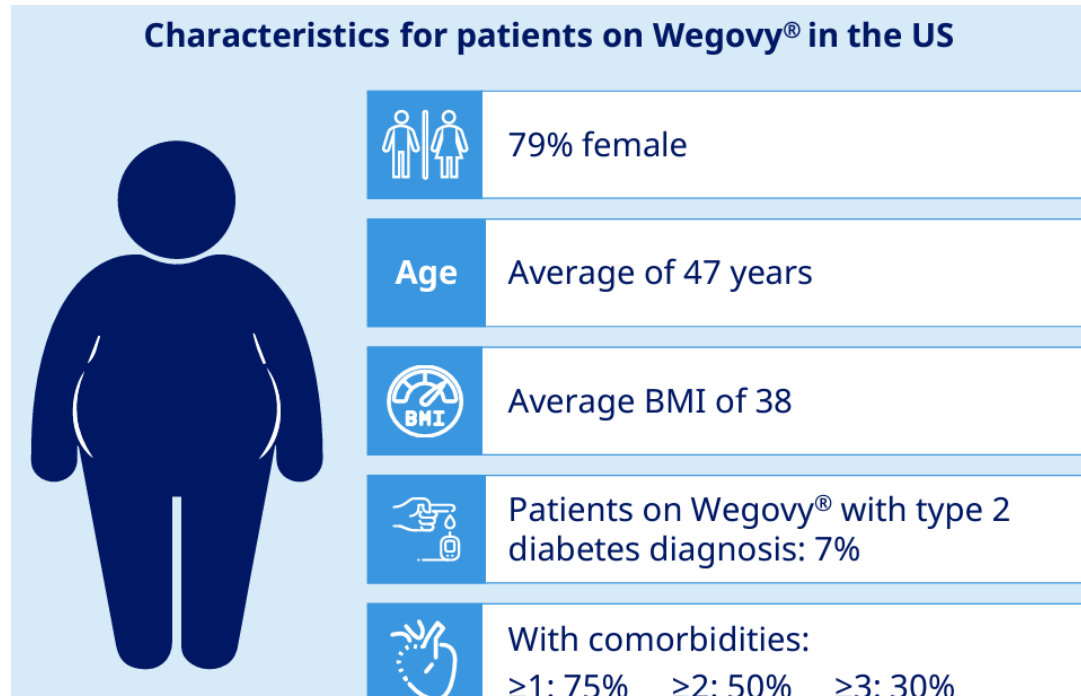
# Potential Obesity Medicines in Pivotal Trials

Medicine Name	Manufacturer	Mechanism(s)	Dosing	Launch
Semaglutide (7.2mg)	Novo Nordisk	GLP-1	Injection=1*weekly	2026
Semaglutide (50mg)	Novo Nordisk	GLP-1	Oral=1*daily	2027?
Orforglipron	Eli Lilly	GLP-1	Oral=1*daily	2027
CagriSema	Novo Nordisk	GLP-1 & Amylin	Injection=1*weekly	2027
Retatrutide	Eli Lilly	GLP-1 & GIP & Glucagon	Injection=1*weekly	2028
Survodutide	B. Ingelheim	GLP-1 & Glucagon	Injection=1*weekly	2028



# Low Male Take-Up a 2<sup>nd</sup> Key Issue

## Novo Nordisk Q2 24 Presentation



## Not an Isolated Statistic

- Pivotal trials 65%-80% female across geographies
- ‘Early adopter’ effect unlikely – 79%-81% female in Q1 22-Q2 24 presentations
- c.90% Weight Watchers’ clients female

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# Concluding Thoughts

- Wegovy & Zepbound = obesity rates fall relative c.10%-20%?
- System of obesity medicines will be developed
- Long-term public health campaign for male take-up
- Fully cost effective by c.2045
- Obesity rates can then fall by relative c.60%-80%

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# Q&A

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Please use the **Q&A function** to ask a question

# Appendix A - Broader Impact of GLP-1

Disease	Semaglutide Status	Tirzepatide Status
Cardiovascular Risk (with T2D)	Approved	Pivotal Trial
Cardiovascular Risk (overweight)	Approved	Pivotal Trial
Chronic Kidney Disease	Approval Awaited	N/A
Heart Failure (pEF)	Approval Awaited	Approval Awaited
MASH (liver cirrhosis)	Approval Awaited	Pivotal Trial Awaited
Obstructive Sleep Apnoea	N/A	Approval Awaited
Alzheimer's	Pivotal Trial Underway	N/A
Diabetic Retinopathy	Pivotal Trial Underway	N/A
Peripheral Artery Disease	Pivotal Trial Underway	N/A