RACAPITAL

Burden of Obesity and Treatment Landscape

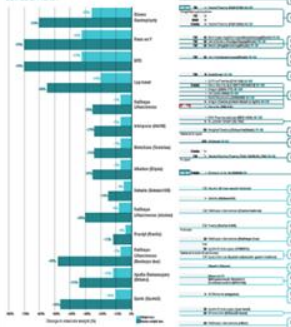
A Brief Background

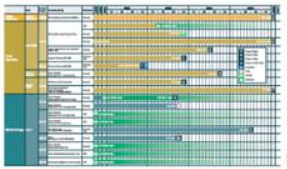
Tess Cameron
RA Capital Management

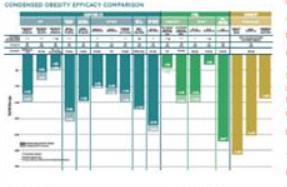
CHARTING A COMPLEX WORLD.

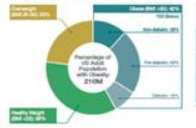
TECHATLAS | OBESITY

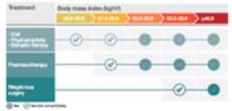
A DIVISION OF RACAPITAL

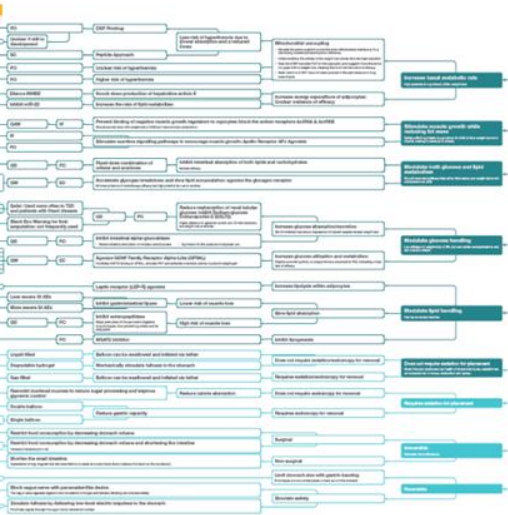


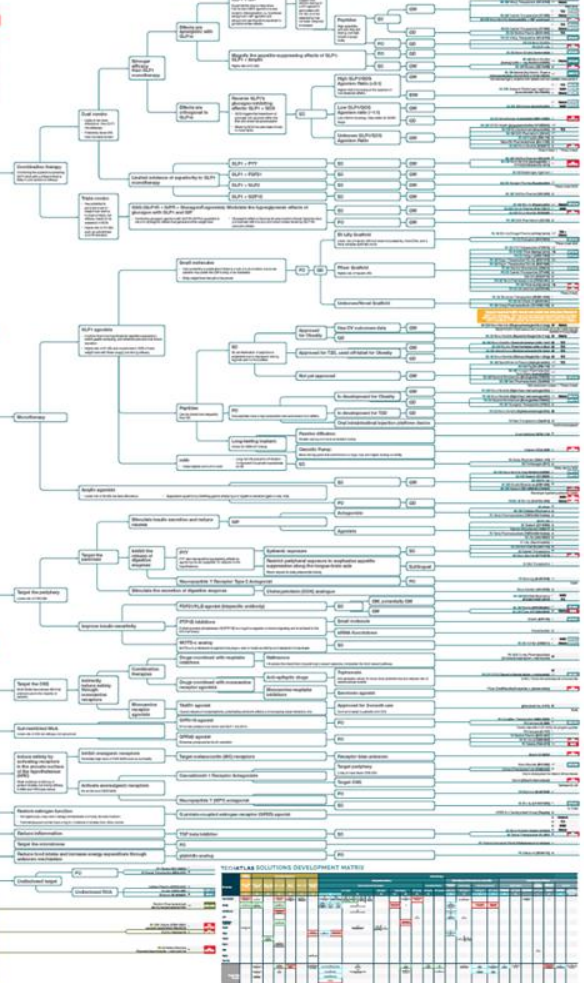




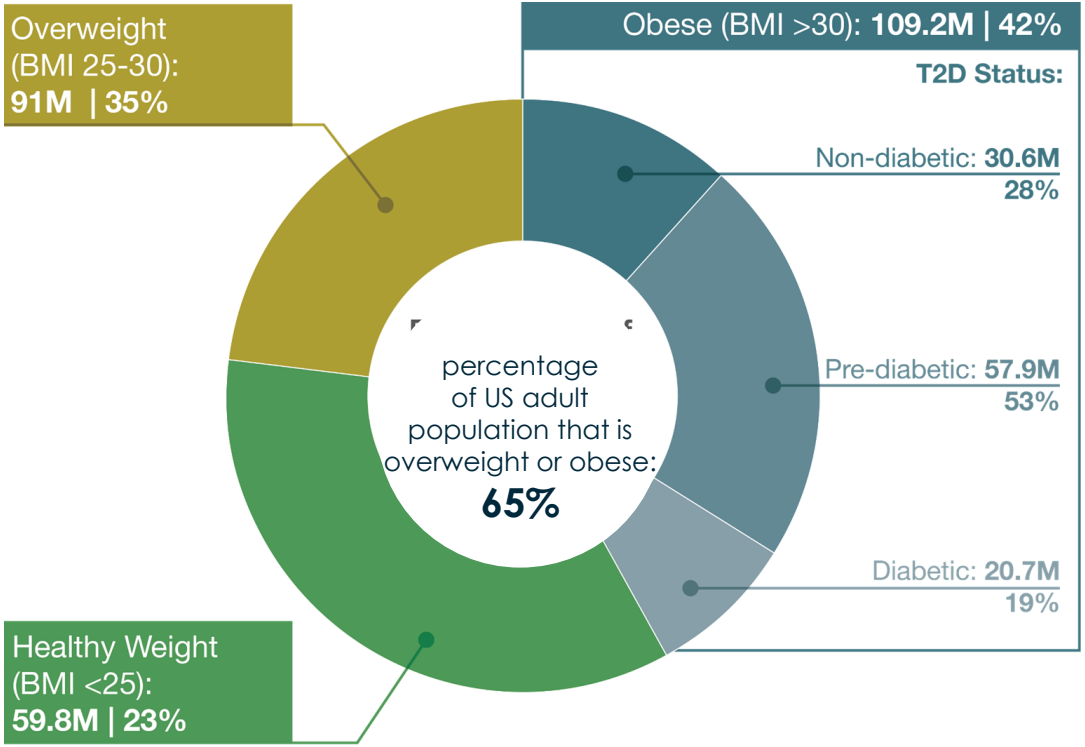




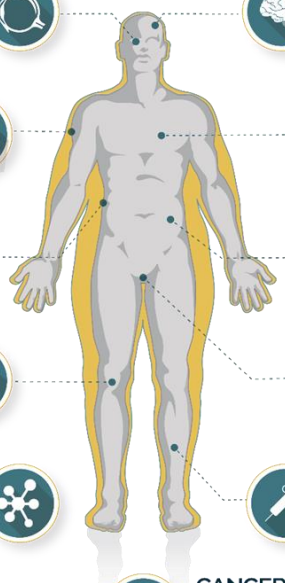




Obesity - A Highly Prevalent Chronic Disease Condition



Obesity contributes to a variety of medical conditions that increase cost and lower quality of life. Cost of overweight and obesity is expected to hit $4.32 trillion annually by 2035 (3% of global GDP).



OCULAR DISORDERS
Uveitis
Dry Eye Syndrome
Cataracts
Diabetic Retinopathy
Glaucoma

NERVOUS SYSTEM DISORDERS
Depression
Anxiety

SKIN DISEASE
Infections
Stretch Marks
Acne

PULMONARY DISEASE
Obstructive Sleep Apnea
COPD
Hypoventilation Syndrome
Pulmonary Embolism
Asthma
Reduced Exercise Capacity
Gastrointestinal Reflux Disease

LIVER AND PANCREATIC DISEASE
Gallbladder Disease
Gallstones
Pancreatitis
Non-alcoholic Fatty Liver Disease
Non-alcoholic Steatohepatitis
Cirrhosis

CARDIORENAL DISEASE
Chronic Kidney Disease
Hypertension
Dyslipidemia
Hypercholesterolemia
Heart Failure
Stroke

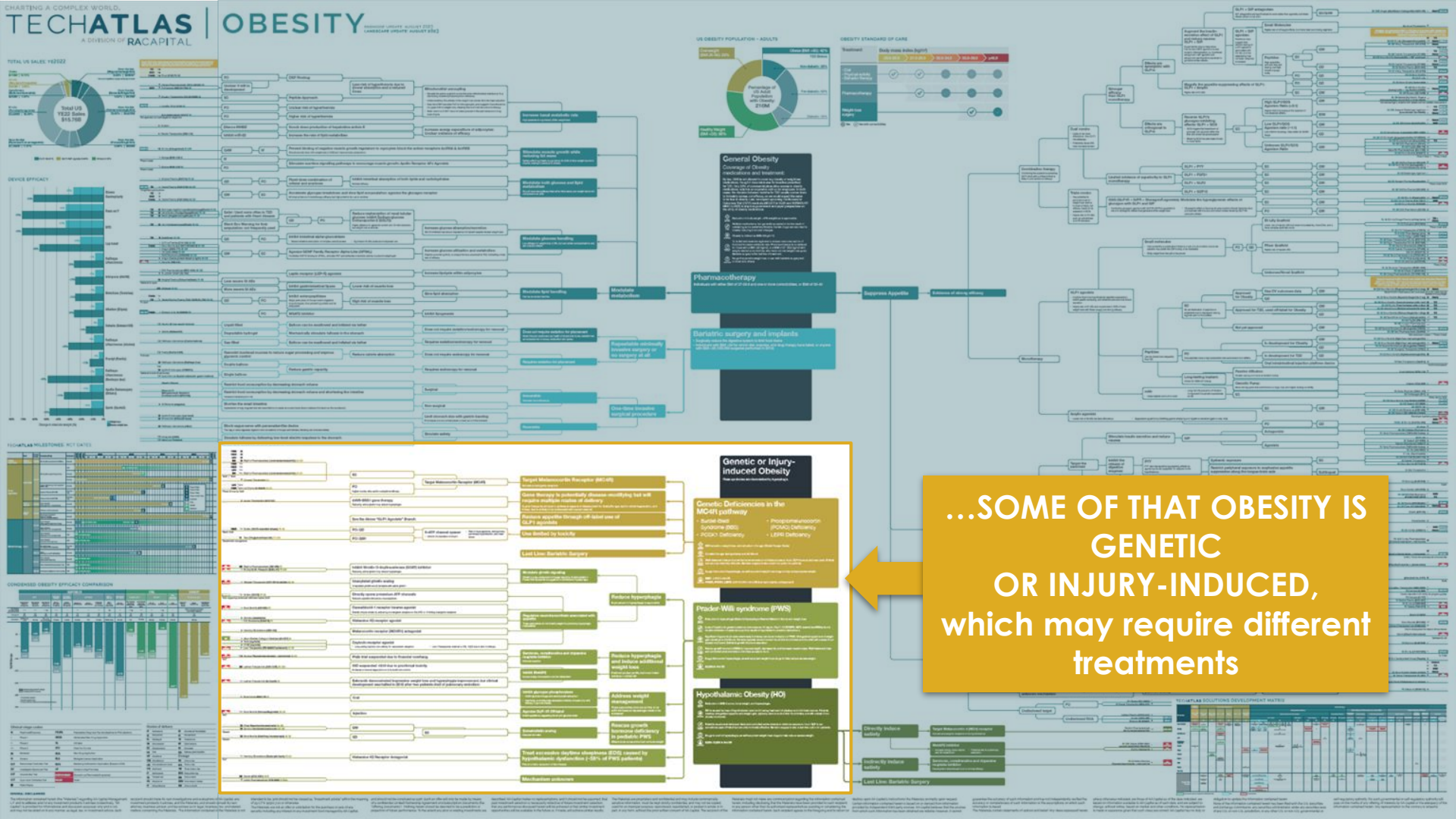
JOINT DISEASE
Increased Risk of Replacement Surgery
Pain
Osteoarthritis
Gout

GYNECOLOGIC DISEASE
Erectile Dysfunction
Low Testosterone
Infertility
Pregnancy Complications
Hormonal Imbalances
Polycystic Ovarian Syndrome
Hypothyroidism
Urinary Tract Infections

METABOLIC DISORDERS
Type 2 Diabetes
Type 1 Diabetes
Metabolic Syndrome

CIRCULATORY DISEASE
Slow Wound Healing
Phlebitis And Deep Vein Thrombosis
Edema
Peripheral Artery Disease

CANCER
Breast
Cervical
Colon
Esophagea
Pancreatic
Renal
Prostate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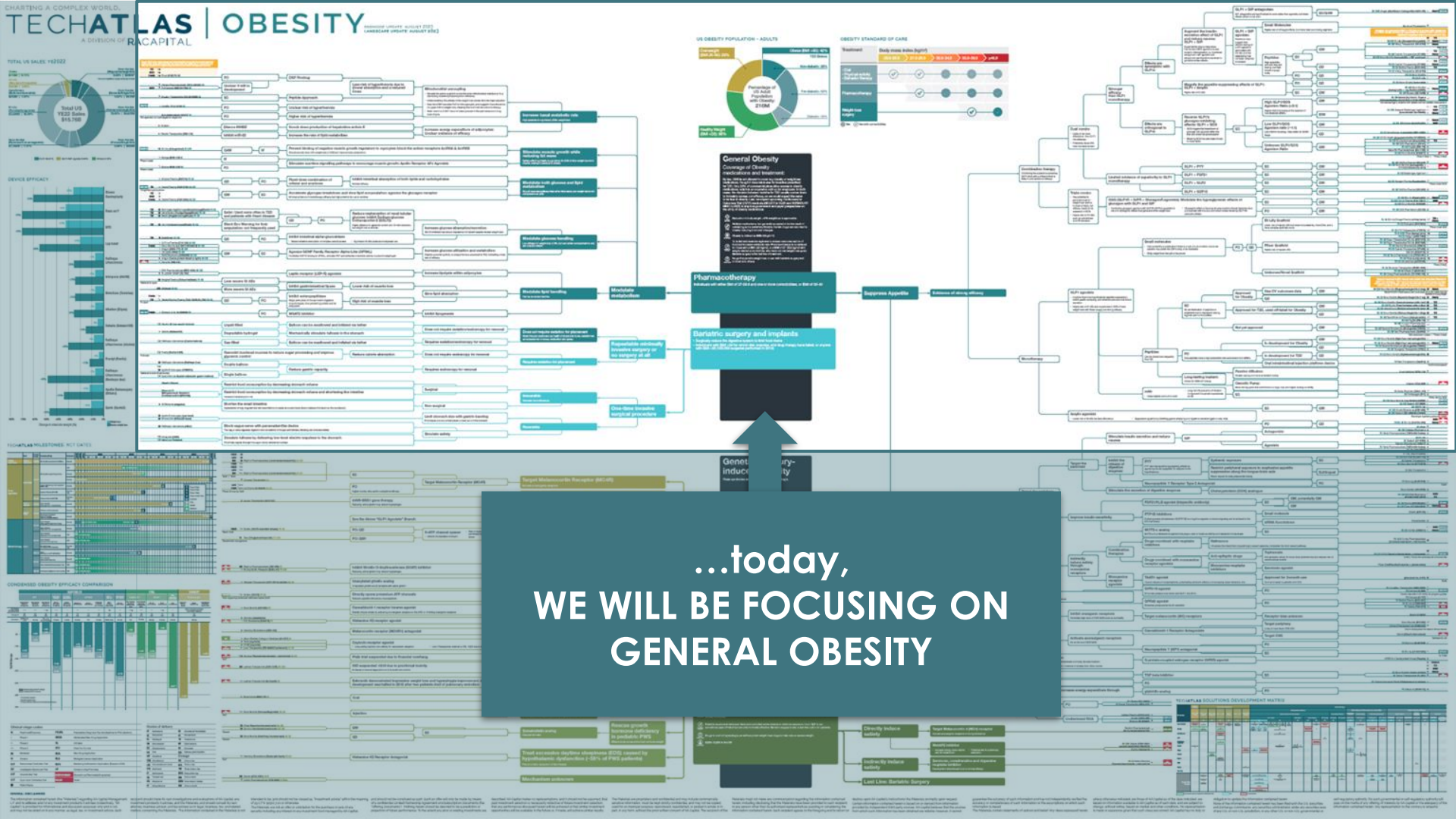
TECHATLAS
A DIVISION OF RACAPITAL
OBESITY
Genetic or Injury-induced Obesity
Genetic Deficiencies in the MC4R pathway
Prader-Willi syndrome (PWS)
Hypothalamic Obesity (HO)
…SOME OF THAT OBESITY IS GENETIC OR INJURY-INDUCED, which may require different treatments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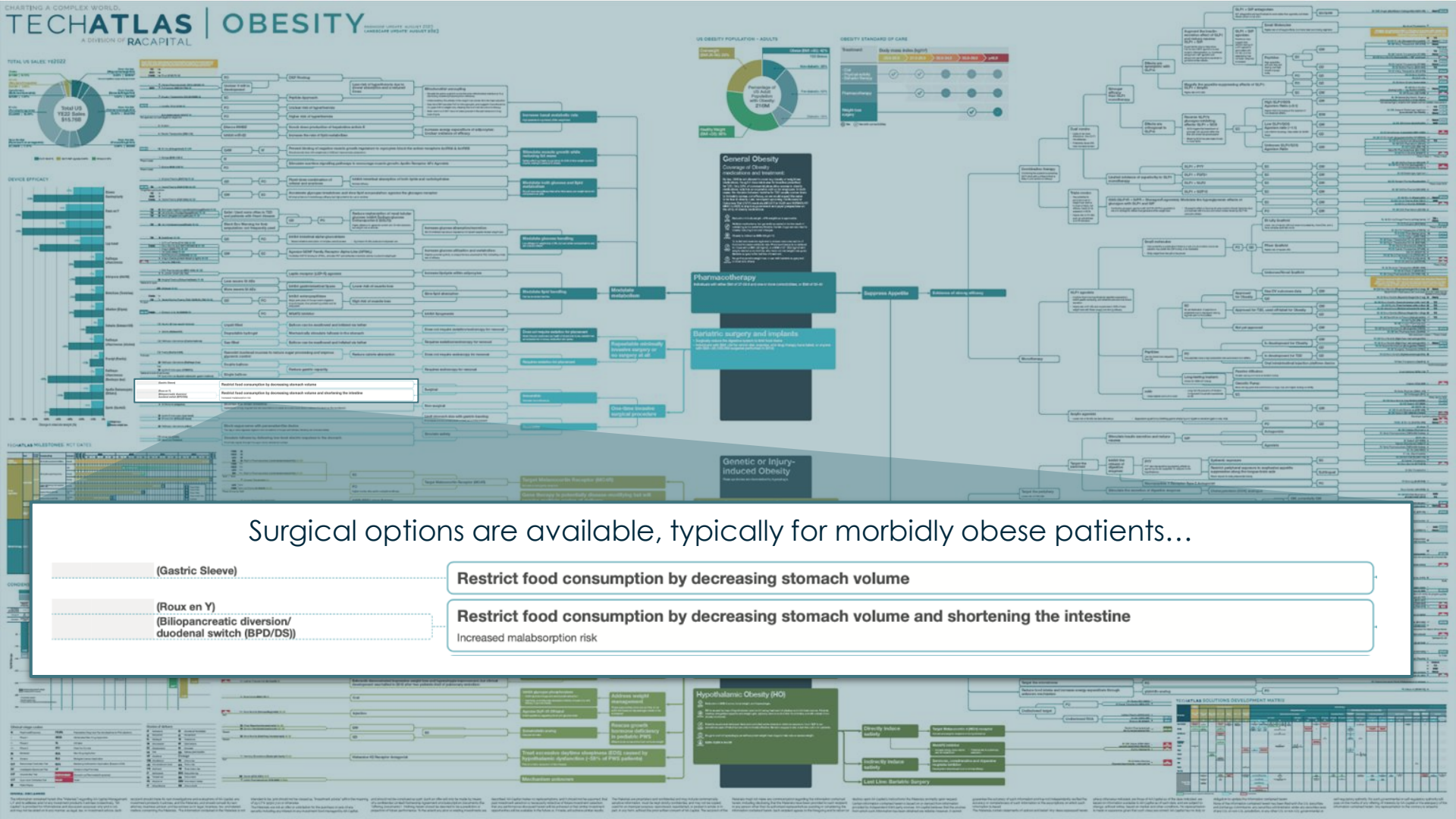
TOTAL US SALES: YE2022
DEVICE EFFICACY
US OBESITY POPULATION - ADULTS
OBESITY STANDARD OF CARE
General Obesity
Coverage of Obesity medications and treatment
Pharmacotherapy
Bariatric surgery and implants
Modulate metabolism
Suppress Appetite
Evidence of strong efficacy
Reversible minimally invasive surgery or no surgery at all
One-time invasive surgical procedure
CONDENSED OBESITY EFFICACY COMPARISON
...today,
WE WILL BE FOCUSING ON
GENERAL OBESITY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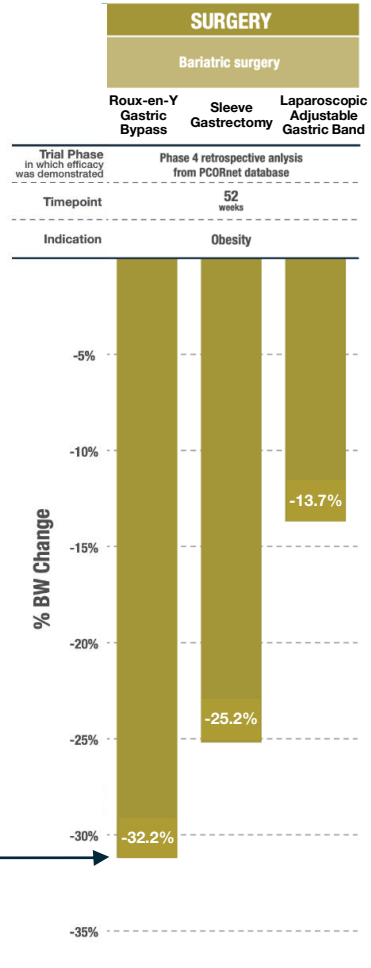
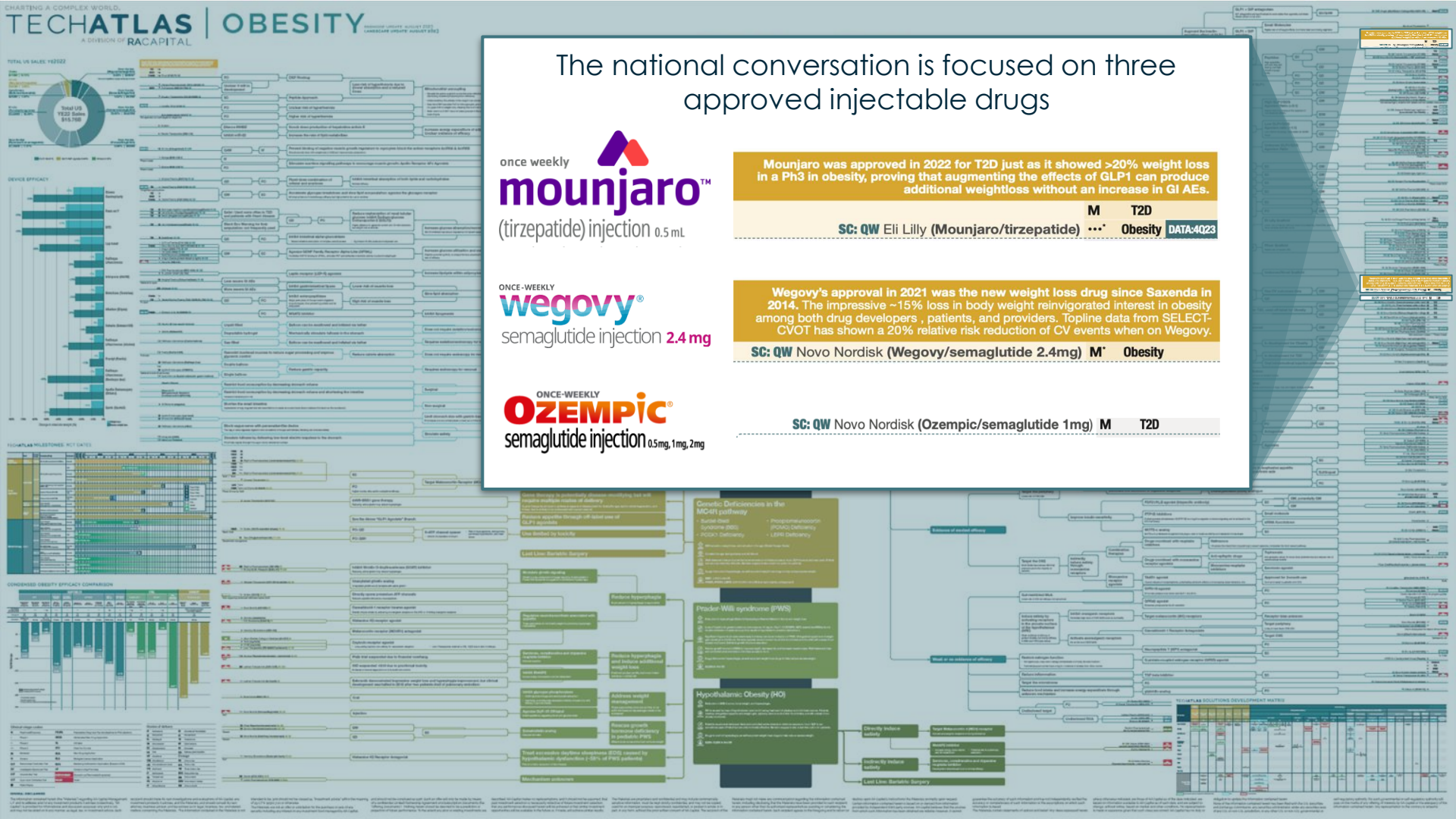
Surgical options are available, typically for morbidly obese patients…
(Gastric Sleeve)
Restrict food consumption by decreasing stomach volume
(Roux en Y)
(Biliopancreatic diversion/
duodenal switch (BPD/DS))
Restrict food consumption by decreasing stomach volume and shortening the intestine
Increased malabsorption risk

Surgical options are available, typically for morbidly obese patients…

which can reduce weight by as much as 32%

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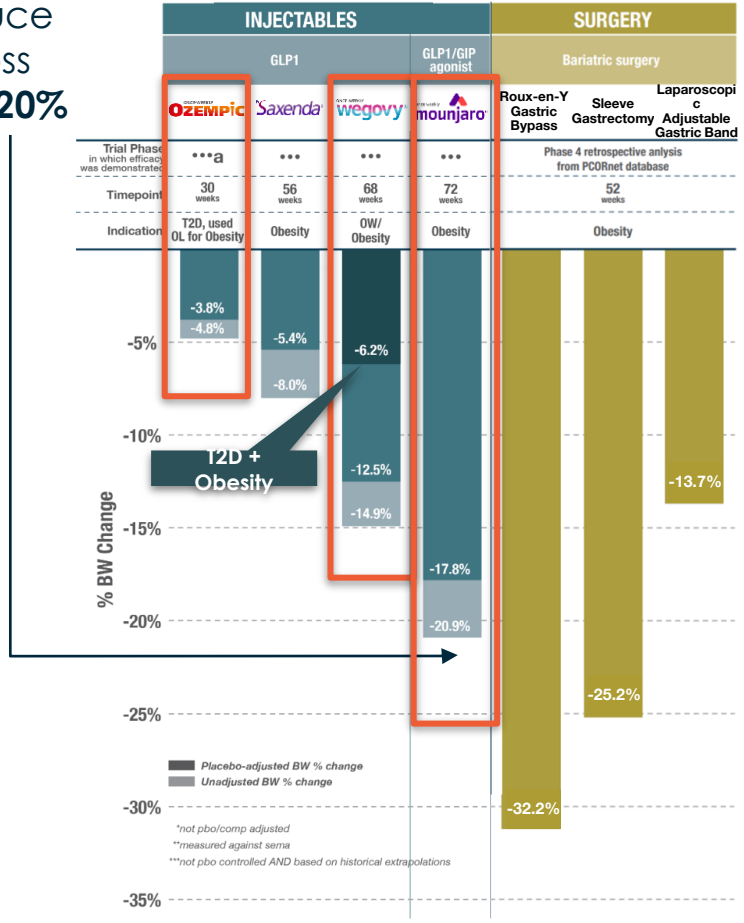
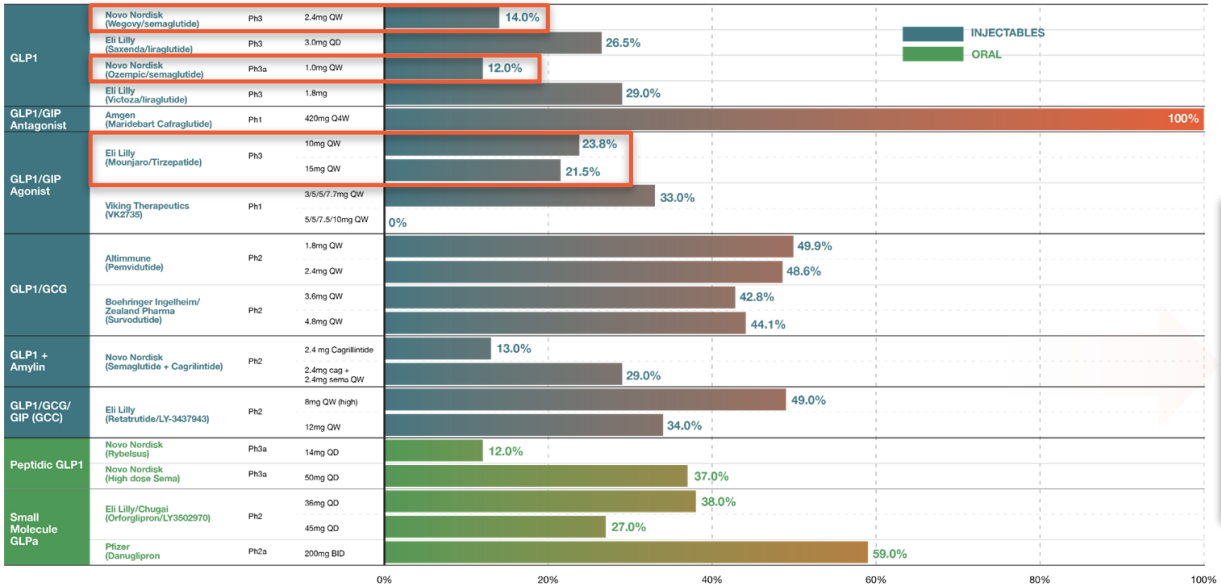
The national conversation is focused on three approved injectable drugs
once weekly
mounjaro™
(tirzepatide) injection 0.5 mL
Mounjaro was approved in 2022 for T2D just as it showed >20% weight loss in a Ph3 in obesity, proving that augmenting the effects of GLP1 can produce additional weightloss without an increase in GI AEs.
M T2D
SC: QW Eli Lilly (Mounjaro/tirzepatide) M* Obesity DATA:4Q23
ONCE-WEEKLY
wegovy®
semaglutide injection 2.4 mg
Wegovy's approval in 2021 was the new weight loss drug since Saxenda in 2014. The impressive ~15% loss in body weight reinvigorated interest in obesity among both drug developers , patients, and providers. Topline data from SELECT-CVOT has shown a 20% relative risk reduction of CV events when on Wegovy.
SC: QW Novo Nordisk (Wegovy/semaglutide 2.4mg) M* Obesity
ONCE-WEEKLY
OZEMPIC®
semaglutide injection 0.5mg, 1mg, 2mg
SC: QW Novo Nordisk (Ozempic/semaglutide 1mg) M T2D

That reduce weight-loss **by up to 20%**



These drugs come with side effects…

% NAUSEA, PBO ADJUSTED



RESULT:
AE-related discontinuations in 1-5% range, typically in first 3 months

Other key AEs: vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distension, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis

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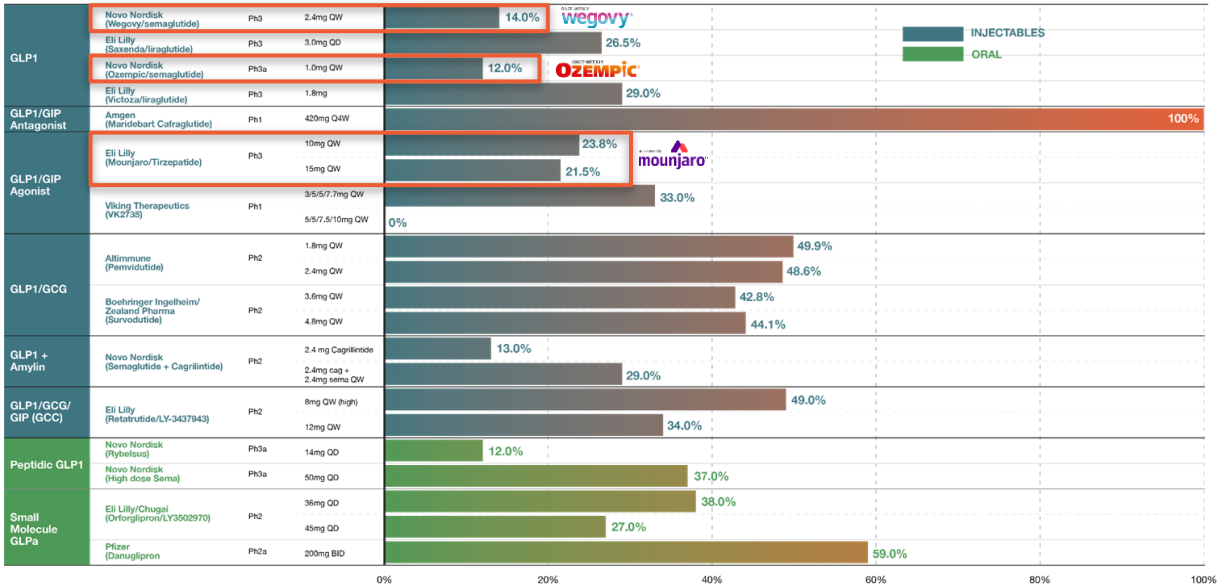

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Arrhythmias? Suicidal ideation?

Such events have been reported by people taking obesity drugs but does not mean they are caused by the drug, since these are also experienced by many, many people not taking these drugs.


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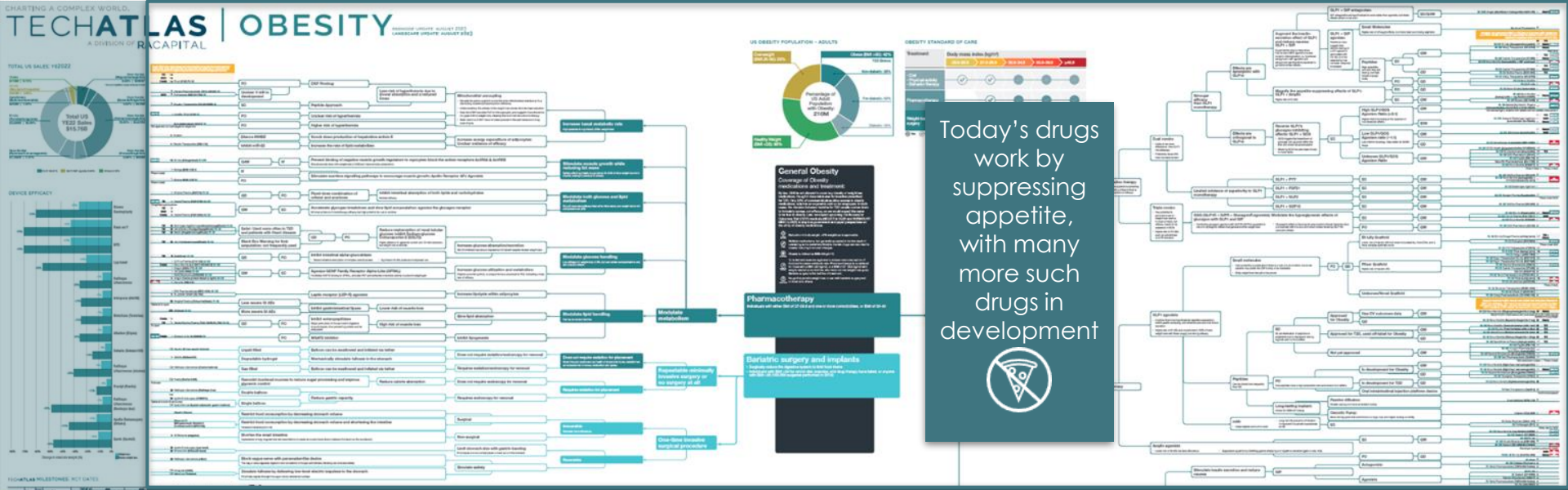
The existing drugs for obesity are transformational, but there is room for improvement - both from better side effect management… and also, better drugs!

The race to develop the best obesity drugs is off to a good start…

The race to develop the best obesity drugs is off to a good start…
and there is more to come!



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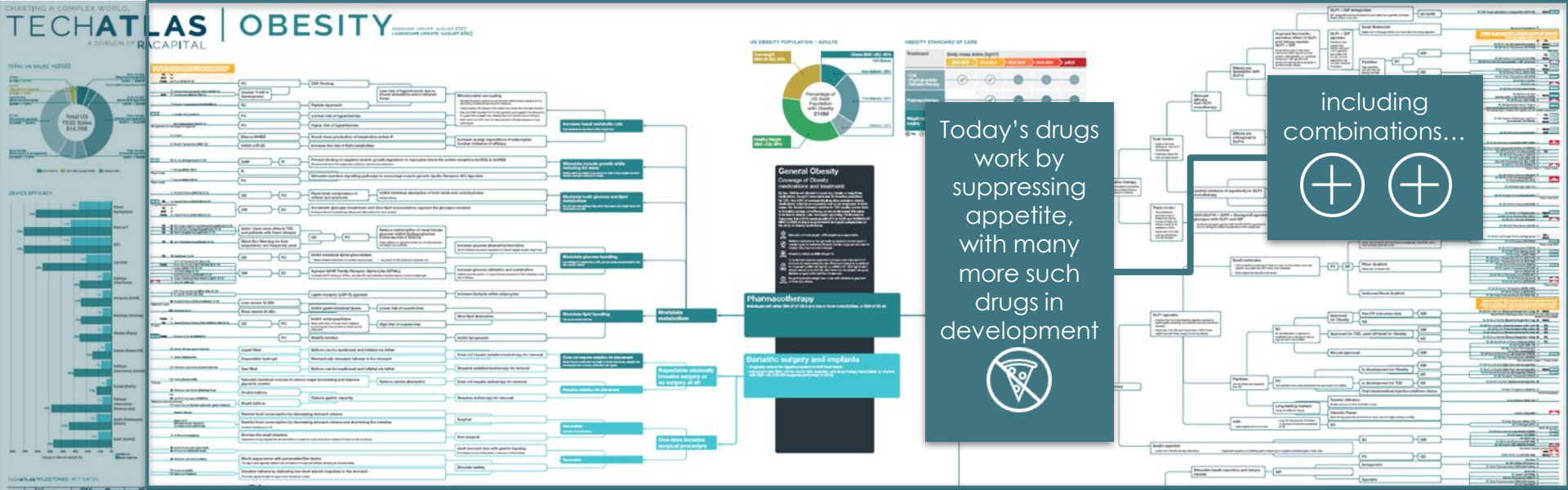

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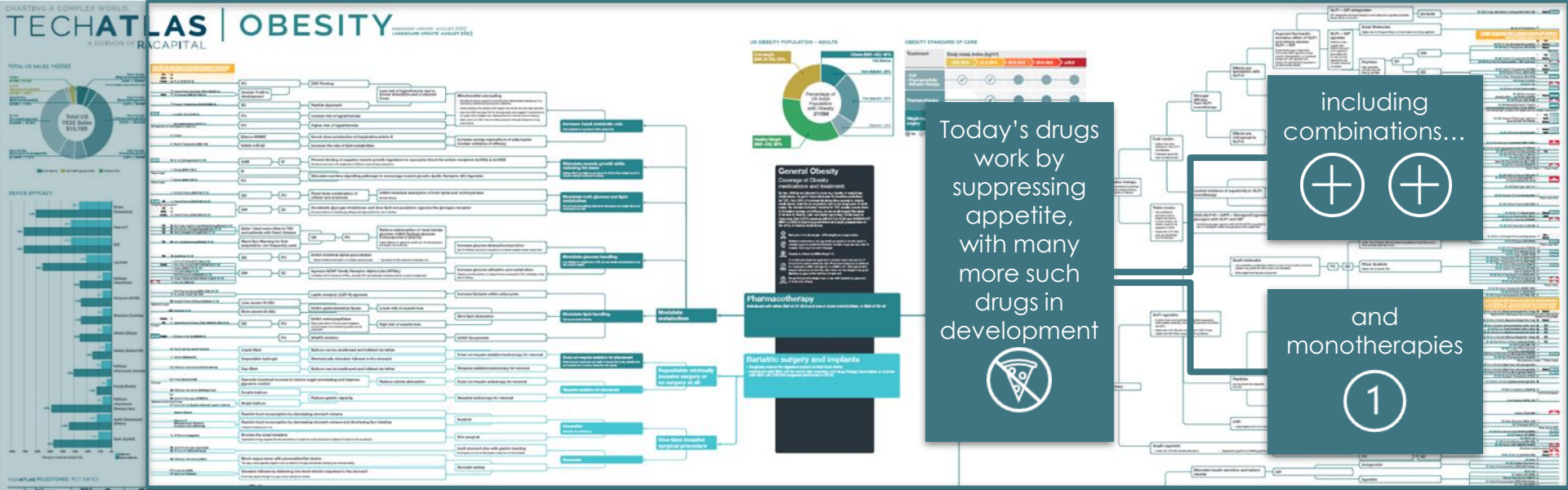

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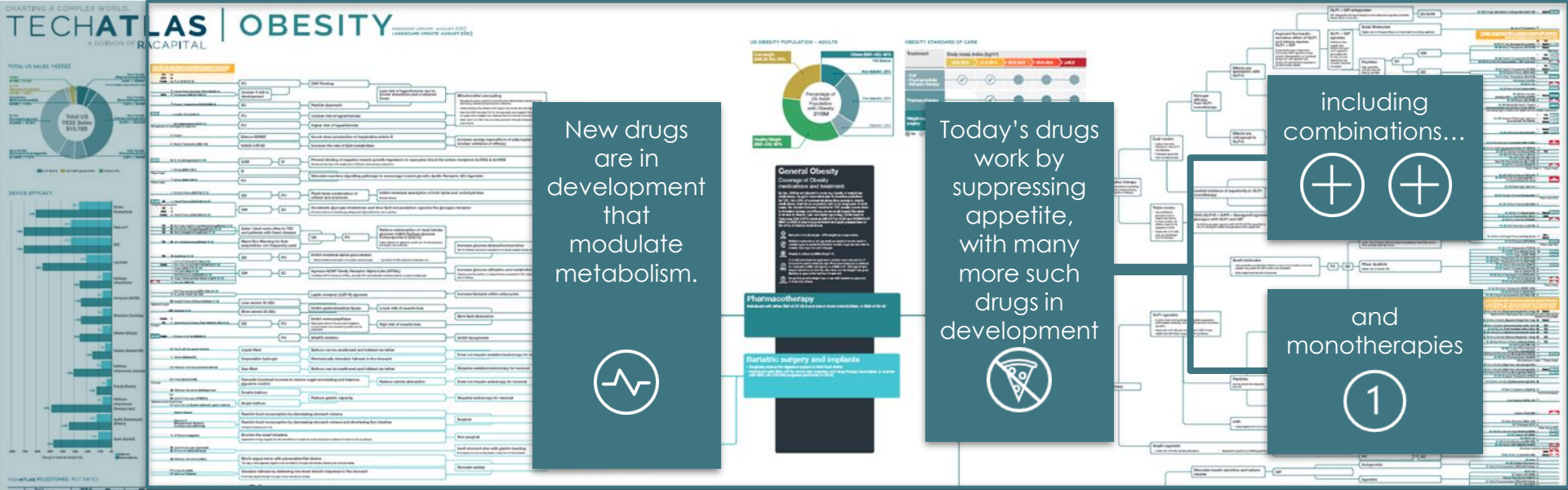

The race to develop the best obesity drugs is off to a good start…
and there is more to come!

So, how do obesity drugs get better than those that are approved today?

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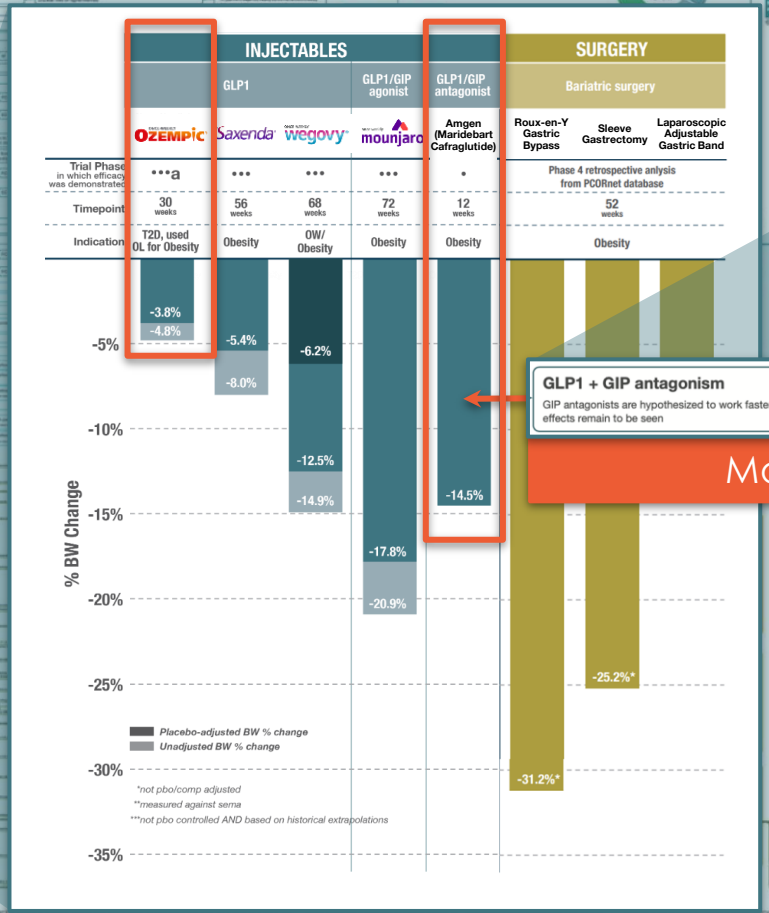


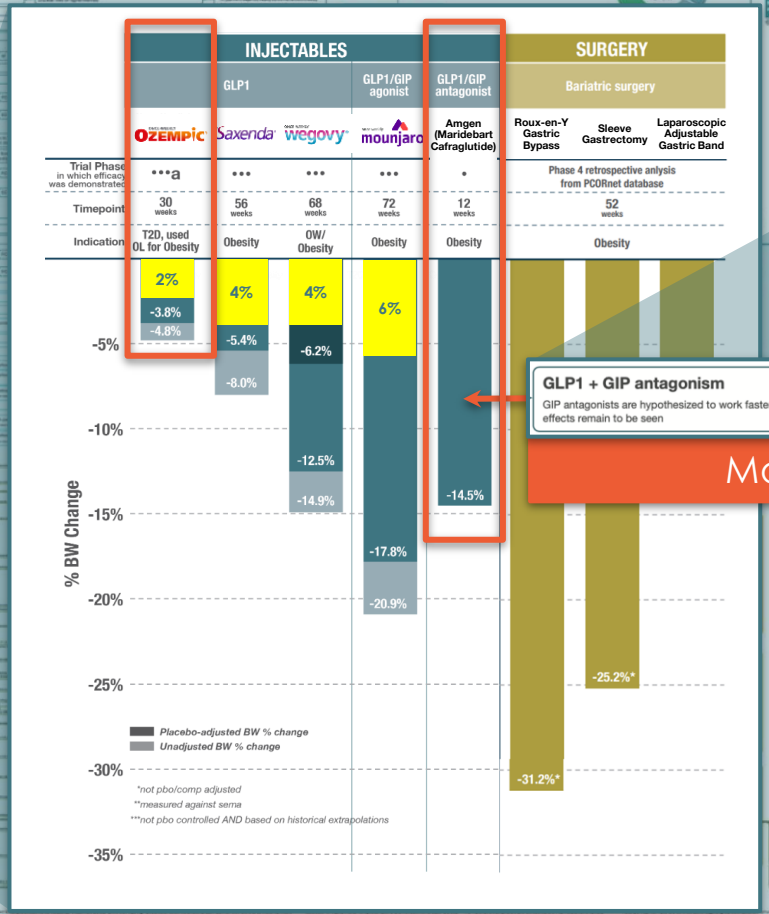
GLP1 + GIP antagonism

GIP antagonists are hypothesized to work faster than agonists, but these effects remain to be seen

→ SC/Q4W

SC: Q4W Amgen (Maridebart Cafraglutide/AMG-133) •• Obesity DATA:1025

More convenient and faster onset?



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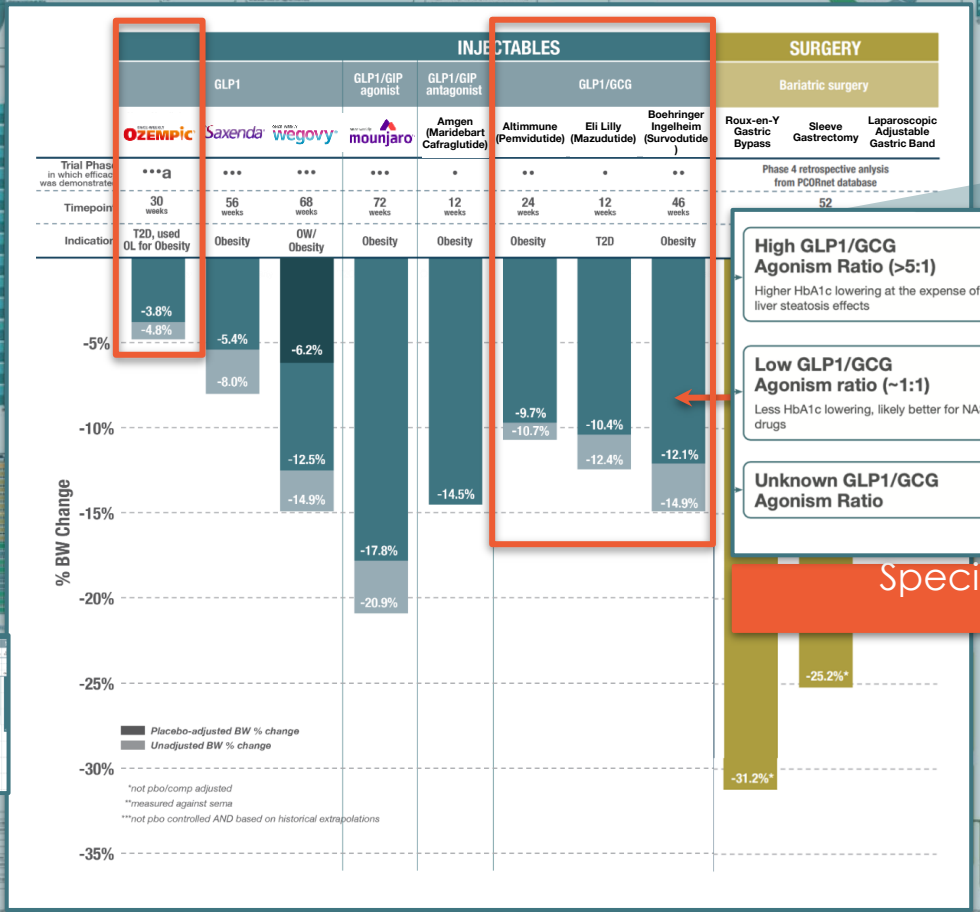

High GLP1/GCG Agonism Ratio (>5:1)
Higher HbA1c lowering at the expense of liver steatosis effects
→ QW
→ BIW

Low GLP1/GCG Agonism ratio (~1:1)
Less HbA1c lowering, likely better for NASH drugs
→ QW
→ QD

Unknown GLP1/GCG Agonism Ratio
→ QW

SC: QW Merck/JNJ/Hanmi Pharma (efinopegdutide/JNJ-64565111/HM12525A) •• COMPLETE
*JNJ returned rights, tested in both diabetic and non-diabetic obese patients
•• T2D DATA:MY23
SC: BIW Zealand/ Boehringer Ingelheim •• NASH DATA:MY23
(Survodutide/ BI-456906) •• Obesity DATA:MY23
•• Obesity DATA:4Q23
SC: QW Altimmune (pemvidutide) •• NASH DATA:1Q23
SC: QD AstraZeneca (cotadutide/MEDI-0382) •• DISCONTINUED
SC: QW OPKO Health (pegapamodutide/OPK88003) •••*
SC: QW Eli Lilly/Innovent (mazdutide) •/•• T2D
SC: QW D&D Pharmatech (DD-01) ••**
SC: QW PegBio (PB-718) •
NeuroBo Pharmaceuticals (DA-1726) •
SC: QW Novo Nordisk (NN9277) • DISCONTINUED
*Phase 3 ready | ** Phase 2 ready

Specifically targeting obese patients with NAFLD/NASH?

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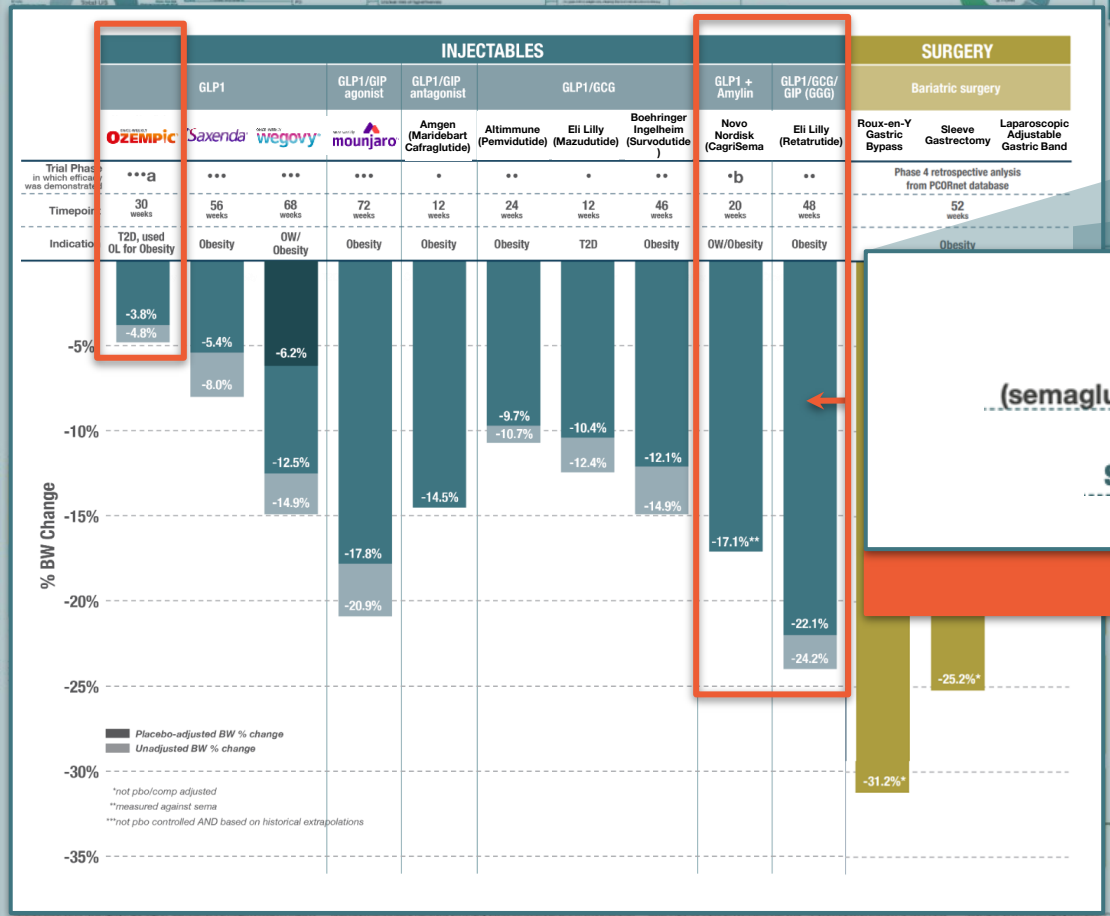

SC: QW Novo Nordisk (semaglutide + cagrilintide/AM833) ••• **Obesity** **DATA:2H24**

SC: QW Eli Lilly **(Retatrutide)** ••• **Obesity** **DATA:1Q26**

Higher efficacy?

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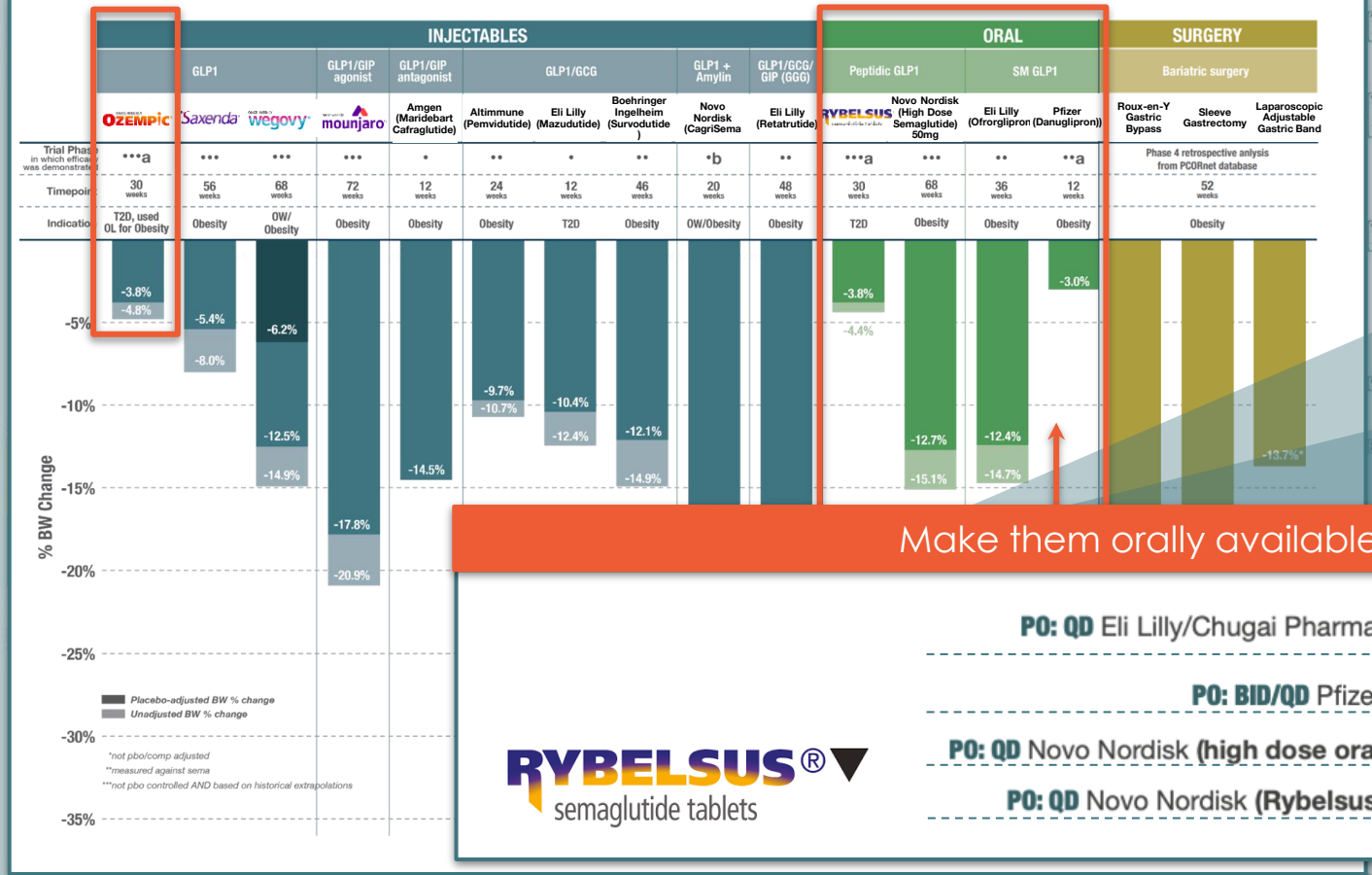

Make them orally available?

RYBELSUS® semaglutide tablets

PO: QD Eli Lilly/Chugai Pharma **(orforglipron)** ••• **T2D + Obesity**

PO: BID/QD Pfizer **(danuglipron)** ••b **DATA:2H23**

PO: QD Novo Nordisk **(high dose oral semaglutide)** ••• **Obesity** **NDA:YE23**

PO: QD Novo Nordisk **(Rybelsus/semaglutide)** **M**

Spare muscle?

Rivus' HU6 is the most advanced mitochondrial uncoupler in development for weight loss. Drug development has neglected the class due to hyperthermia risk, but creative PK engineering has increased HU6's therapeutic window.

- **T2D** ••a
- **NASH** ••a
- **Obesity** ••a Rivus **(HU6) P0: QD**

- Otsuka Pharmaceuticals **(OPC-163493) P0**
- **NASH** Protheragen **(MB-X01Y03) P0**
- Equator Therapeutics **(EQ-0016988) SC**
- DATA:YE23 OrsoBio **(TLC-6740) P0**
- **(2,4-dinitrophenol (DNP))* P0**

**Not approved, but used illegally for weight loss*

	INJECTABLES									ORAL					SURGERY		
	GLP1			GLP1/GIP agonist	GLP1/GIP antagonist	GLP1/GCG			GLP1 + Amylin	GLP1/GCG/ GIP (GGG)	Peptidic GLP1		SM GLP1		Mito-chondrial Uncouplers	Bariatric surgery		
	Ozempic	Saxenda	Wegovy	Mounjaro	Amgen (Maridebart Cafraglutide)	Altimmune (Pemvidutide)	Eli Lilly (Mazudutide)	Boehringer Ingelheim (Survodutide)	Novo Nordisk (CagriSema	Eli Lilly (Retatrutide)	Rybelsus	Novo Nordisk (High Dose Semaglutide) 50mg	Eli Lilly (Ofrorglipron	Pfizer (Danuglipron)	(2-4 nitrophenol)	Roux-en-Y Gastric Bypass	Sleeve Gastrectomy	Laparoscopic Adjustable Gastric Band
Trial Phase in which efficacy was demonstrated	•••a	•••	•••	•••	•	••	•	••	•b	••	•••a	•••	••	••a	•	Phase 4 retrospective anlysis from PCORnet database		
Timepoint	30 weeks	56 weeks	68 weeks	72 weeks	12 weeks	24 weeks	12 weeks	46 weeks	20 weeks	48 weeks	30 weeks	68 weeks	36 weeks	12 weeks	48 weeks	52 weeks		
Indication	T2D, used OL for Obesity	Obesity	OW/ Obesity	Obesity	Obesity	Obesity	T2D	Obesity	OW/Obesity	Obesity	T2D	Obesity	Obesity	Obesity	Obesity	Obesity		
	-2.8%		-6.2%			-9.7%	-10.4%	-12.1%			-3.8%		-12.4%	-3.0%				
			-12.5%		-14.5%	-10.7%	-12.4%	-14.9%	-17.1%**	-22.1%	-4.4%	-12.7%	-14.7%		-27%***	-31.2%*	-25.2%*	-13.7%*
			-14.9%	-17.8%						-24.2%		-15.1%						
				-20.9%														

*change

on historical extrapolations

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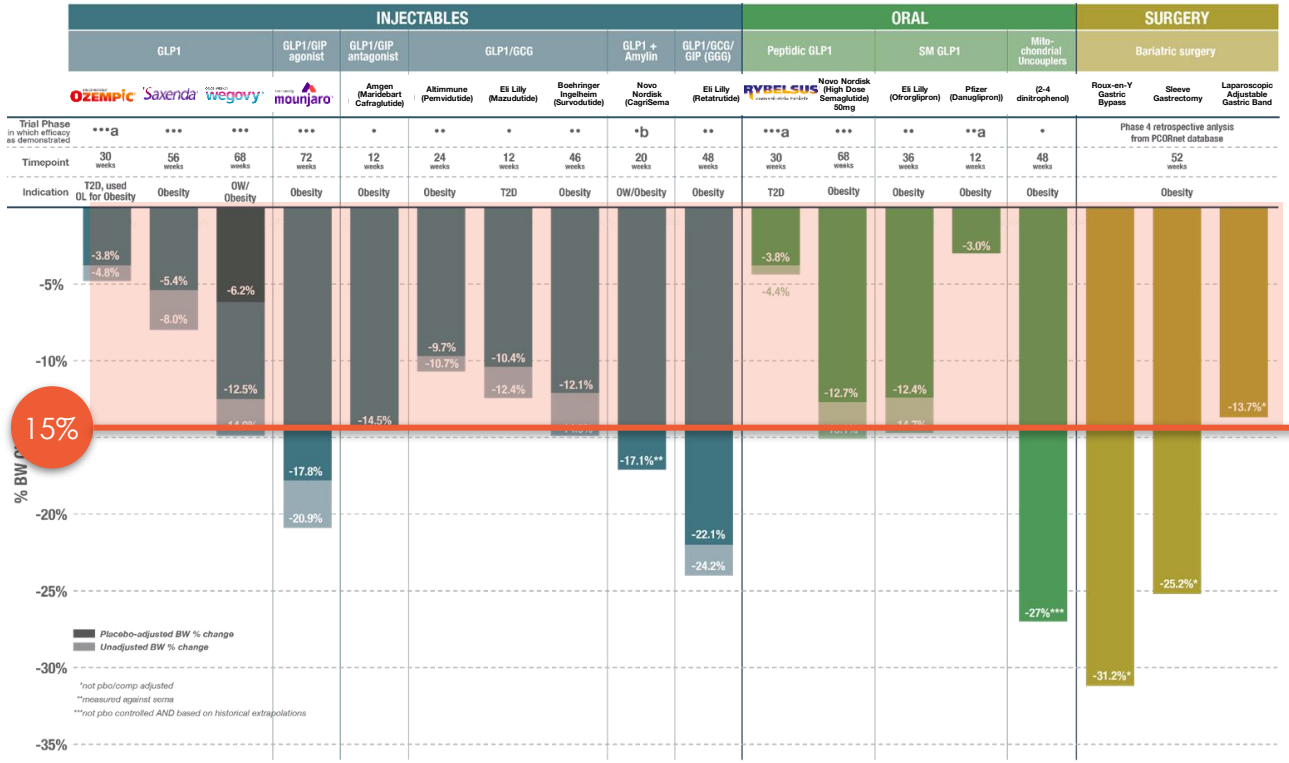
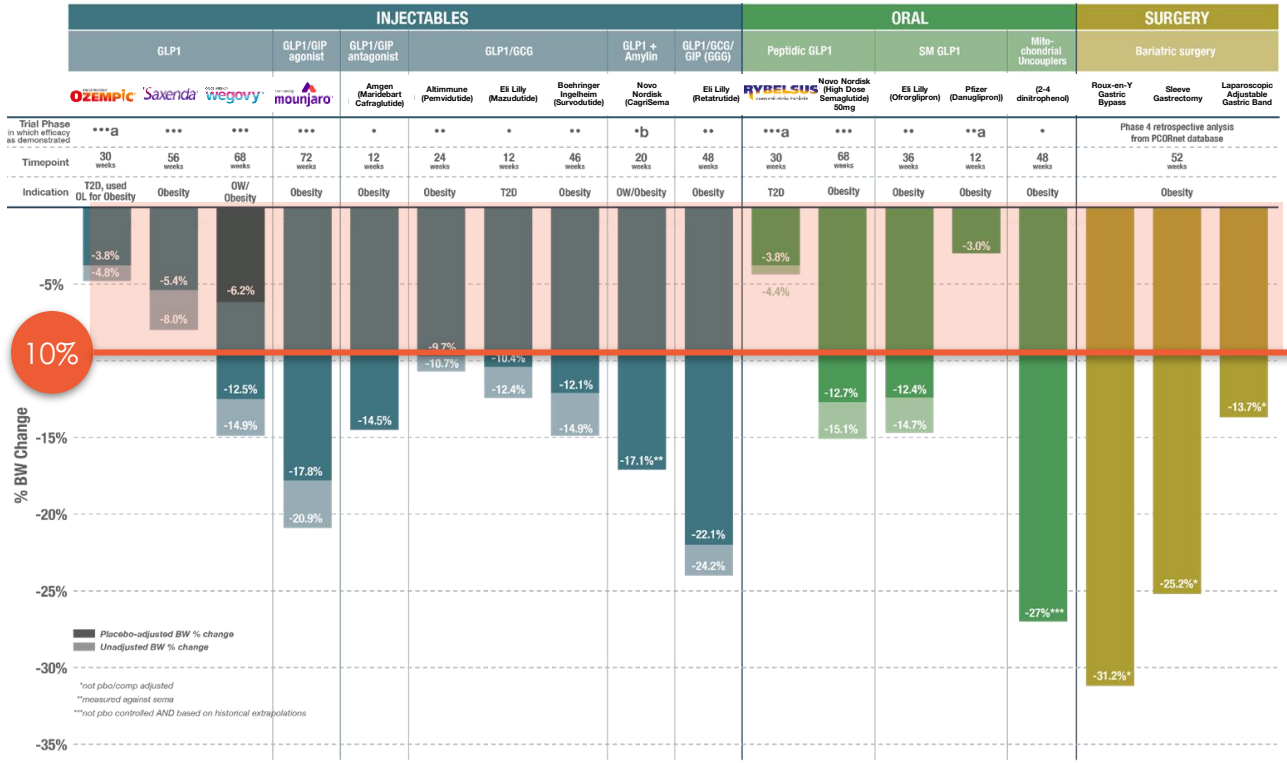
There are so many ways to make these drugs better!

How much weight loss do people need?



What if, for many people,
15% is enough?

How much weight loss do people need?



What if, for many people,
10% is enough?

Now imagine if…

There was a well-tolerated pill that cost $100/mo and led to 10% WL... affordable enough to be paid for OOP but so cheap that payers (incl. Medicare / Medicaid) cover it with no copay for anyone whose doctor prescribes it

How do we get there?

Enable broad coverage and uptake for obesity drugs, which will encourage the development of more and better drugs, increase competition, and ultimately drive down prices

What if we restrict access until existing obesity drugs go "generic"? Risk that the next generation of better obesity medications are not funded

- Understanding the societal benefits of innovative obesity treatments is essential to balance access and innovation.

- Generalized cost-effectiveness analysis (GCEA) provides an effective solution to derive estimates of societal benefits and aid decision-making.