Incretin receptor agonists

One cure for all?
A rapid-fire overview

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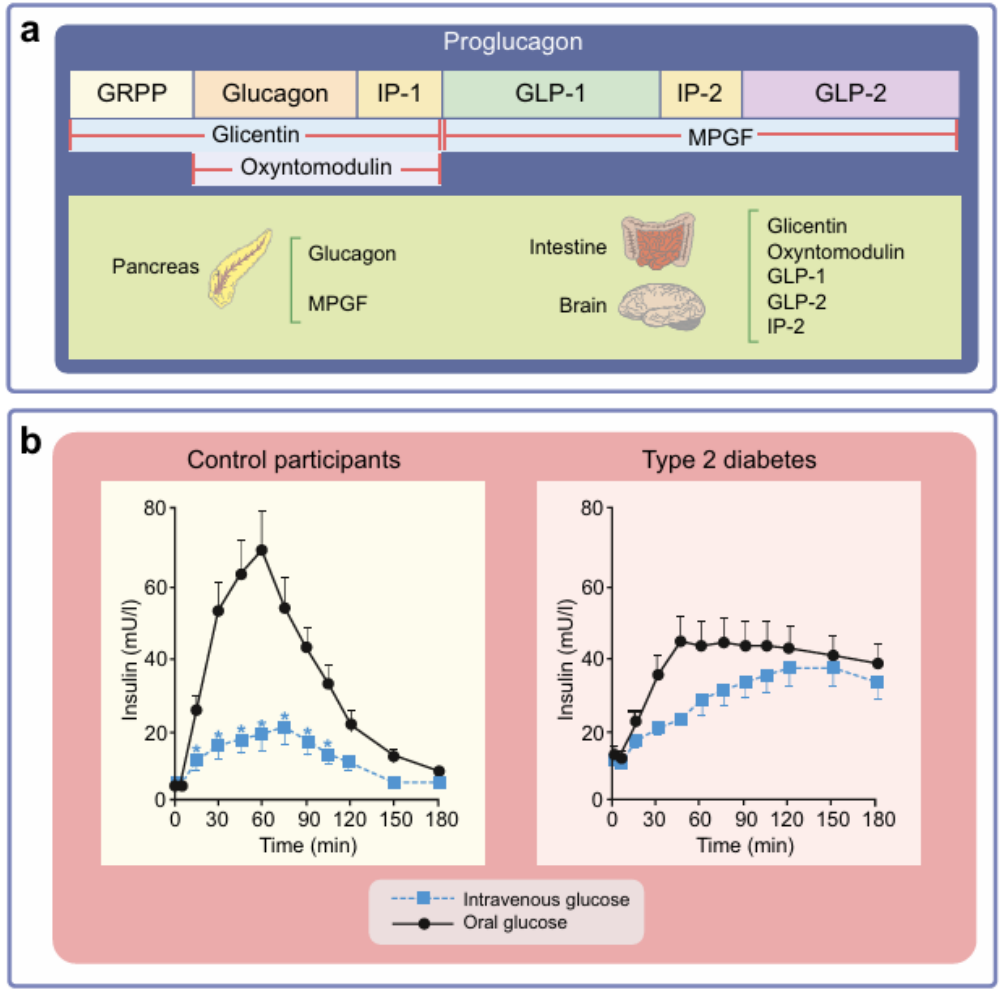
Let’s pay homage to the Gila Monster

1. What is the mechanism of action of these drugs?

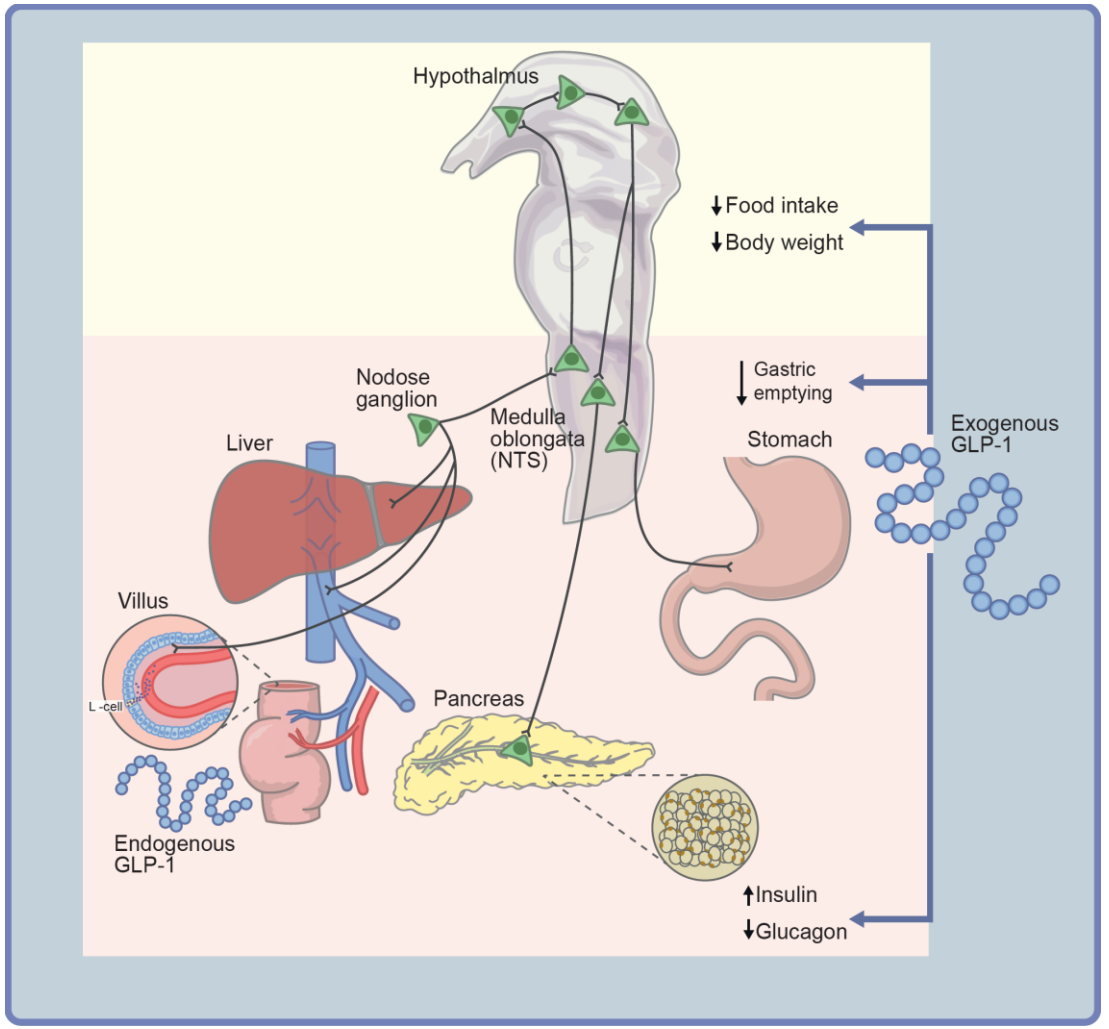
Fig. 1 (**a**) A schematic of the structure of proglucagon is shown. Processing of proglucagon-derived peptides occurs in a tissue-specific manner, with glucagon and MPGF generated in the pancreas, and glicentin, oxyntomodulin, GLP-1, GLP-2 and intervening peptide (IP)-2 generated in the intestine and brain. (**b**) The incretin effect is defined as the augmentation of insulin secretion when nutrients or glucose is administered into the gut, resulting in a greater increment in insulin secretion, relative to an isoglycaemic exposure achieved through parenteral or i.v. glucose infusion. The incretin effect is diminished in people with type 2 diabetes, largely reflecting impairment of beta cell function. Asterisks denote significant difference ($p \leq 0.05$). The original conversion factor used was 1 mU/l insulin = 7.3 pmol/l. Adapted from Nauck et al [10] with permission. This figure is available as part of a downloadable slideset



Oral glucose dependent insulin release

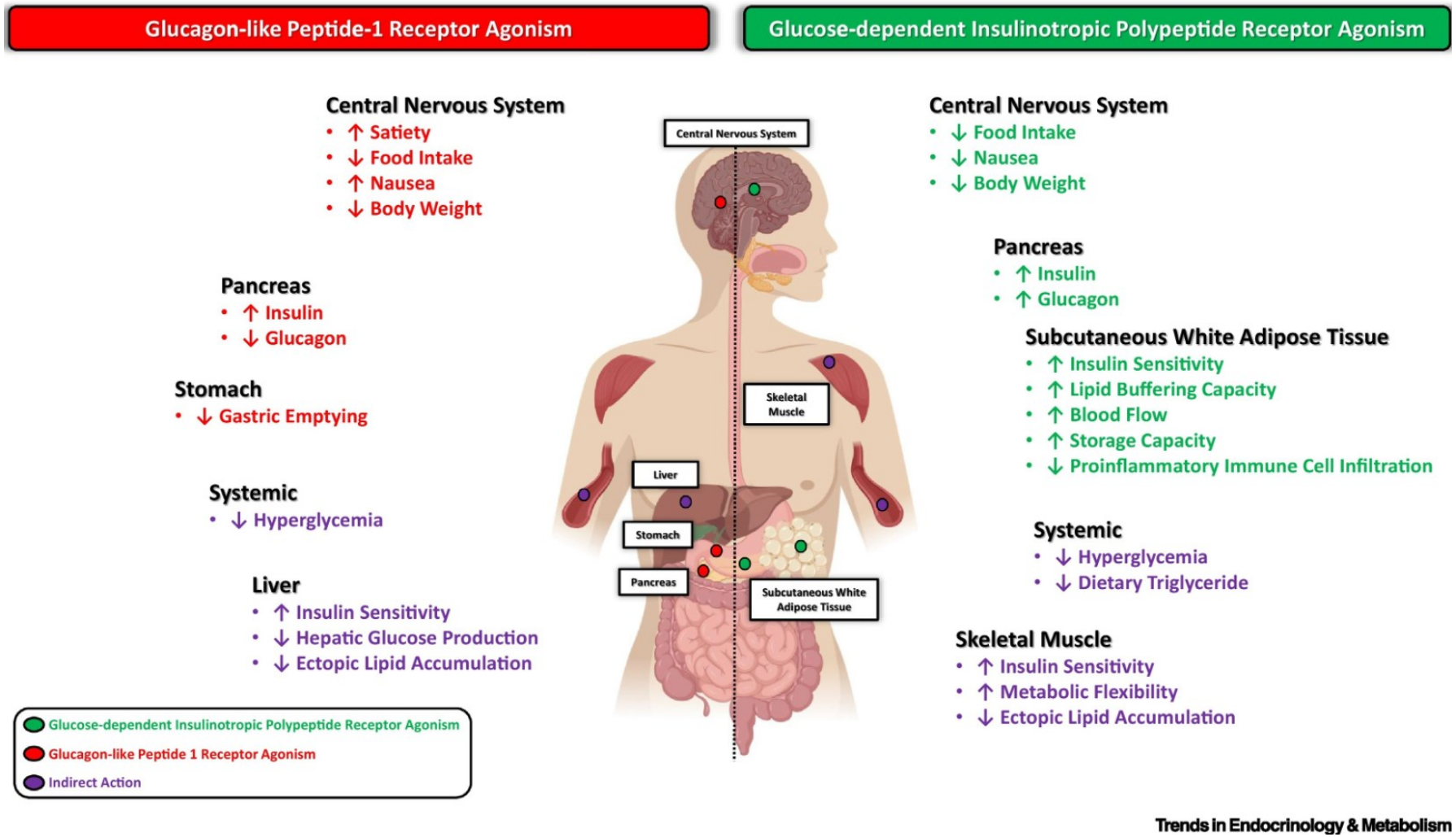
Drucker, D. J., & Holst, J. J. (2023). The expanding incretin universe: from basic biology to clinical translation. Diabetologia, 66(10), 1765–1779. https://doi.org/10.1007/s00125-023-05906-7

Action on the gut and brain



Drucker and Holst (2023) Diabetologia DOI 10.1007/s00125-023-05906-7

2. What are the actions of GLP-1 and GIP receptor agonism?



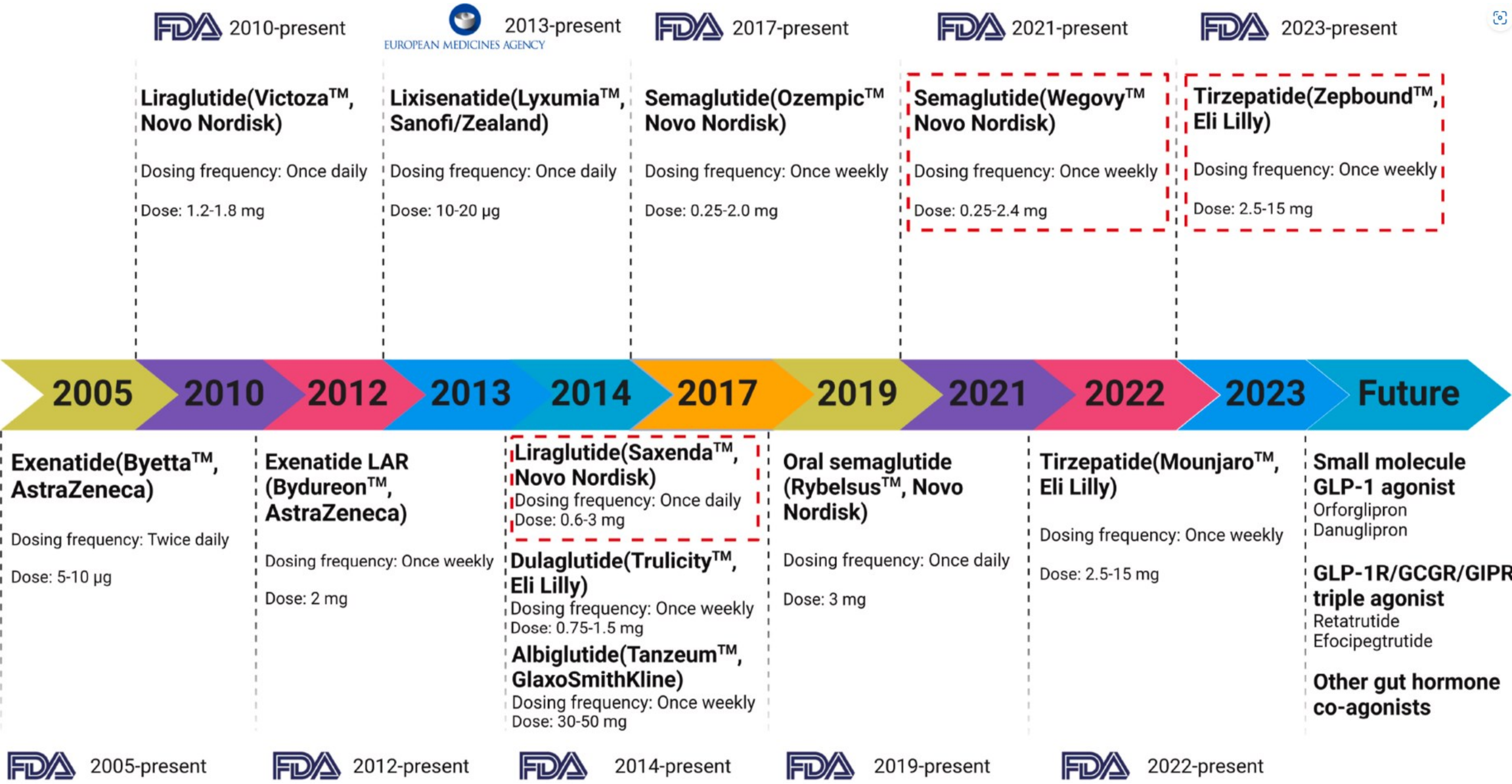
Samms, R. J., Coghlan, M. P., & Sloop, K. W. (2020). How May GIP Enhance the Therapeutic Efficacy of GLP-1?. Trends in endocrinology and metabolism: TEM, 31(6), 410–421. https://doi.org/10.1016/j.tem.2020.02.006

3. Which are the FDA approved incretin agonists for type 2 diabetes in the US?

Drug name and year of approval	Admin	Manufacturer	Brand	Doses
Exenatide (2005)	SQ	Eli Lilly	Byetta	5 or 10 mcg twice daily
Exenatide (2012)	SQ	AstraZeneca	Bydureon	2 mcg weekly
Lixisenatide (2016)	SQ	Sanofi	Adlyxin	10→20mcg daily
Liraglutide (2010)	SQ	Novo Nordisk	Victoza	0.6→1.2, 1.8mg daily
Dulaglutide (2014)	SQ	Eli Lilly	Trulicity	0.75, 1.5, 3, 4.5mg weekly
Semaglutide (2017)	SQ	Novo Nordisk	Ozempic	0.25→0.5, 1, 2mg weekly
Semaglutide (2019)	Oral	Novo Nordisk	Rybelsus	3→7, 14mg daily
Tirzepatide (2022)	SQ	Eli Lily	Mounjaro	2.5→5, 7.5, 10, 12.5, 15mg weekly

4. Which are the FDA approved incretin agonists for obesity in the US?

Drug name and year of approval	Admin	Manufacturer	Brand	Doses
Liraglutide (2014)	SQ	Novo Nordisk	Saxenda	0.6→1.2→1.8→3mg daily
Semaglutide (2021)	SQ	Novo Nordisk	Wegovy	0.25→0.5→1→1.7 or 2.4mg weekly
Tirzepatide (2023)	SQ	Eli Lily	Zepbound	2.5→5, 7.5, 10, 12.5, 15mg weekly


FDA 2010-present
EUROPEAN MEDICINES AGENCY 2013-present
FDA 2017-present
FDA 2021-present
FDA 2023-present
Liraglutide(Victoza™, Novo Nordisk)
Dosing frequency: Once daily
Dose: 1.2-1.8 mg
Lixisenatide(Lyxumia™, Sanofi/Zealand)
Dosing frequency: Once daily
Dose: 10-20 µg
Semaglutide(Ozempic™ Novo Nordisk)
Dosing frequency: Once weekly
Dose: 0.25-2.0 mg
Semaglutide(Wegovy™ Novo Nordisk)
Dosing frequency: Once weekly
Dose: 0.25-2.4 mg
Tirzepatide(Zepbound™, Eli Lilly)
Dosing frequency: Once weekly
Dose: 2.5-15 mg
2005
2010
2012
2013
2014
2017
2019
2021
2022
2023
Future
Exenatide(Byetta™, AstraZeneca)
Dosing frequency: Twice daily
Dose: 5-10 µg
Exenatide LAR (Bydureon™, AstraZeneca)
Dosing frequency: Once weekly
Dose: 2 mg
Liraglutide(Saxenda™, Novo Nordisk)
Dosing frequency: Once daily
Dose: 0.6-3 mg
Dulaglutide(Trulicity™, Eli Lilly)
Dosing frequency: Once weekly
Dose: 0.75-1.5 mg
Albiglutide(Tanzeum™, GlaxoSmithKline)
Dosing frequency: Once weekly
Dose: 30-50 mg
Oral semaglutide (Rybelsus™, Novo Nordisk)
Dosing frequency: Once daily
Dose: 3 mg
Tirzepatide(Mounjaro™, Eli Lilly)
Dosing frequency: Once weekly
Dose: 2.5-15 mg
Small molecule GLP-1 agonist
Orforglipron
Danuglipron
GLP-1R/GCGR/GIPR triple agonist
Retatrutide
Efocipegtrutide
Other gut hormone co-agonists
FDA 2005-present
FDA 2012-present
FDA 2014-present
FDA 2019-present
FDA 2022-present

5. What are the FDA approved indications for incretin agonists beyond diabetes and obesity?

- 12/20/2024: **Zepbound** FDA approved for moderate-to-severe obstructive sleep apnea in adults with obesity (based on the results of the SURMOUNT-OSA trial).

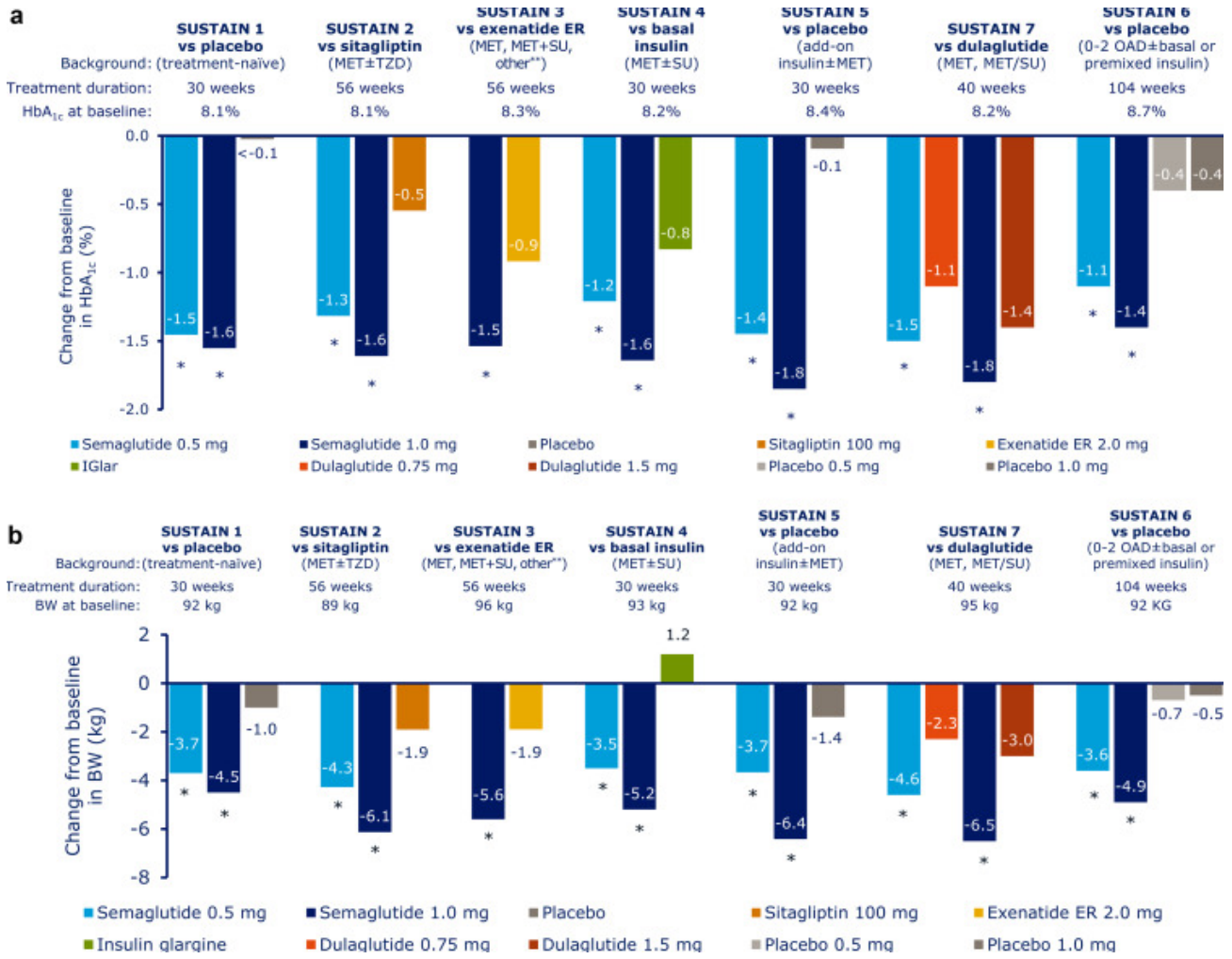
- 3/8/2024: **Wegovy** FDA approved for reducing the risk of cardiovascular death, heart attack and stroke in adults with cardiovascular disease and either obesity or overweight. (based on the results of the SELECT trial)

https://www.fda.gov/news-events/press-announcements/fda-approves-first-medication-obstructive-sleep-apnea
FDA Approves First Treatment to Reduce Risk of Serious Heart Problems Specifically in Adults with Obesity or Overweight | FDA

6. Which are important trials for incretin agonists to reference and quote?

TRIALS	DRUG	SUMMARY
LEADER	SQ Liraglutide	CVD reduction; T2DM; Placebo
LEAN	SQ Liraglutide	Safety and efficacy; overweight + MASH; Placebo
AWARD	SQ Dulaglutide	Safety, efficacy and superiority; T2DM; Comparator studies
SUSTAIN 1-7	SQ Semaglutide	Safety, efficacy and superiority; T2DM; Comparator studies
STEP & STEP-HFpEF	SQ Semaglutide	Weight (+symp) reduction; Obesity (and HFpEF); Placebo
FLOW	SQ Semaglutide	CVD reduction; T2DM and DKD with albuminuria; Placebo
SELECT	SQ Semaglutide	CVD reduction; Obesity; Placebo
PIONEER 1-6	Oral Semaglutide	Safety, efficacy and superiority; T2DM; Comparator studies
SOUL	Oral Semaglutide	CVD reduction; T2DM + ASCVD +/- DKD; Placebo
SURMOUNT	SQ Tirzepatide	Weight reduction; Obesity; Placebo
SURPASS & SURPASS-SWITCH	SQ Tirzepatide	Safety, efficacy and superiority; T2DM; Comparator studies
SUMMIT	SQ Tirzepatide	CVD reduction; Obesity + HFpEF; Placebo
SYNERGY-NASH	SQ Tirzepatide	MASH resolution; MASH with F2/F3 fibrosis; Placebo

Example of Comparator Studies



Aroda, V. R., Ahmann, A., Cariou, B., Chow, F., Davies, M. J., Jódar, E., Mehta, R., Woo, V., & Lingvay, I. (2019). Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1-7 trials. Diabetes & metabolism, 45(5), 409–418. https://doi.org/10.1016/j.diabet.2018.12.001

7. Which incretin agonists can be used for MASLD?

- **Liraglutide**: LEAN trial

- **Semaglutide**:

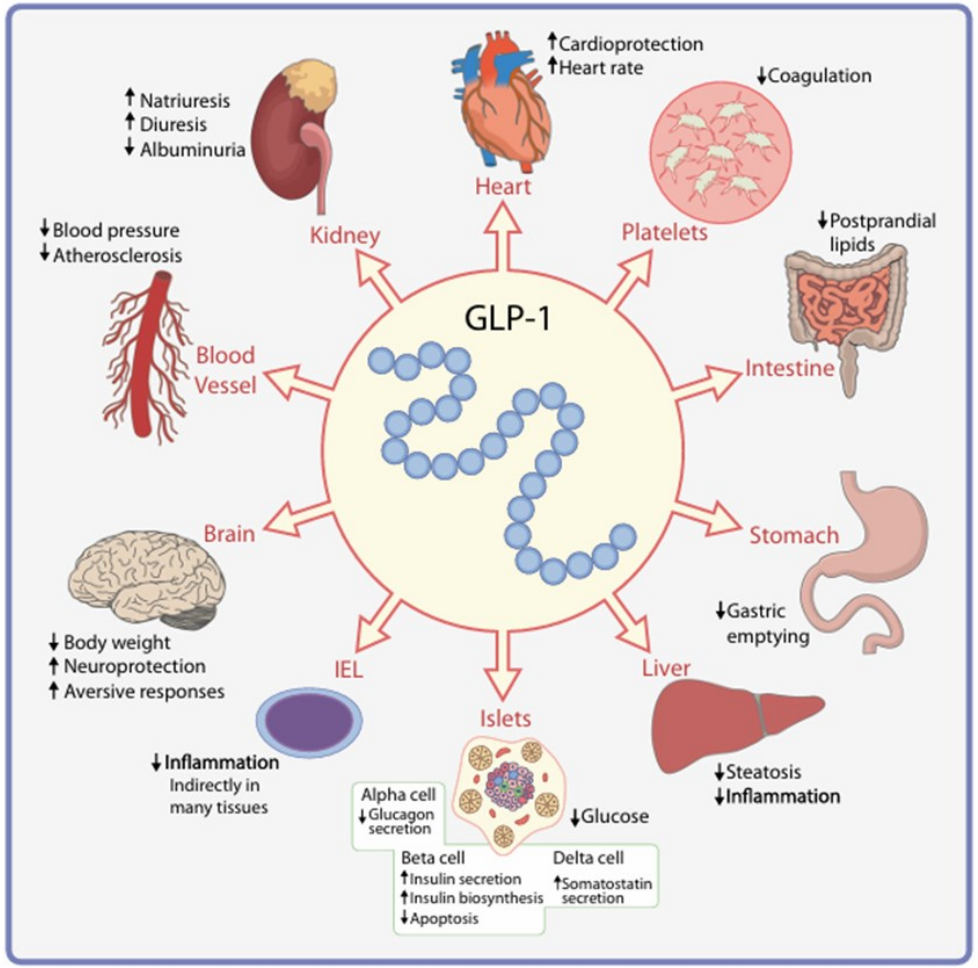
-2021 Placebo controlled trial

-ESSENCE trial Phase 3 results announced 1/11/2024

- **Tirzepatide**: SYNERGY-NASH trial

8. What are the indications for incretin agonists currently approved or being studied?

- **T2DM**
- **Obesity**
- T1DM (off-label)
- MASLD
- Obstructive sleep Apnea
- Fertility and PCOS
- Cardiovascular risk reduction: stroke, MI, HFpEF
- Chronic Kidney Disease
- Osteoarthritis
- Post bariatric surgery hypoglycemia (paradox)
- COVID-19 and asthma
- Chemical dependency (alcohol)
- Parkinson's and Alzheimer's disease



9. Can incretin agonists be used in patients with T1DM and Obesity on MDI?

TABLE 2 Recommended Insulin Titration for People Using an MDI Regimen or Non-AID CSII at Initiation of GLP-1 Receptor Agonist Therapy

Insulin Titration	People With TIR ≥70%*† or A1C <7%	People With TIR ≥60%*† or A1C 7–7.5%	People With TIR ≥50%* or A1C 7.5–8.5%	People With TIR <50%* or A1C >8.5%
MDI regimen				
TDD‡	↓ 25%	↓ 15–20%	↓ 5–10%	↔
Basal insulin dose§	↓ 20%	↓ 10%	↔	↔
Bolus insulin (using fixed dose, sliding scale, or ICR)	↓ 30%	↓ 20–25%	↓ 10–15%	↔
CF (ISF)	↑ 20%‖	↑ 10%	↔	↔
Non-AID CSII				
Basal infusion rates¶	↓ 20%	↓ 10%	↔	↔
ICR	↑ 30%	↑ 20–25%	↑ 10–15%	↔
CF (ISF)	↑ 20%‖	↑ 10%	↔	↔
AIT (CSII users)	↑ to 4 hours	↑ to 3–4 hours	↔	↔

*If TIR available and more recent than A1C, TIR should be prioritized for dose reduction using clinical judgment. †Ensure that TBR is <4%; if TBR >4%, reduce basal rates by an additional 10%. ‡It is important to clarify that a 30% reduction in bolus insulin and a 20% reduction in basal insulin in individuals with an A1C <7% does not equate to a 50% reduction in TDD, but approximately a TDD reduction of ~25% (rough average of the bolus and basal reductions). §We do not recommend the initial adjustment to be any different between long-acting and ultra-long-acting basal insulins, although further titration may be done less frequently with ultra-long-acting insulins. ‖Reduce strength of CF by using the 2,000 formula (2000/TDD = CF) instead of the 1,700 formula to allow for increased insulin sensitivity from GLP-1 or dual GIP/GLP-1 receptor agonist use. ¶Temp basal setting may also be used temporarily to offset any hypoglycemia while CSII parameters are being adjusted. ↔, changes may not be needed; AIT, active insulin time; CF, correction factor; ICR, insulin-to-carbohydrate ratio; ISF, insulin sensitivity factor.

Zeb I. Saeed, Halis K. Akturk, Grazia Aleppo, Davida Kruger, Carol J. Levy, Julia K. Mader, Jennifer L. Sherr, Viral N. Shah; Insulin Titration Recommendations When Using Glucagon-Like Peptide 1 Receptor Agonist Therapy in Adults With Type 1 Diabetes. Clin Diabetes 2024; cd240067. https://doi.org/10.2337/cd24-0067

10. Can incretin agonists be used in patients with T1DM and Obesity on insulin pumps?

TABLE 3. Recommended Adjustments in AID System Settings for Initiation of GLP-1 Receptor Agonist Therapy in People With Type 1 Diabetes, by System Brand

Setting Changes	MiniMed 780G	Control IQ	Omnipod 5	iLet Bionic Pancreas
Basal rate	✓*	✓†	✓*	⁄
Bolus features				
ICR	Weaken ratio by 0–30%‡	Weaken ratio by 0–30%‡	Weaken ratio by 0–30%	Use "lower than usual" meal
CF (ISF)	⁄	Weaken factor by 0–20%‡	Weaken factor by 0–20%‡	⁄
AIT	May change to 3–4 hours	⁄ (fixed at 5 hours)	May change to 3–4 hours§	⁄
Target glucose	May consider higher target glucose up to 120 mg/dL	May consider using exercise mode (140–160 mg/dL)	May consider higher glucose target (130–150 mg/dL)	May consider "higher than usual" target (130 mg/dL)

*Although the basal rate does not matter in automated mode in this pump, we suggest reducing the basal rate based on Table 2 recommendations because this setting may be used during manual mode/rescue. †Reduce the basal rate based on Table 2 recommendations. ‡Adjust bolus ICR or CF based on Table 2 recommendations from default of 100%. §AIT does not matter in automated mode for this pump but may change as suggested for manual bolus dosing. ✓, modifiable parameter; ⁄, nonmodifiable parameter or not applicable; AIT, active insulin time; CF, correction factor; ICR, insulin-to-carbohydrate ratio, ISF, insulin sensitivity factor.

Zeb I. Saeed, Halis K. Akturk, Grazia Aleppo, Davida Kruger, Carol J. Levy, Julia K. Mader, Jennifer L. Sherr, Viral N. Shah; Insulin Titration Recommendations When Using Glucagon-Like Peptide 1 Receptor Agonist Therapy in Adults With Type 1 Diabetes. Clin Diabetes 2024; cd240067. https://doi.org/10.2337/cd24-0067

11. What are the contraindications and FDA boxed warnings with therapy?

CONTRAINDICATIONS

Family or personal history of medullary thyroid carcinoma, MEN2

BOXED WARNING

Depression, suicidal ideation

Pulmonary aspiration during general anesthesia or deep sedation.

12. What are the adverse effects of therapy?

- Nausea, vomiting, bloating, GERD, dysgeusia
- Constipation, ileus progression, small bowel obstruction; rarely diarrhea
- Cholelithiasis and cholecystitis
- Pancreatitis
- Worsening depression or suicidal thoughts
- Delayed/decreased absorption of oral medications
- Hypoglycemia in patient on insulin or sulfonylurea

- Injection site reaction
- Increased heart rate
- AKI on CKD
- Dehydration after bariatric surgery
- Aspiration with anesthesia
- Diabetic retinopathy progression
- Muscle and bone loss
- Decreased thirst and kidney stones
- Anaphylaxis and angioedema
- Non-arteritic Anterior Ischemic Optic Neuropathy

13. How can we tackle the side effects of therapy?

14. What is the effect of these drugs on muscle and bone?

Implications of GLP-1-based therapies for muscle health

GLP-1-based therapies can result in weight loss with a simultaneous reduction in muscle volume

Adverse muscle composition

- In the UK Biobank study
  - 11% of the 39,000 enrolled participants had adverse muscle composition
  - Adverse muscle composition was linked to all-cause mortality
- Prevalence of adverse muscle composition is higher in participants with metabolic diseases like steatotic liver disease
- Linked to higher morbidity with increased incidence of diabetes and coronary heart disease

Studies involving liraglutide (GLP-1RA) and tirzepatide (GLP-1R/GIP-RA)

- Treatment with liraglutide or 5 mg of tirzepatide showed similar changes in muscle volume z-scores
- Tirzepatide
  - At 10 mg and 15 mg – higher weight loss and greater reductions in muscle volume z-score
- Liraglutide
  - Participants with adverse muscle composition decreased from 11.0% to 8.2%
- Placebo
  - No changes in normal muscle composition and adverse muscle composition after follow-up
  - Slight decrease in the number of participants with only high muscle fat (27.3%–21.8%)
  - Increase in proportion of participants with only low muscle volume (5.5%–12.7%)

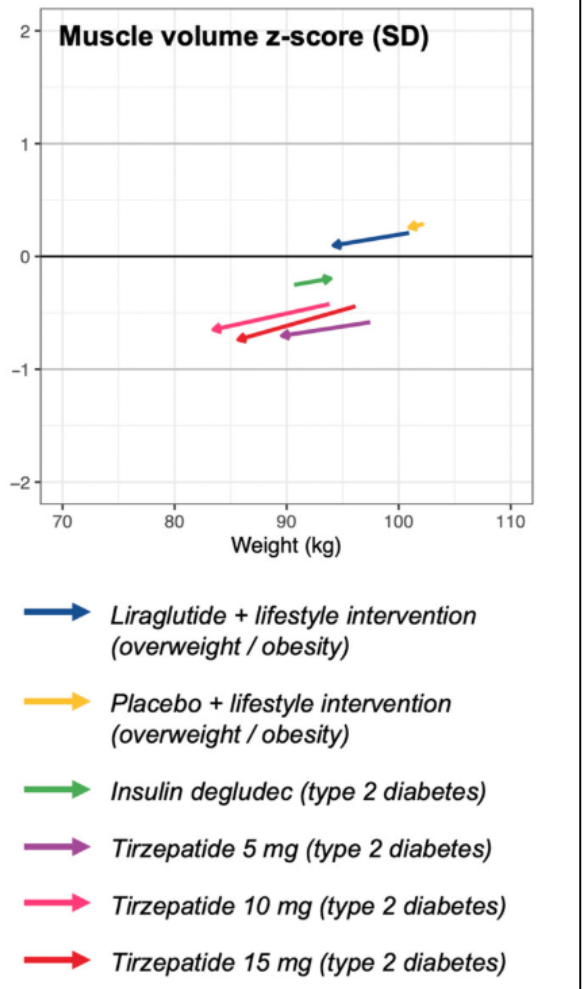
Strategies to reduce muscle loss during weight loss therapies

- Dietary modifications
  - Increased intake of proteins
    - Preserves lean mass
    - Reduces adaptive thermogenesis
    - Causes negative energy balance
  - Whey proteins
    - Can increase the secretion of insulin and GLP-1
    - High dosage requirements restrict regular use
  - Branched-chain amino acids
    - Aided the maintenance of muscle mass and improved muscle strength in post-menopausal women with sarcopenic obesity
- Exercise
  - Endurance and resistance-type exercises aid in preserving muscle mass
  - Resistance-based exercises improve muscle strength

Combining protein supplementation with resistance training exercises may further induce increases in lean body mass

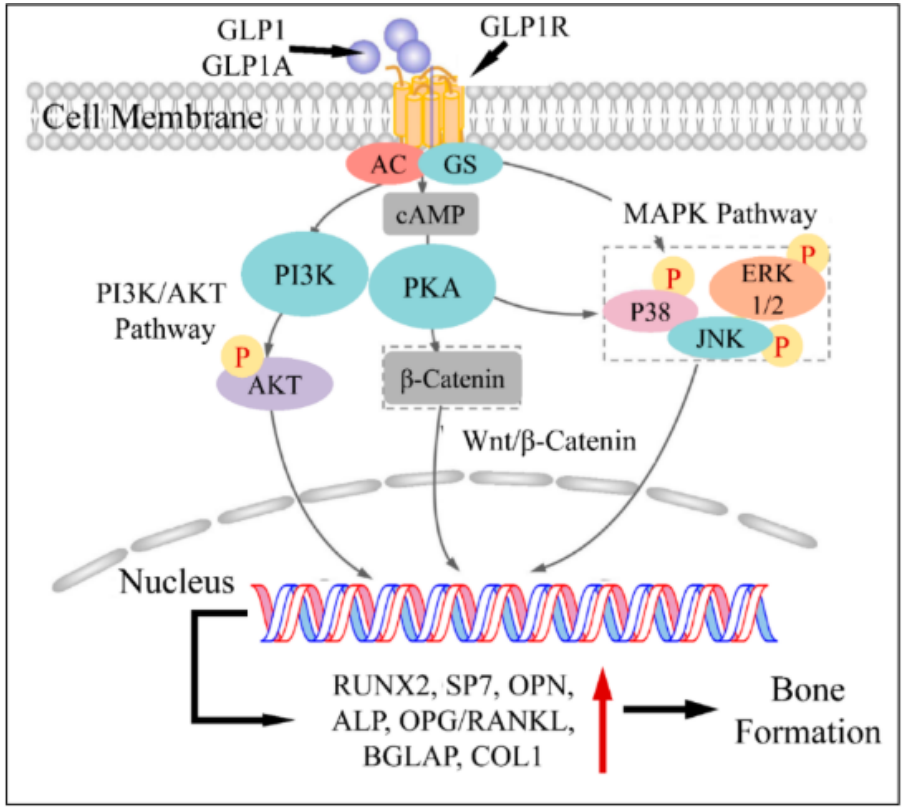
- Growth hormone
  - ✓ Improves body composition and reduces body weight
  - ✓ Reduces postoperative muscle mass loss after bariatric surgery
- Bimagrumab
  - Monoclonal antibody that binds to activin type II receptor of activin A and myostatin
  - Results in: • 6.5% loss in weight • 3.6% increase in lean mass • 20.5% reduction in fat mass

(B) Change in muscle volume z-score with liraglutide and tirzepatide.



Neeland et al. (2024) | Diabetes, Obesity and Metabolism | DOI: 10.1111/dom.15728

The controversial effects of incretin agonists on bone health



Daniilopoulou, I., Vlachou, E., Lambrou, G. I., Ntikoudi, A., Dokoutsidou, E., Fasoi, G., Govina, O., Kavga, A., & Tsartsalis, A. N. (2022). The Impact of GLP1 Agonists on Bone Metabolism: A Systematic Review. Medicina (Kaunas, Lithuania), 58(2), 224. https://doi.org/10.3390/medicina58020224

Original Investigation | Nutrition, Obesity, and Exercise

June 25, 2024

Bone Health After Exercise Alone, GLP-1 Receptor Agonist Treatment, or Combination Treatment

A Secondary Analysis of a Randomized Clinical Trial

Simon Birk Kjær Jensen, PhD[1]; Victor Sørensen, MSc[2]; Rasmus Michael Sandsdal, MD[1]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2024;7(6):e2416775. doi:10.1001/jamanetworkopen.2024.16775

Key Points

Question Does exercise alone, glucagon-like peptide-1 receptor agonist (GLP-1 RA) treatment, or both treatments combined preserve clinically relevant site-specific bone mineral density (BMD) during weight loss?

Findings In this secondary analysis of a randomized clinical trial among 195 adults with obesity, the combination of exercise and GLP-1 RA preserved hip, spine, and forearm BMD despite larger weight loss. GLP-1 RA treatment alone reduced hip and spine BMD compared with placebo or exercise alone.

Meaning These findings suggest that the addition of exercise to GLP-1 RA treatment is an effective weight loss strategy while preserving bone health.

BREAKING NEWS!!

Amgen speaks out about bone density concerns with obesity drug

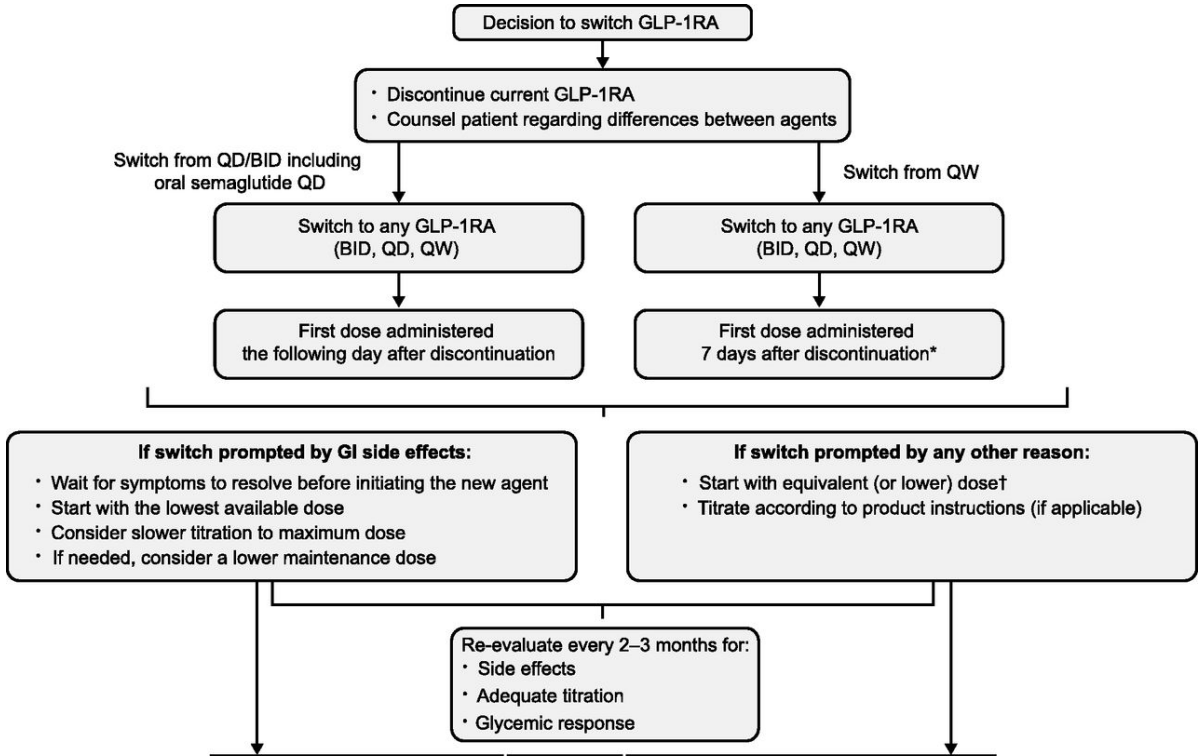
Amgen's stock fell 7% after an analyst posted a note on MariTide's influence on bone density which was noticed in a data spreadsheet.

Ross Law | November 14, 2024

KEY POINTS

- Amgen said there is no link between its experimental weight loss drug, MariTide, and changes in bone density.
- The statement comes a day after that potential safety concern wiped off more than $12 billion from its market value.
- Analysts chewed over early data showing the highest dose of Amgen's MariTide was linked to roughly 4% loss of bone mineral density over 12 weeks.

15. Can one switch between incretin agonists?



Agent	Frequency	Equivalent Dose†			
Exenatide	QW			2 mg	
Dulaglutide	QW		0.75 mg	1.5 mg	
Semaglutide	QW		0.25 mg	0.5 mg	1 mg
Liraglutide	QD	0.6 mg	1.2 mg	1.8 mg	
Lixisenatide	QD	10 µg	20 µg		
Oral semaglutide	QD	3 mg	7 mg	14 mg	
Exenatide	BID	5 µg	10 µg		

Almandoz, J. P., Lingvay, I., Morales, J., & Campos, C. (2020). Switching Between Glucagon-Like Peptide-1 Receptor Agonists: Rationale and Practical Guidance. Clinical diabetes : a publication of the American Diabetes Association, 38(4), 390–402. https://doi.org/10.2337/cd19-0100

Guidance on stopping/restarting therapy

Agent	Last dose administered	Recommendation(s) for resuming therapy
Dulaglutide	1.5 mg once weekly 3 or 4.5 mg once weekly	▪ Resume at 1.5 mg once-weekly dose. ▪ Expect comparable tolerability to that experienced prior to dose interruption. ▪ Use best judgment if ≥3 doses are missed. • It is unknown whether tolerance to the GI adverse events will remain if reinitiated at the higher dose after ≥3 missed doses. • Decision can be informed by patient's prior GI tolerability. • In consideration of the above, clinicians may consider reinitiating at 1.5 mg once weekly.
Injectable semaglutide	1 mg once weekly	▪ If ≤2 doses are missed, reinitiate at 1 mg once weekly. ▪ If 3 to 4 doses are missed, reinitiate at 0.5 mg weekly. ▪ If ≥5 doses are missed, reinitiate at 0.25 mg once weekly.
Tirzepatide	≥5 mg once weekly	▪ If ≤2 doses are missed, reinitiate at the same dose (provided the dose was adequately tolerated). ▪ If ≥3 doses are missed, reinitiate at 5 mg once weekly.

16. Which are the insulin-incretin combinations available in the market and their advantages?

1. Xultophy (insulin degludec + liraglutide)

Doses: Naïve: 10 units + 0.36mg; On previous therapy: 16 units + 0.58mg; titrate upwards or downwards by 2 units (insulin degludec 2 units/liraglutide 0.072 mg) once or twice weekly (every 3 to 4 days) until the desired fasting plasma glucose is achieved. Maximum dose: 50 units (insulin degludec 50 units/liraglutide 1.8 mg)/day.

2. Soliqua (insulin glargine + lixisenatide)

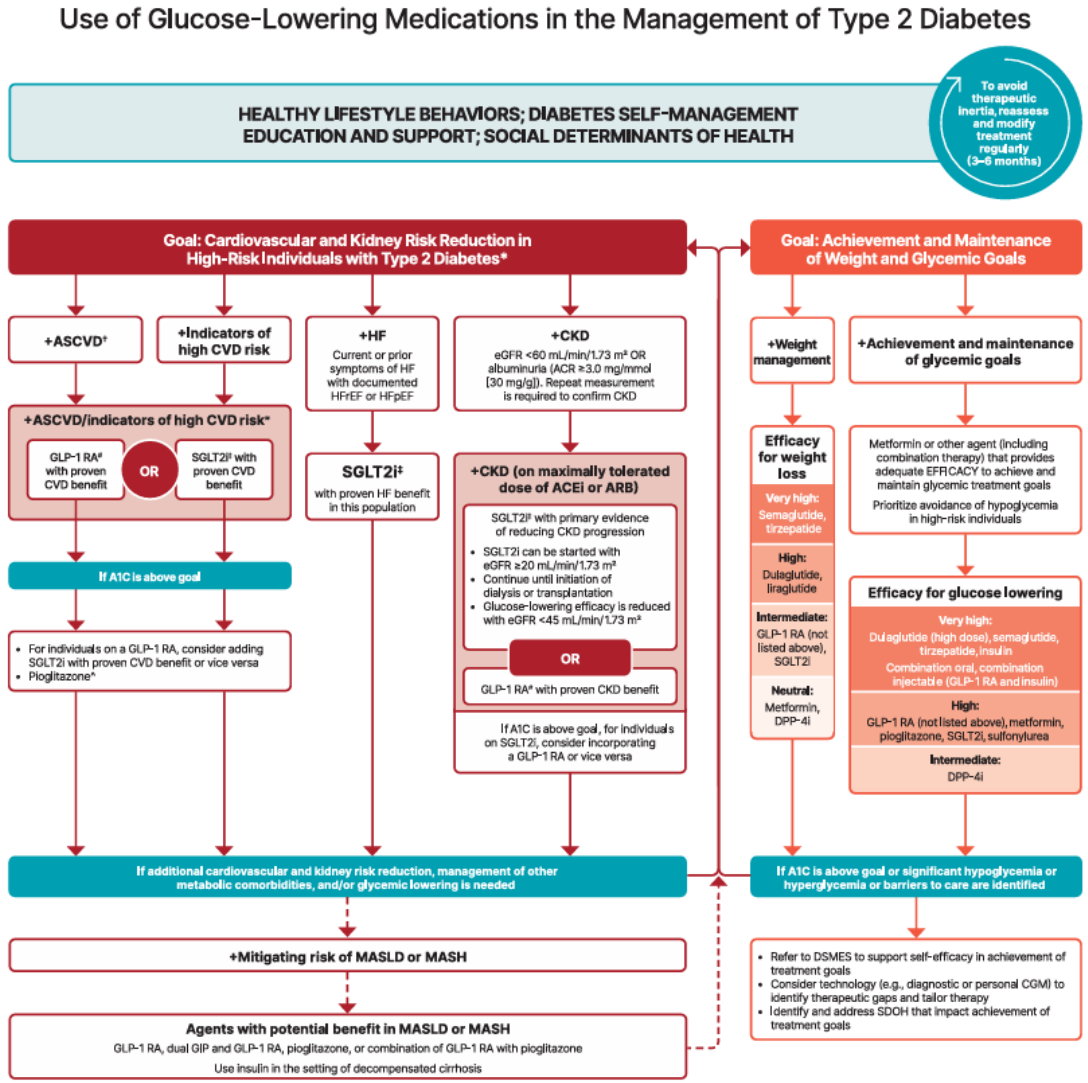
Doses: Naïve: 15 units + 5mcg; On previous therapy 30 units + 10mcg; titrate the dosage upwards or downwards by 2 to 4 units (insulin glargine 2 to 4 units/lixisenatide 0.66 to 1.32 mcg) every week until the desired fasting plasma glucose is achieved. Maximum dose 60 units (insulin glargine 60 units/lixisenatide 20 mcg)/day.

-Improved adherence to therapy

-Older patients

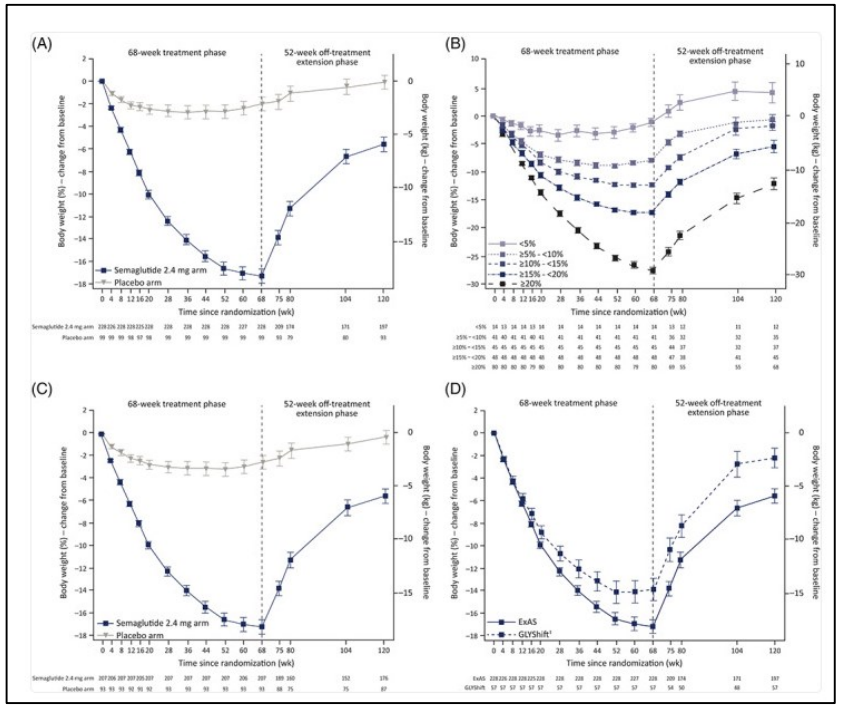
-Needle phobia

17. When should the drugs be initiated per the ADA 2025 algorithm?

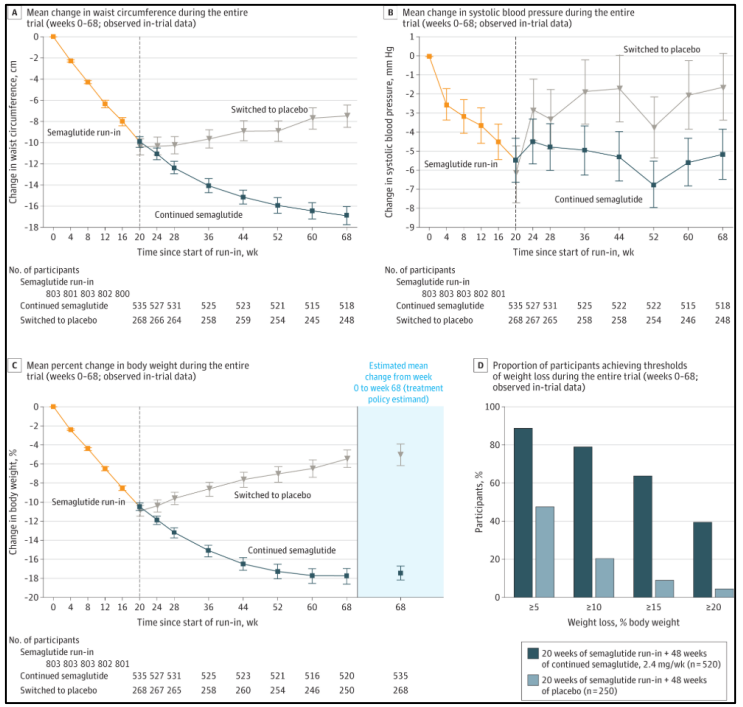


18. Can incretin agonists be dose-reduced or stopped once target weight is achieved?

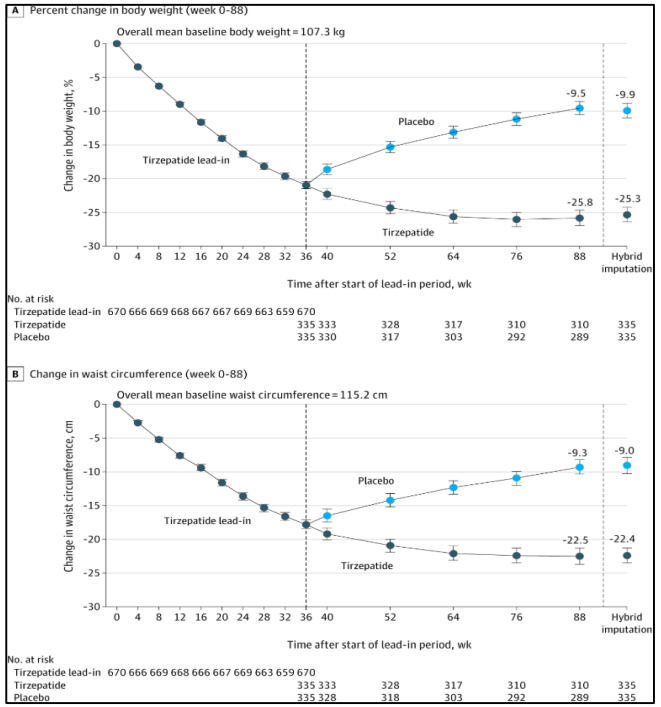
STEP 1 extension trial



STEP 4 withdrawal trial



SURMOUNT 4 trial



Obesity A Research Journal

THE OBESITY SOCIETY

ORIGINAL ARTICLE | Open Access

Weight maintenance on cost-effective antiobesity medications after 1 year of GLP-1 receptor agonist therapy: a real-world study

Nina U. Paddu, Brianna Lawrence, Sydnee Wong, Sabrina J. Poon, Gitanjali Srivastava

First published: 18 November 2024 | https://doi.org/10.1002/oby.24177 | Citations: 1

Study Importance

What is already known?

- Glucagon-like peptide-1 (GLP-1) receptor agonist (RA) medications have demonstrated effectiveness in weight reduction. However, discontinuation often leads to weight regain.
- Long-term access to GLP-1 RA medications faces several barriers, including insurance coverage gaps, cost considerations, and supply issues from manufacturers.

What does this study add?

- Older-generation antiobesity medications (AOMs) can mitigate weight regain commonly observed after discontinuing GLP-1 RA therapy.
- In a real-world study, individuals maintained their weight loss for up to 24 months by transitioning from 12-month GLP-1 RA therapy to generic AOMs.
- The most frequently used AOMs for weight maintenance after GLP-1 RA therapy were metformin (used by 80% of patients), topiramate (used by 32.5% of patients), and bupropion (used by 32.5% of patients).

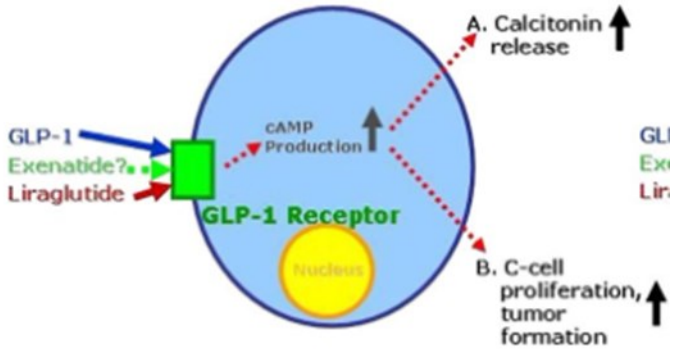
How might these results change the direction of research or the focus of clinical practice?

- Given challenges with long-term GLP-1 RA access, second-generation AOM therapy could offer an effective and affordable solution to prevent weight regain.
- Patients who respond well to GLP-1 RA therapy within the first year may be suitable candidates for transitioning to generic AOMs after 12 months.
- Future research should explore the long-term efficacy of older-generation AOMs following initial GLP-1 RA treatment across a broader and more diverse patient population to validate these findings.

19. Do these drugs increase the risk of cancer?

A theoretical increased risk of:

- Medullary thyroid carcinoma
- Papillary thyroid carcinoma



Original Investigation | Pharmacy and Clinical Pharmacology

January 4, 2024

Glucagon-Like Peptide-1 Receptor Agonists and Pancreatic Cancer Risk in Patients With Type 2 Diabetes

Rachel Dankner, MD, MPH[1,2]; Havi Murad, PhD[3]; Nirit Agay, PhD[1,3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2024;7(1):e2350408. doi:10.1001/jamanetworkopen.2023.50408

Key Points

Question Is treatment with glucagon-like peptide-1 receptor agonists (GLP-1RA) of patients with type 2 diabetes associated with excess risk of pancreatic cancer?

Findings In this cohort study of 543 595 patients, compared with treatment with basal insulin, treatment of comparable patients with type 2 diabetes with GLP-1RA was not associated with excess risk of pancreatic cancer.

Meaning Using several analytic approaches, these findings do not suggest an increase in pancreatic cancer incidence over 7 years following start of GLP-1RA treatment.

20. Do we need to monitor for thyroid cancer on these drugs?

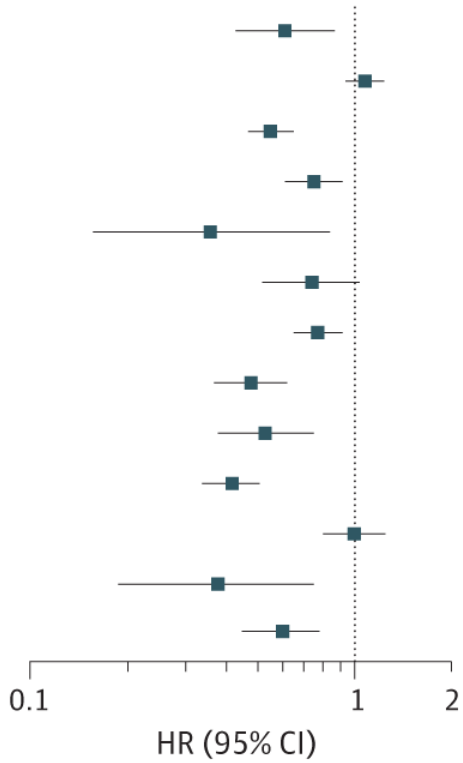
- Counsel patients regarding the potential risk for MTC with the use of incretin receptor agonists and inform them of symptoms of thyroid tumors (eg, a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

- Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with incretin receptor agonists.

- Causes of falsely elevated calcitonin: hypercalcemia, renal failure, pancreatitis, Graves' disease, gastritis, pernicious anemia, GI bleed, stress, trauma, MI, ZE syndrome, smoking, alcohol, pancreatitis, prostate and breast CA, sepsis

21. Do these drugs decrease the risk of cancer?

Outcome (N = 1 651 452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48 983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1 044 745)	HR (95% CI)
Esophageal cancer (n = 48 437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13 768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48 443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25 750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48 587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48 449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48 322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48 397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25 739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48 490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48 527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48 518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48 527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes. JAMA Netw Open. 2024;7(7):e2421305. doi:10.1001/jamanetworkopen.2024.21305

22. Should the drugs be stopped prior the surgery?

- **New Multi-Society guideline released 10/29/2024: Most Patients Can Continue Diabetes, Weight Loss GLP-1 Drugs Before Surgery, Those at Highest Risk for GI Problems Should Follow Liquid Diet Before Procedure.**

- The team should take into account patient-specific risk factors for delayed stomach emptying and consider the following guidance for patients at highest risk:

1. Patients in the escalation phase of GLP-1 drugs (early in treatment) are more likely to have delayed stomach emptying.
2. 2Patients who have GI symptoms, including nausea, vomiting, abdominal pain, shortness of breath or constipation should wait until their symptoms have dissipated before proceeding with elective surgery.
3. Patients on a higher dose of the GLP-1 drug typically have more GI side effects and should follow a liquid diet for 24 hours before the procedure.
4. Patients with other medical conditions that slow stomach emptying, such as Parkinson's disease may further modify the perioperative management plan

23. Can the medications be used during pregnancy and lactation?

- Pregnant rats: increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body
- Pregnant rabbits: maternal mortality or abortion in a few rabbits occurred at all dose levels.

Breastfeeding: no data
Stop 2 months prior to planned pregnancy

Original Investigation

December 11, 2023

Safety of GLP-1 Receptor Agonists and Other Second-Line Antidiabetics in Early Pregnancy

Carolyn E. Cesta, PhD[1]; Ran Rotem, ScD[2,3]; Brian T. Bateman, MD, MSc[4]; et al

Author Affiliations | Article Information

JAMA Intern Med. 2024;184(2):144-152. doi:10.1001/jamainternmed.2023.6663

January 3, 2024

First Large Study of GLP-1 Receptor Agonists During Pregnancy

Emily Harris

Article Information

JAMA. 2024;331(4):280. doi:10.1001/jama.2023.26112

24. What are the potential medication adjustments that need to be made while using incretin agonists?

- HIV medications
- Levothyroxine
- Antiseizure medications
- Warfarin
- OCP

-Delayed absorption of drugs

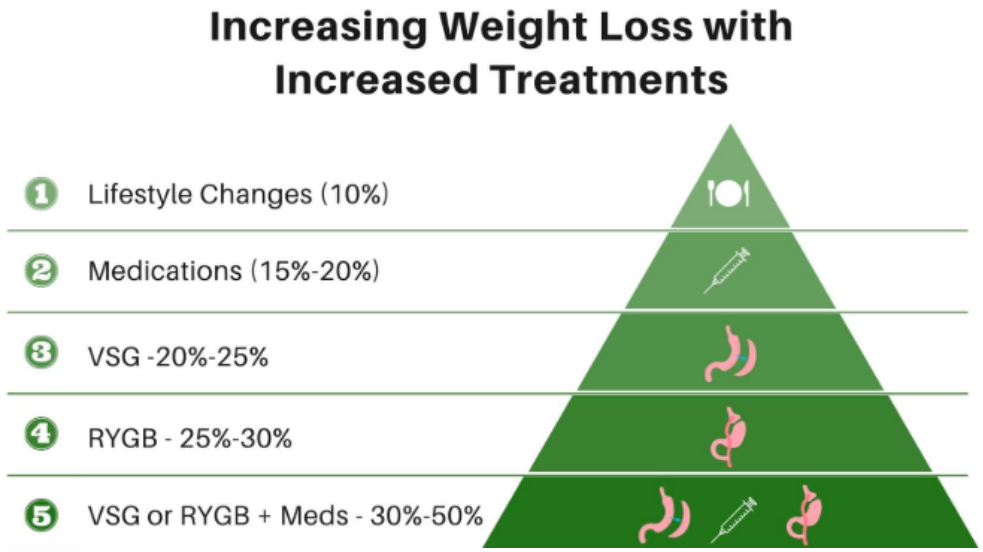
-Rybelsus (empty stomach)

25. What is the advice regarding contraceptives measures on these medications?

- Unreliable absorption of OCP
- Use alternate form of contraception
- OR can add a barrier method of contraception for 4 weeks after initiation of therapy and 4 weeks after each dose escalation
- “Mounjaro/Ozempic babies”: rapid improvement in fertility and unreliable OCP

26. In the age of medical weight loss drugs, is there still a role of bariatric surgery?

- A more than 2-fold increase in use of GLP-1 RAs as anti-obesity medications from 2022 to 2023, with a 25.6% decrease in the rate of metabolic bariatric surgery during the same period
- Mortality benefit for MBS
- MBS still has more significant weight reduction
- Incretin agonists before enrolling in MBS
- Tackling post MBS weight gain (also ?substance use) with GLP-1s



Lin K, Mehrotra A, Tsai TC. Metabolic Bariatric Surgery in the Era of GLP-1 Receptor Agonists for Obesity Management. JAMA Netw Open. 2024;7(10):e2441380. doi:10.1001/jamanetworkopen.2024.41380

Dicker D, Sagy YW, Ramot N, et al. Bariatric Metabolic Surgery vs Glucagon-Like Peptide-1 Receptor Agonists and Mortality. JAMA Netw Open. 2024;7(6):e2415392. doi:10.1001/jamanetworkopen.2024.15392

27. Are there patient assistance programs for these drugs?

- Lilly Cares: Trulicity
- Novo Nordisk: Ozempic, Rybelsus, Victoza, Xultophy

Who can participate in the Patient Assistance Program?

To be eligible for this program, you must:

- Be a US citizen or legal resident
- Have a total household income that is at or below 400% of the federal poverty level (FPL). Visit the NeedyMeds website, which lists the current FPL guidelines
- Have Medicare or no insurance (Note: If you have private or commercial insurance, you are not eligible for the PAP)
- Not be enrolled in or qualify for any other federal, state, or government program such as Medicaid, Low Income Subsidy, or Veterans Affairs (VA) Benefits
    - If you are eligible for Medicaid, you must sign the Patient Declaration section of the latest version of the PAP application stating that you are not enrolled in, plan to enroll in, or are eligible for Medicaid or Medicare Extra Help/LIS (proof of denial must be submitted if requested)

28. What is the FDA position statement on compounded formulations of these drugs?

- Compounded drugs are not FDA approved
- FDA received multiple reports of adverse events, some requiring hospitalization, that may be related to dosing errors associated with compounded injectable semaglutide products. These dosing errors resulted from patients measuring and self-administering incorrect doses of the drug, and in some cases, health care professionals miscalculating doses of the drug.
- As of November 30, 2024, FDA has received:

-more than 392 reports of adverse events with compounded semaglutide.

-more than 215 reports of adverse events with compounded tirzepatide.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1-drugs-used-weight-loss

29. Is there coverage for patients with MediCare and Medicaid? Are generic versions available?

- **Medicare Part D:** Plans cover GLP-1 drugs that the FDA has approved for treating type 2 diabetes (T2DM) and cardiovascular disease (CVD). As of August 2024, these drugs include Ozempic, Mounjaro, Rybelsus, and Wegovy. However, Medicare is currently prohibited from covering GLP-1 drugs for obesity.

- **Medicaid:** Medicaid programs are required to cover GLP-1s for type 2 diabetes, including Ozempic (semaglutide), Rybelsus (semaglutide), Victoza (liraglutide), and Mounjaro (tirzepatide). As of August 2024, 13 states cover GLP-1s for obesity, including California, Kansas, Minnesota, Wisconsin, Michigan, Mississippi, Pennsylvania, Virginia, North Carolina, Massachusetts, New Hampshire, Delaware, and Rhode Island.

- Liraglutide generic approved as of: 12/23/2024

- The politics of Obesity management

30. Which drugs are in the pipeline for the near future?

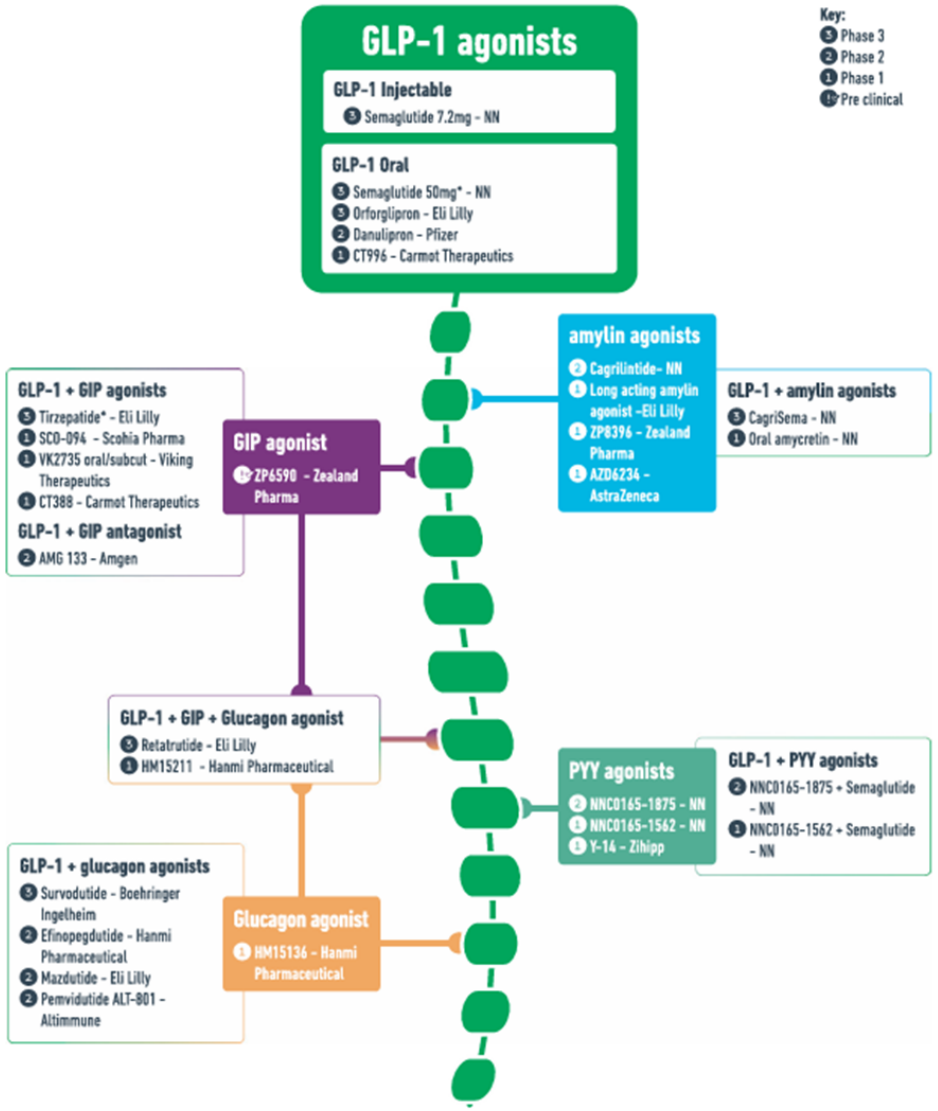
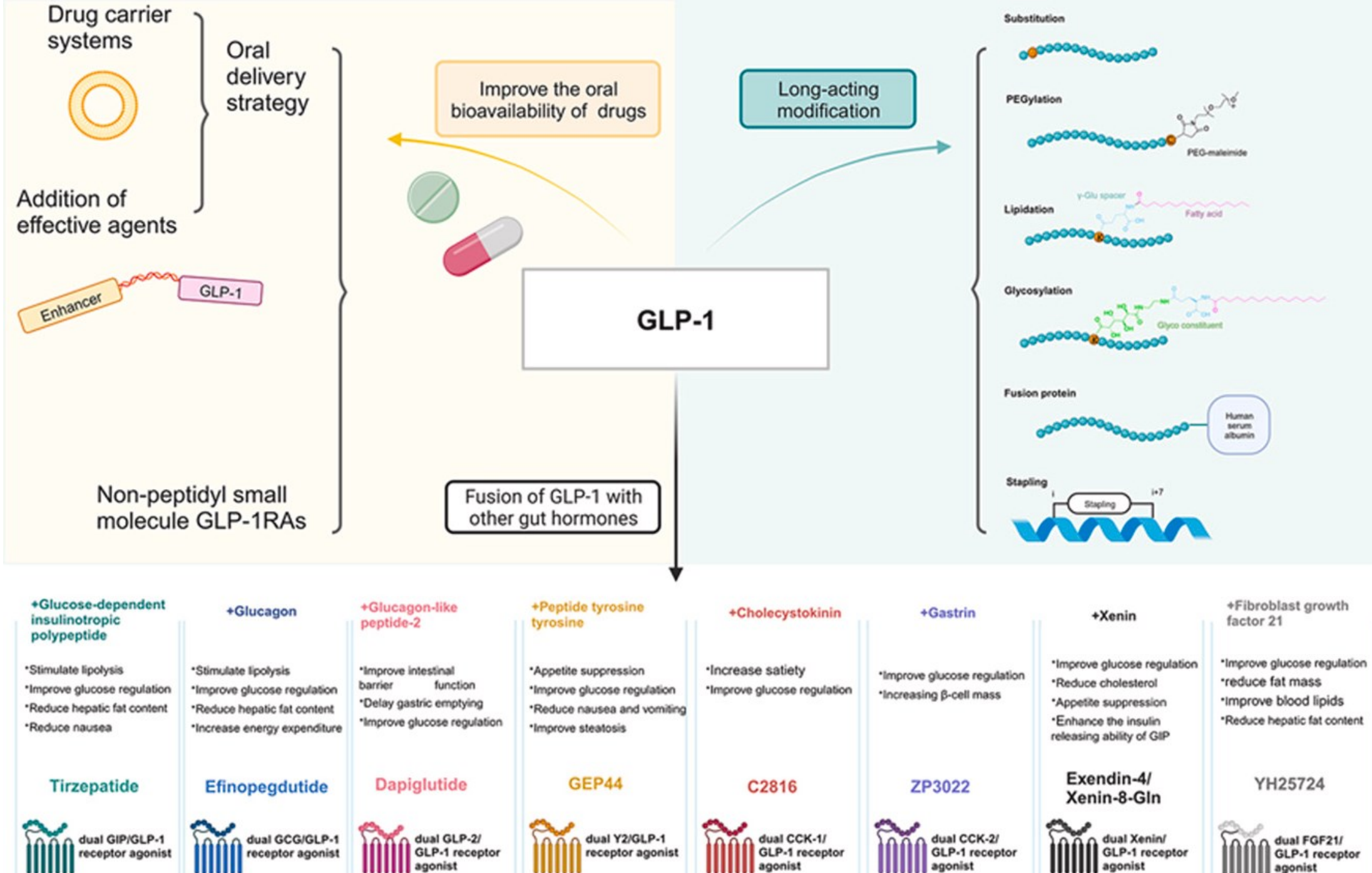


Fig. 2 Glucagon-like peptide-1 as the backbone of the pipeline for gut hormone-based obesity treatments. GLP-1 glucagon like peptide-1, GIP glucose-dependent insulinotropic polypeptide, PYY peptide YY, NN: novo nordisk, *completed phase 3 trials for obesity.


Drug carrier systems
Oral delivery strategy
Addition of effective agents
Enhancer
GLP-1
Non-peptidyl small molecule GLP-1RAs
Improve the oral bioavailability of drugs
Long-acting modification
GLP-1
Fusion of GLP-1 with other gut hormones
Substitution
PEGylation
PEG-maleimide
Lipidation
γ-Glu spacer
Fatty acid
Glycosylation
Glyco constituent
Fusion protein
Human serum albumin
Stapling
i
i+7
Stapling
+Glucose-dependent insulinotropic polypeptide
•Stimulate lipolysis
•Improve glucose regulation
•Reduce hepatic fat content
•Reduce nausea
Tirzepatide
dual GIP/GLP-1 receptor agonist
+Glucagon
•Stimulate lipolysis
•Improve glucose regulation
•Reduce hepatic fat content
•Increase energy expenditure
Efinopegdutide
dual GCG/GLP-1 receptor agonist
+Glucagon-like peptide-2
•Improve intestinal barrier function
•Delay gastric emptying
•Improve glucose regulation
Dapiglutide
dual GLP-2/ GLP-1 receptor agonist
+Peptide tyrosine tyrosine
•Appetite suppression
•Improve glucose regulation
•Reduce nausea and vomiting
•Improve steatosis
GEP44
dual Y2/GLP-1 receptor agonist
+Cholecystokinin
•Increase satiety
•Improve glucose regulation
C2816
dual CCK-1/ GLP-1 receptor agonist
+Gastrin
•Improve glucose regulation
•Increasing β-cell mass
ZP3022
dual CCK-2/ GLP-1 receptor agonist
+Xenin
•Improve glucose regulation
•Reduce cholesterol
•Appetite suppression
•Enhance the insulin releasing ability of GIP
Exendin-4/ Xenin-8-Gln
dual Xenin/ GLP-1 receptor agonist
+Fibroblast growth factor 21
•Improve glucose regulation
•reduce fat mass
•improve blood lipids
•Reduce hepatic fat content
YH25724
dual FGF21/ GLP-1 receptor agonist

Take Home Points

- The uses of incretin agonists are vastly expanding beyond just type 2 diabetes: One cure for all?
- Not a substitute for lifestyle interventions
- Risk, benefit, cost, insurance coverage, contraindications, side effects must be addressed prior to starting the drug.
- No significant increase in cancer risk; rather these drugs can decrease the risk of obesity related cancers.
- Newer incretin agonists are slowly matching MBS in terms of weight reduction.
- Strategies to address muscle and bone loss are vital. Fluid, fiber, protein, exercise is the mantra.
- Long term safety data, reproductive data unknown.
- Use of prescription drugs only, avoiding the use of compounded versions of the drug.