Shaping the future management of obesity.

Zealand Pharma
Obesity R&D Event

December 5th, 2023

Forward-looking statements

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Agenda

December 5th, 2023,
from 1.30–4.30 pm GMT

		Presenter(s)	Time
1	Welcome and introduction to speakers	Anna Krassowska	5 min
2	The obesity pandemic	Adam Steensberg	15 min
3	Targeting obesity and low-grade inflammation with GLP-1/GLP-2 receptor agonists – ***dapiglutide***	Daniel Drucker David Kendall	40 min including Q&A
4	**Break**		20 min
5	Amylin: a next-generation weight-loss medication, representing an alternative to GLP-1 receptor agonists – ***petrelintide***	Louis Aronne David Kendall	40 min including Q&A
6	Targeting obesity and NASH with glucagon/GLP-1 receptor agonists – ***survodutide***	Carel Le Roux David Kendall	40 min including Q&A
7	Concluding remarks	Adam Steensberg	10 min

GLP-1=glucagon-like peptide-1; GLP-2=glucagon-like peptide-2; NASH=nonalcoholic steatohepatitis.

Today’s Zealand Pharma speakers

Adam Steensberg

President and
Chief Executive Officer

David Kendall

Chief Medical Officer and
Head of Research & Development

Today’s external speakers

Dr. Daniel Drucker

Professor of Medicine
at the University of Toronto

Dr. Louis Aronne

Professor of Clinical
Medicine at Weill
Cornell Medicine

Dr. Carel Le Roux

Professor of Experimental
Pathology at University
College Dublin

By embracing this historic opportunity, and rising to the challenge together, we can address one of the biggest health crises of our time.

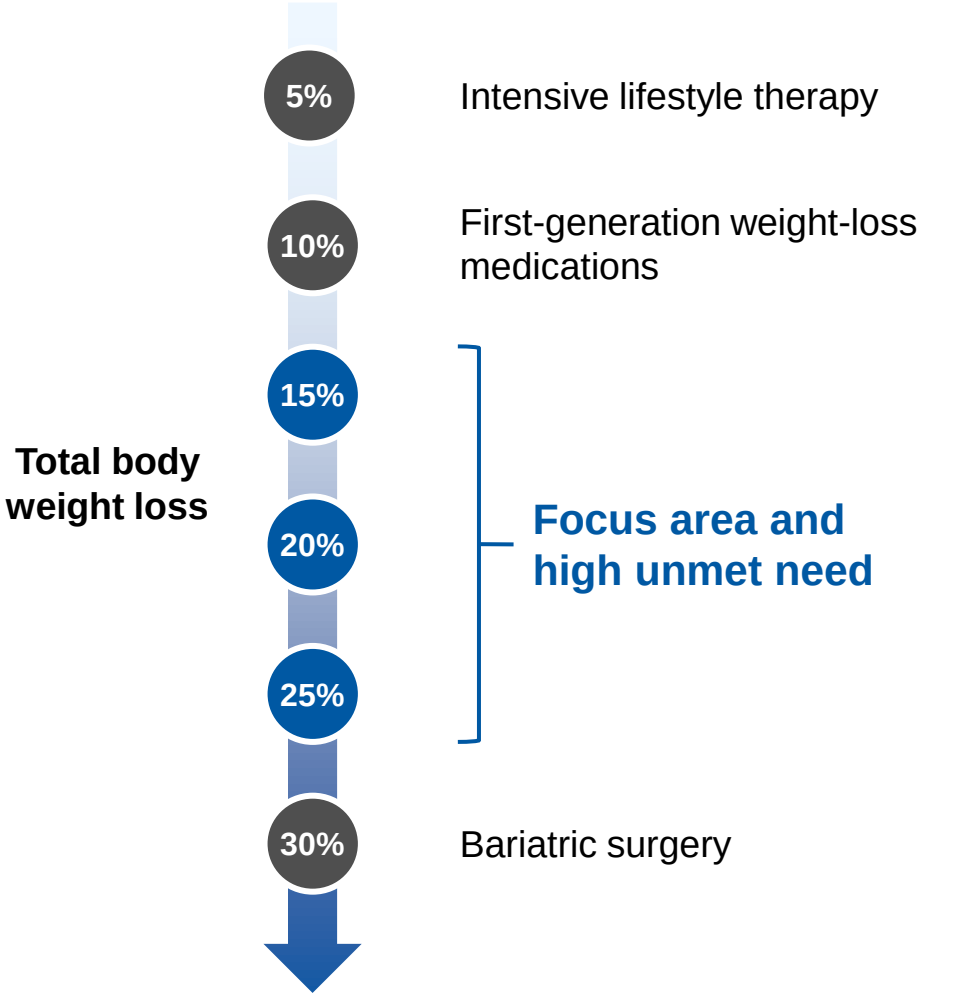
Our mission

We are committed to changing lives with next generation peptide therapeutics.

Our ambition

We strive to be the world's best peptide drug discovery and development company.

We believe in a shift from maximizing weight loss towards quality of weight loss and effects on comorbidities…



Segment characteristics and drivers

Payer-reimbursed segment (prescriber-driven)

Demand driven by health outcomes data

- Relative weight loss
- Comorbidity risk reduction
- Safety
- Tolerability

Self-pay segment (consumer-driven)

Demand driven by ‘quality’ and convenience

- Desired weight loss
- Tolerability
- Convenience and administration
- Patients’ willingness-to-pay

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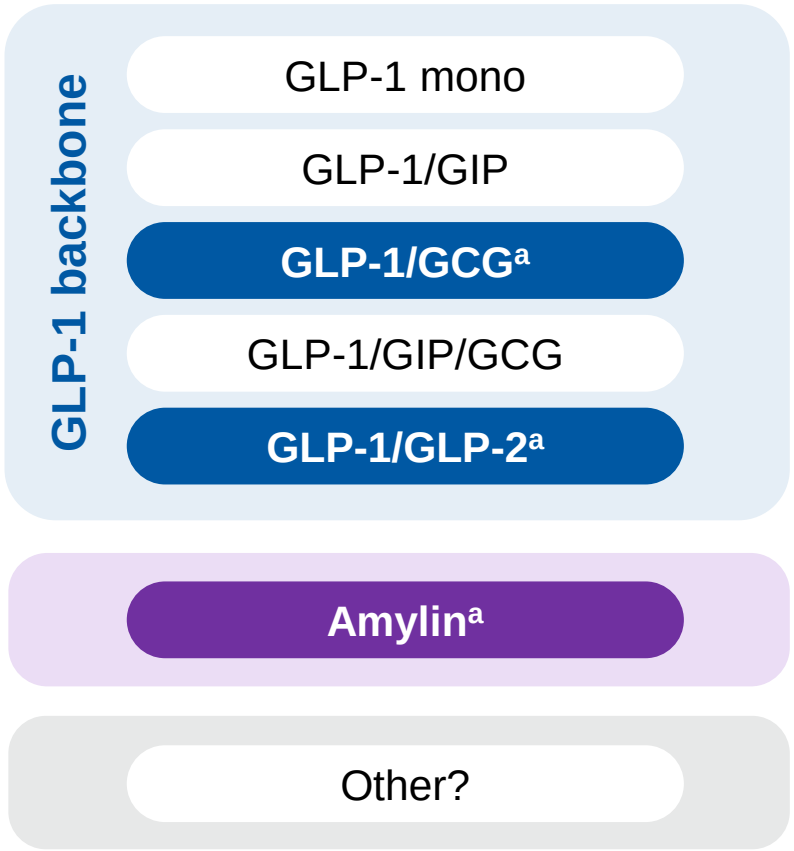
...and that success of future weight-loss medications will be determined by differentiation on multiple fronts

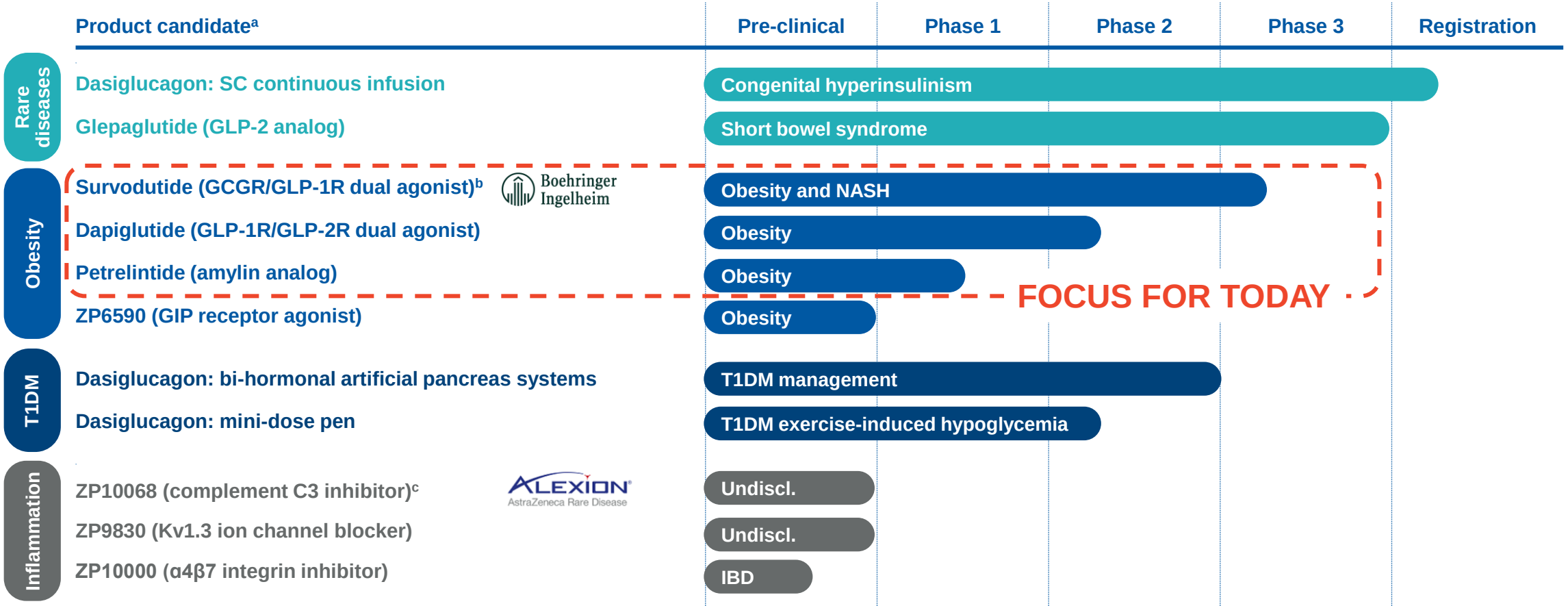


Examples of differentiation factors

- Effects on obesity-related **comorbidities**
- **Improved tolerability** by addressing GI side effects
- Unique **non-incretin mechanisms**
- Offer **greater convenience** through dosing regimen and/or delivery method
- Develop fixed or loose **'flexible-use' combinations** for patient segments that need the highest weight loss

[a]Zealand Pharma clinical development pipeline.
Content developed by Zealand Pharma.
GCG=glucagon; GI=gastrointestinal; GIP=gastric inhibitory polypeptide; GLP-1=glucagon-like peptide-1; GLP-2=glucagon-like peptide-2.

Our research and development pipeline addresses unmet medical needs across several therapeutic areas



[a]Investigational compounds whose safety and efficacy have not been evaluated or approved by the FDA or any other regulatory authority; [b]co-invented by Boehringer Ingelheim and Zealand: EUR €345 million outstanding potential development, regulatory and commercial milestones, including EUR €30 million upon Phase 3 initiation and high single to low double digit percentage royalties on global sales to Zealand; [c]licensed to Alexion: USD $610 million potential development, regulatory and commercial milestones and high single to low double digits percentage royalties on net sales.
Content developed by Zealand Pharma.
FDA=US Food and Drug Administration; GCGR=glucagon receptor; GIP=gastric inhibitory polypeptide; GLP-1R=glucagon-like peptide-1 receptor; GLP-2=glucagon-like peptide-2; GLP-2R=glucagon-like peptide-2 receptor; IBD=inflammatory bowel disease; NASH=nonalcoholic steatohepatitis; SC=subcutaneous; T1DM=type 1 diabetes mellitus.

Targeting obesity and low-grade inflammation with GLP-1/GLP-2 receptor agonists

Dapiglutide

December 5th, 2023

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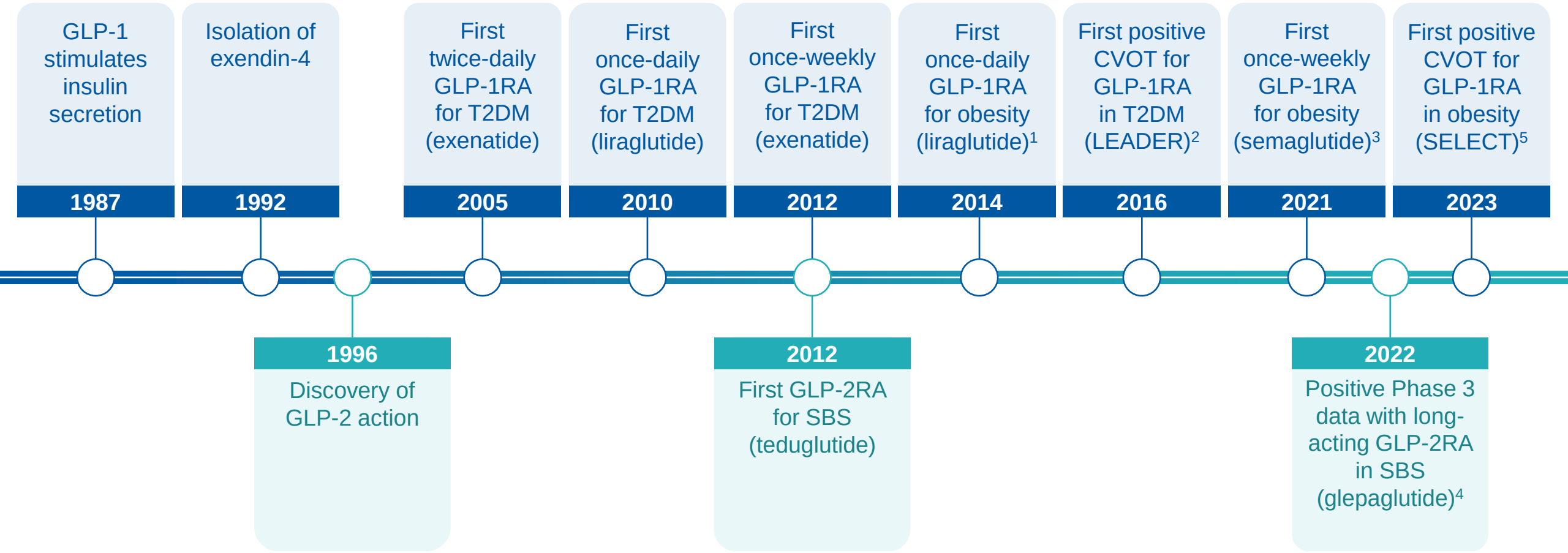
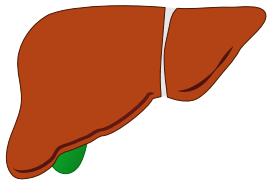
The discovery and development of glucagon-like peptides



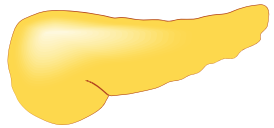
Sources: Figure adapted from Drucker et al. J Clin Invest 2017;127(12):4217–4227, with permission from the American Society for Clinical Investigation conveyed through Copyright Clearance Center Inc.; 1. FDA NDA approval letter. Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf, accessed November 2023; 2. Marso et al. N Engl J Med 2016;375(4):311–322; 3. FDA press release. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-chronic-weight-management-first-2014, accessed November 2023; 4. Zealand Pharma press release. Available at https://www.globenewswire.com/news-release/2022/09/30/2525830/0/en/Zealand-Pharma-Announces-Positive-Results-from-Phase-3-Trial-of-Glepaglutide-in-Patients-with-Short-Bowel-Syndrome-EASE-1.html, accessed November 2023; 5. Novo Nordisk press release. Available at https://www.novonordisk.com/news-and-media/news-and-ir-materials/news-details.html?id=166301, accessed November 2023.
CVOT=cardiovascular outcome trial; GLP-1=glucagon-like peptide-1; GLP-1RA=glucagon-like peptide-1 receptor agonist; GLP-2=glucagon-like peptide-2; GLP-2RA=glucagon-like peptide-2 receptor agonist; SBS=short bowel syndrome; T2DM=type 2 diabetes mellitus.

GLP-1 reduces appetite, delays gastric emptying, and regulates glycemic control

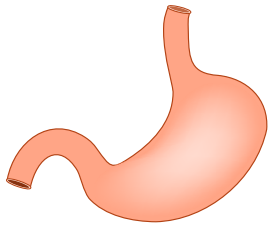
- ↓ Appetite
- ↓ Food intake



- ↓ Hepatic steatosis
- ↓ Lipid content



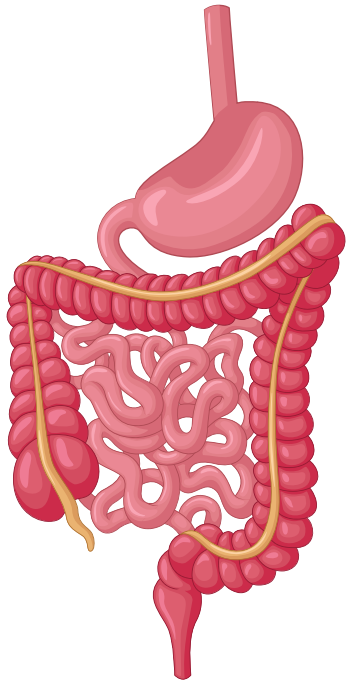
- ↑ Insulin secretion



- ↓ Gastric emptying
- ↓ GI motility

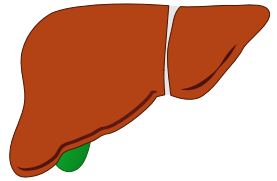
Source: Figure adapted from Wang et al. Front Endocrinol (Lausanne) 2023;14:1085799, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The figure has been reformatted. The publication is available at https://doi.org/10.3389/fendo.2023.1085799.
GI=gastrointestinal; GLP-1=glucagon-like peptide-1.

GLP-2 enhances intestinal repair and potentially has beneficial effects on other organs as well

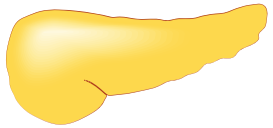


- ↓ Inflammation[1]
- ↓ Epithelium apoptosis[1]
- ↓ GI motility[1]
- ↓ Gastric acid secretion[1]
- ↓ Gut permeability[1]
- ↑ Crypt cell proliferation[1]
- ↑ Blood flow[1]
- ↑ Nutrient absorption[1]

- ↓ Inflammation[2]
- ↓ GI motility[1]
- ↓ Blood pressure[1]
- ↓ Food intake[1]



- ↓ Inflammation[1]
- ↓ Stellate cell activation[3,4]



- ↑ Glucagon secretion[1]

Sources: 1. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 2. Nuzzo et al. Neurobiol Dis 2019;121:296–304; 3. Fuchs et al. JCI Insight 2020;5(8):e136907; 4. Fuchs et al. Cell Mol Gastroenterol Hepatol 2023;16(5):847–856.
GI=gastrointestinal; GLP-2=glucagon-like peptide-2.

People with obesity have increased low-grade inflammation, which drives several related comorbidities

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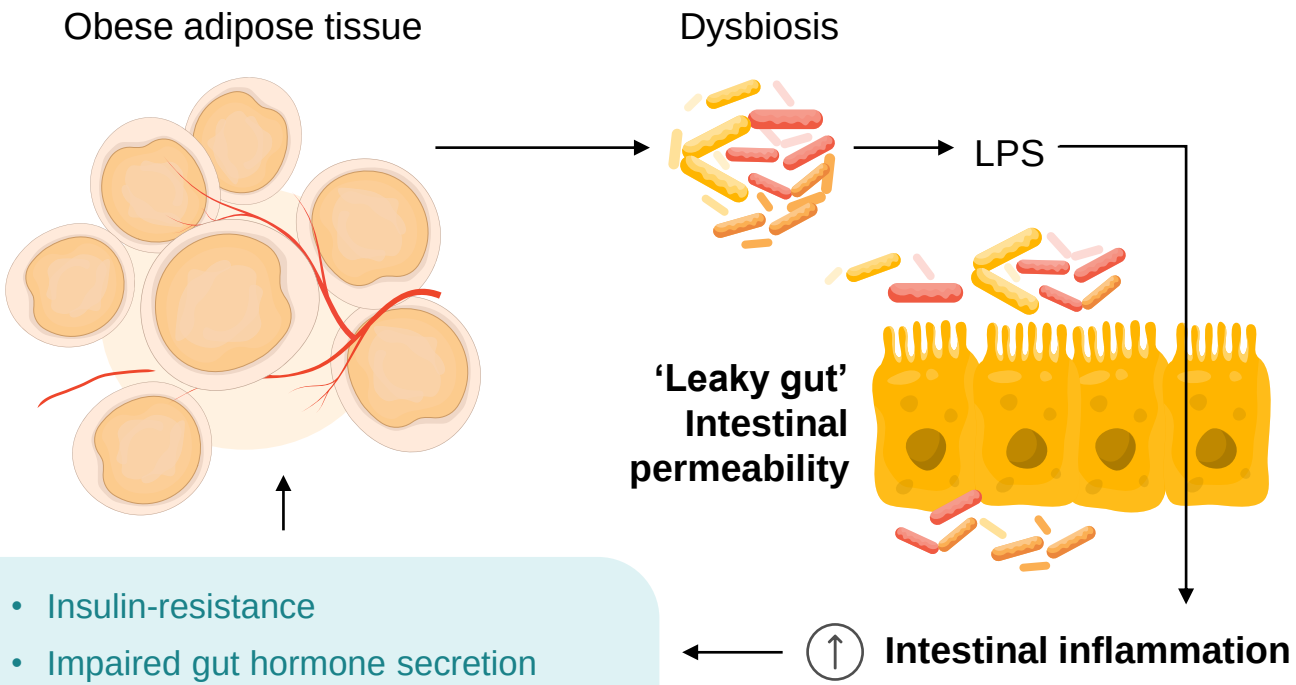
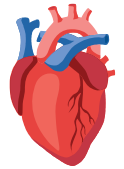
Excess fat storage can trigger low-grade systemic inflammation through reduced intestinal barrier integrity[1]

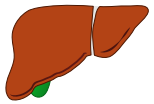


- Insulin-resistance
- Impaired gut hormone secretion
- Dysregulation of gut–brain–fat axis

Obesity-related low-grade inflammation can result in:



CVD as increased inflammation drives residual risk in people with CVD[2]



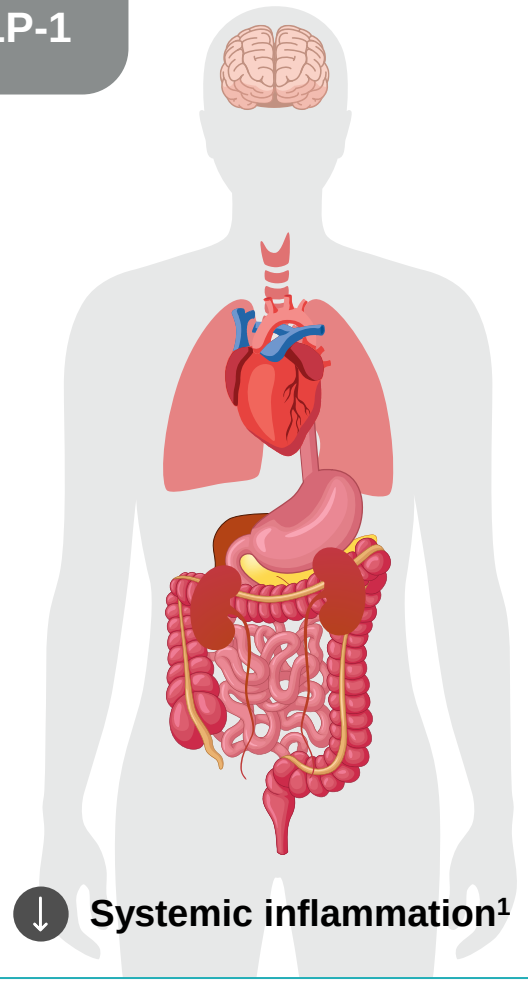
Liver disease due to abnormal accumulation of triglycerides in the liver[3]

Neuro-inflammation due to excess circulating proinflammatory cytokines and changes in the integrity of the blood–brain barrier[4]

Sources: 1. Figure adapted from Vetrani et al. Nutrients 2022;14(10):2103, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The figure has been reformatted. The publication is available at https://doi.org/10.3390/nu14102103; 2. Ridker et al. Lancet 2023;401(10384):1293–1301; 3. Luo & Lin. Immun Inflamm Dis 2021;9(1):59–73; 4. Salas-Venegas et al. Front Integr Neurosci 2022;16:798995.
CVD=cardiovascular disease; LPS=lipopolysaccharides.

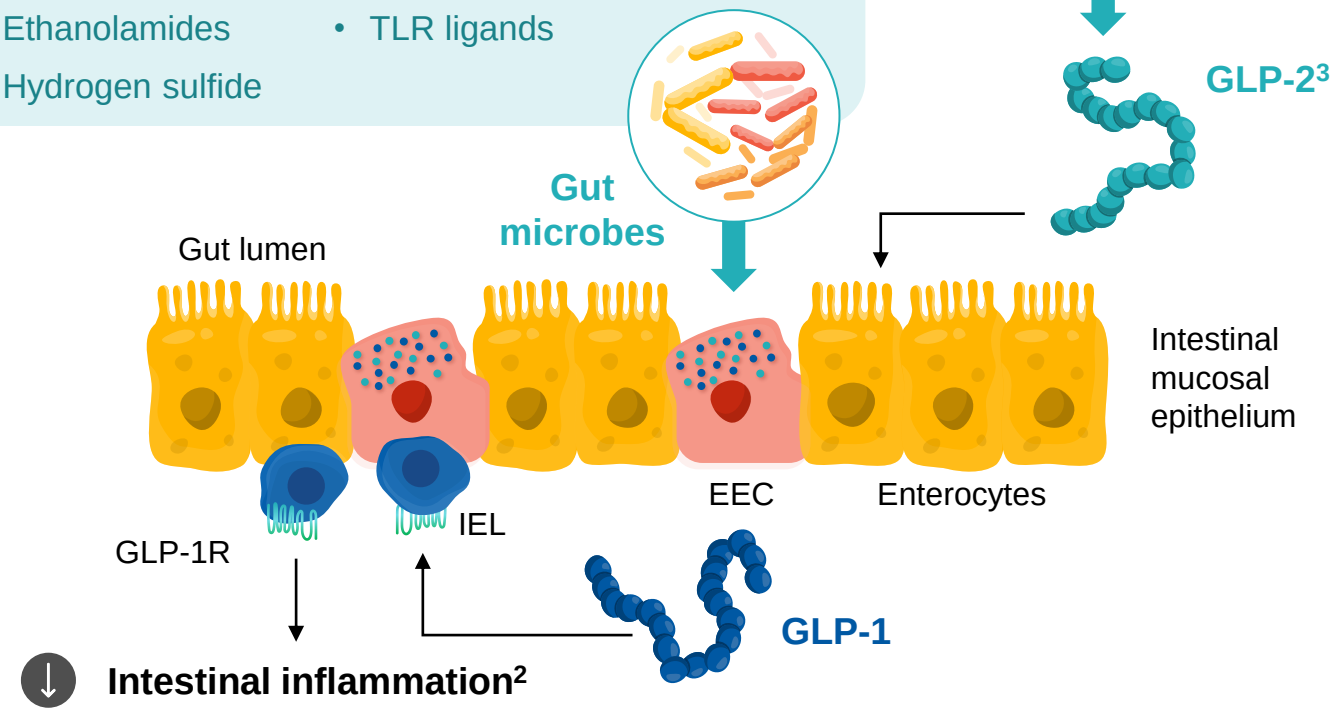
GLP-1 and GLP-2 reduce inflammation

GLP-1



↓ Systemic inflammation[1]

- Bacterial proteins
- Bile acids
- Endotoxins
- Ethanolamides
- Hydrogen sulfide
- Indole
- LPS
- Short- & long-chain fatty acids
- TLR ligands



↓ Intestinal inflammation[2]

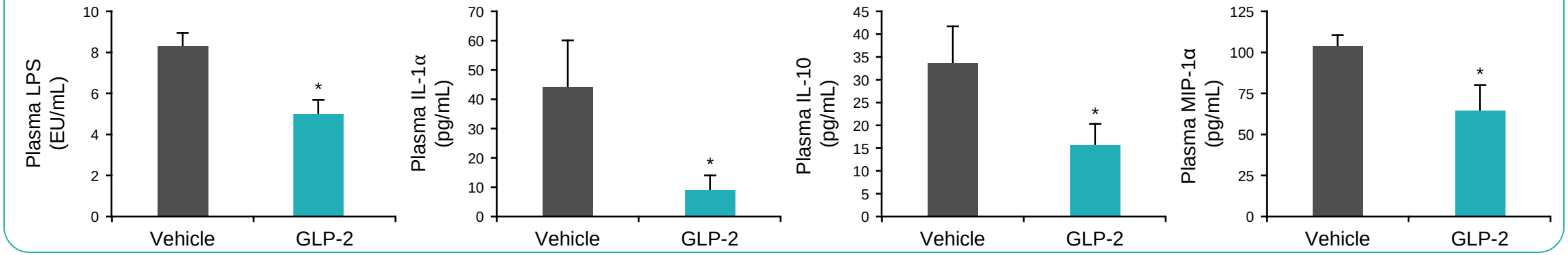
GLP-1 and GLP-2 reduce low-grade inflammation[1-3]

Sources: 1. Figure adapted from Drucker. Cell Metab 2016;24(1):15–30; 2. Figure adapted from Drucker. Cell Metab 2018;27(4):740–756, with permission from Elsevier conveyed through Copyright Clearance Center Inc.; 3. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583.

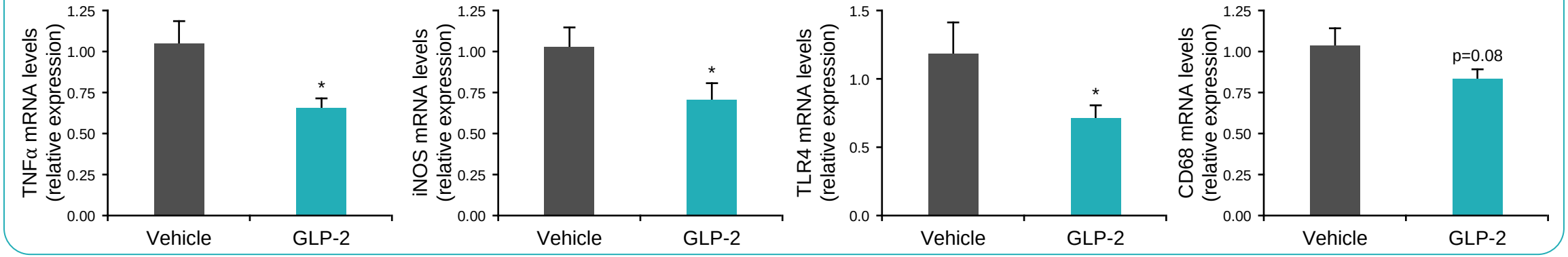
EEC=enteroendocrine cell; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; GLP-2=glucagon-like peptide-2; IEL=intraepithelial lymphocyte; LPS=lipopolysaccharides; TLR=toll-like receptor.

GLP-2RA reduced intestinal permeability and inflammation in obese mice

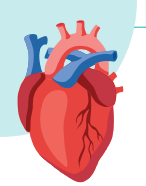
Plasma LPS[a] and inflammatory tone (IL-1α, IL-10, and MIP-1α)



Markers of inflammation, oxidative stress, and macrophage infiltration



*p<0.05 vs the vehicle group; n=6 per group; data presented are mean (SEM).
[a]LPS significantly contributes to the development of obesity-related inflammatory liver diseases, such as NAFLD and NASH.
Source: Figures adapted from Cani et al. Gut 2009;58(8):1091–1103, with permission from BMJ Publishing Group Ltd conveyed through Copyright Clearance Center Inc.
GLP-2=glucagon-like peptide-2; GLP-2RA=glucagon-like peptide-2 receptor agonist; IL-1α=interleukin 1 alpha; IL-10=interleukin 10; iNOS=inducible nitric oxide synthase; LPS=lipopolysaccharides; MIP-1α=macrophage inflammatory protein-1 alpha; mRNA=messenger ribonucleic acid; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; SEM=standard error of the mean; TLR4=toll-like receptor 4; TNFα=tumor necrosis factor alpha.



Contributory mechanisms for GLP-1/GLP-2 and effects on CV outcomes in people with T2DM and/or obesity

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GLP-1

- ↓ Blood pressure[1]
- ↓ Postprandial lipemia[2]
- ↓ Postprandial glucose[2]
- ↓ Body weight[1]
- ↓ Inflammation[1]
- ↑ Heart rate[1]
- ✓ Cardioprotective effects[3]

GLP-2

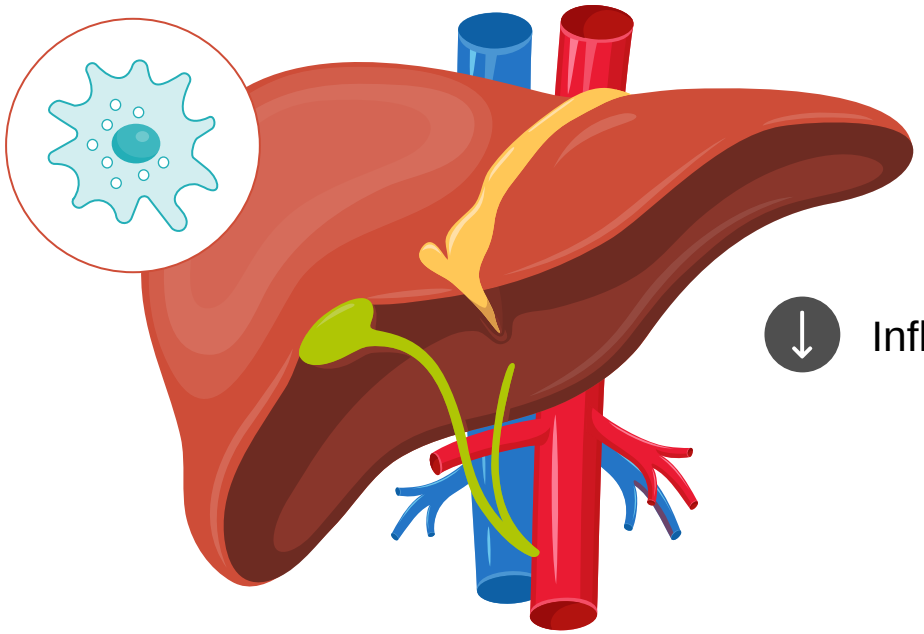
- ↓ Systemic and hepatic inflammation[4]
- ↑ Blood flow to the GI tract[5]
- ↑ Intestinal barrier function[5]

Sources: 1. Drucker. Cell Metab 2018;27(4):740–756; 2. Drucker. Cell Metab 2016;24(1):15–30; 3. Drucker et al. J Clin Invest 2017;127(12):4217–4227; 4. Kim et al. Hepatology 2022;75(6):1523–1538; 5. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583.

CV=cardiovascular; GI=gastrointestinal; GLP-1=glucagon-like peptide-1; GLP-2=glucagon-like peptide-2; T2DM=type 2 diabetes mellitus.

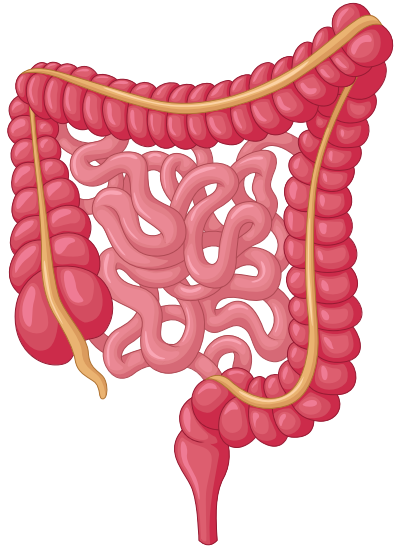
GLP-2 action in the liver

↓ Stellate cell activation[1,2]



↓ Inflammation[1,2]

↑ Intestinal barrier function[3]



Increased **barrier function** helps to **restrict gut microbiota** and inflammatory byproducts, which has a **positive indirect effect on the liver**[4]

Sources: 1. Fuchs et al. JCI Insight 2020;5(8):e136907; 2. Fuchs et al. Cell Mol Gastroenterol Hepatol 2023;16(5):847–856; 3. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 4. Kim et al. Hepatology 2022;75(6):1523–1538.
GLP-2=glucagon-like peptide-2.

GLP-1R/GLP-2R dual agonists may reduce liver steatosis, inflammation, and fibrosis

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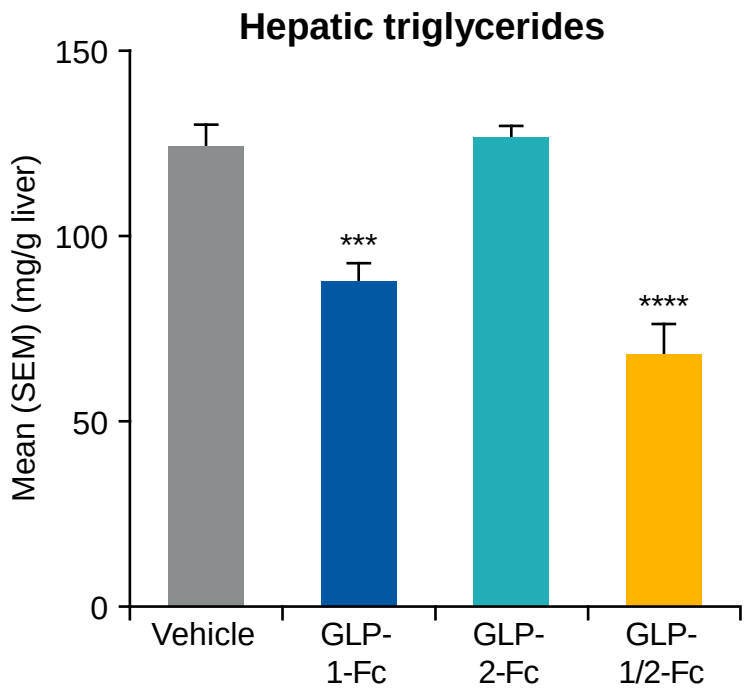
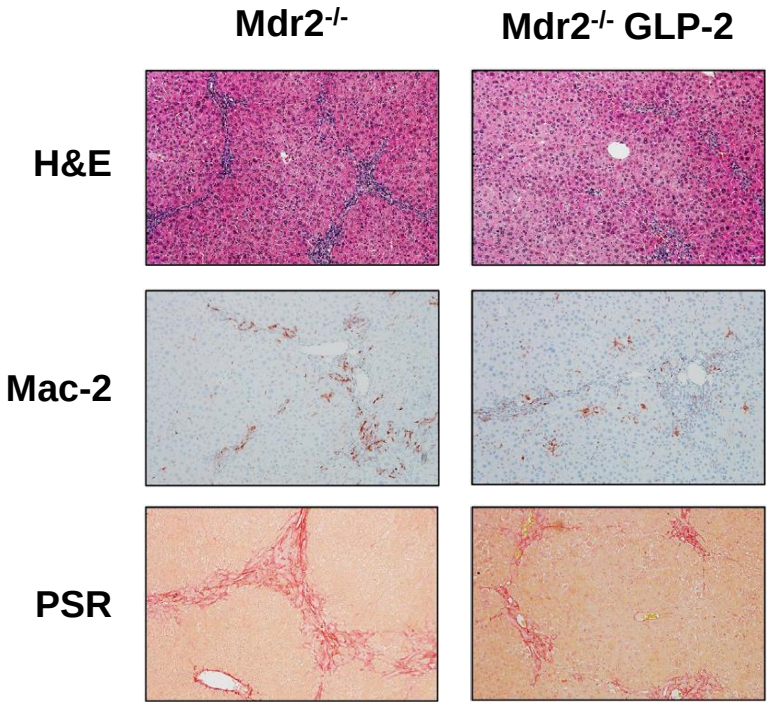
GLP-1/GLP-2 reduces hepatic lipids in NASH mouse model[1]



GLP-2 reduces hepatic inflammation and fibrosis in Mdr2$^{-/-}$ mice[2]



***p<0.001, ****p<0.0001 vs the vehicle group.

Source: 1. Figure adapted from Kim et al. Hepatology 2022;75(6):1523–1538, with permission from John Wiley & Sons, Inc.; 2. Fuchs et al. Cell Mol Gastroenterol Hepatol 2023;16(5):847–856, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The publication is available at https://doi.org/10.1016/j.jcmgh.2023.08.003.

GLP-1=glucagon-like peptide-1; GLP-1-Fc=glucagon-like peptide-1 Fc; GLP-1/2-Fc=glucagon-like peptide-1/2 Fc fusion; GLP-2=glucagon-like peptide-2; GLP-2-Fc=glucagon-like peptide-2 Fc; H&E=hematoxylin–eosin stain; NASH=nonalcoholic steatohepatitis; PSR=picrosirius red; SEM=standard error of the mean.

GLP-2 analog has shown neuroprotective effects in high-fat diet-fed mice

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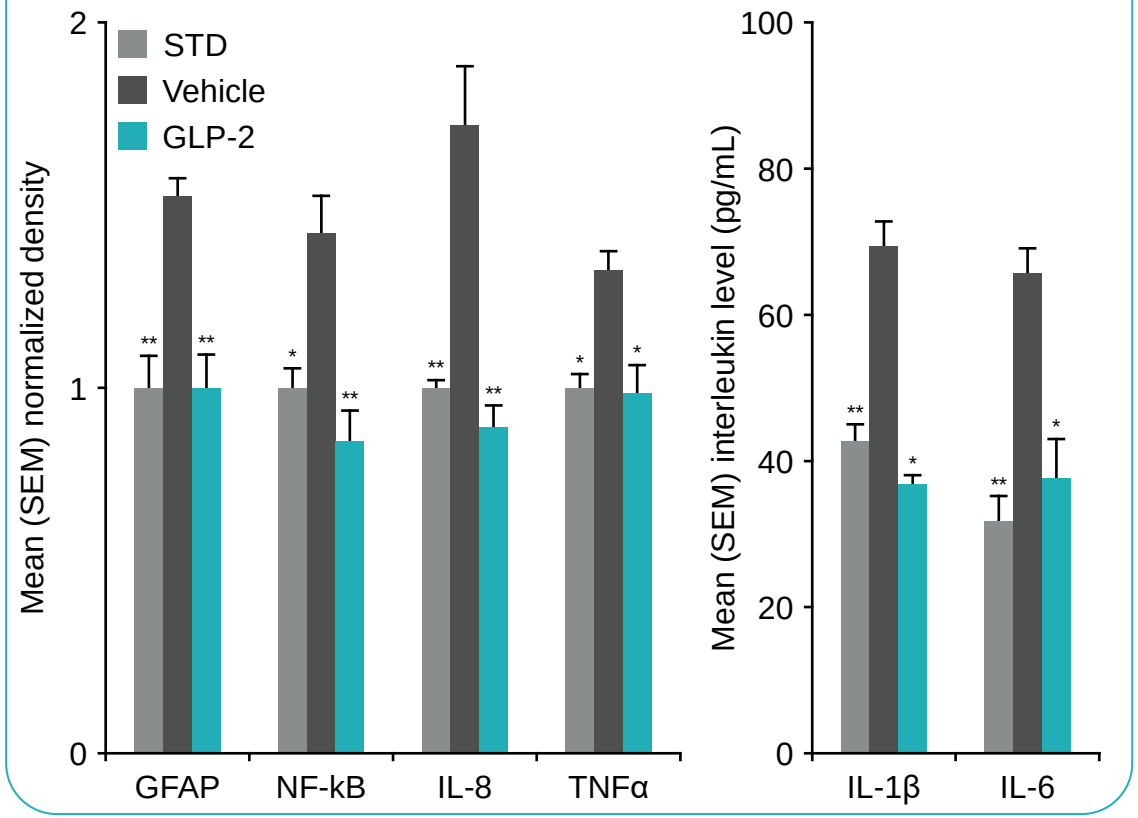
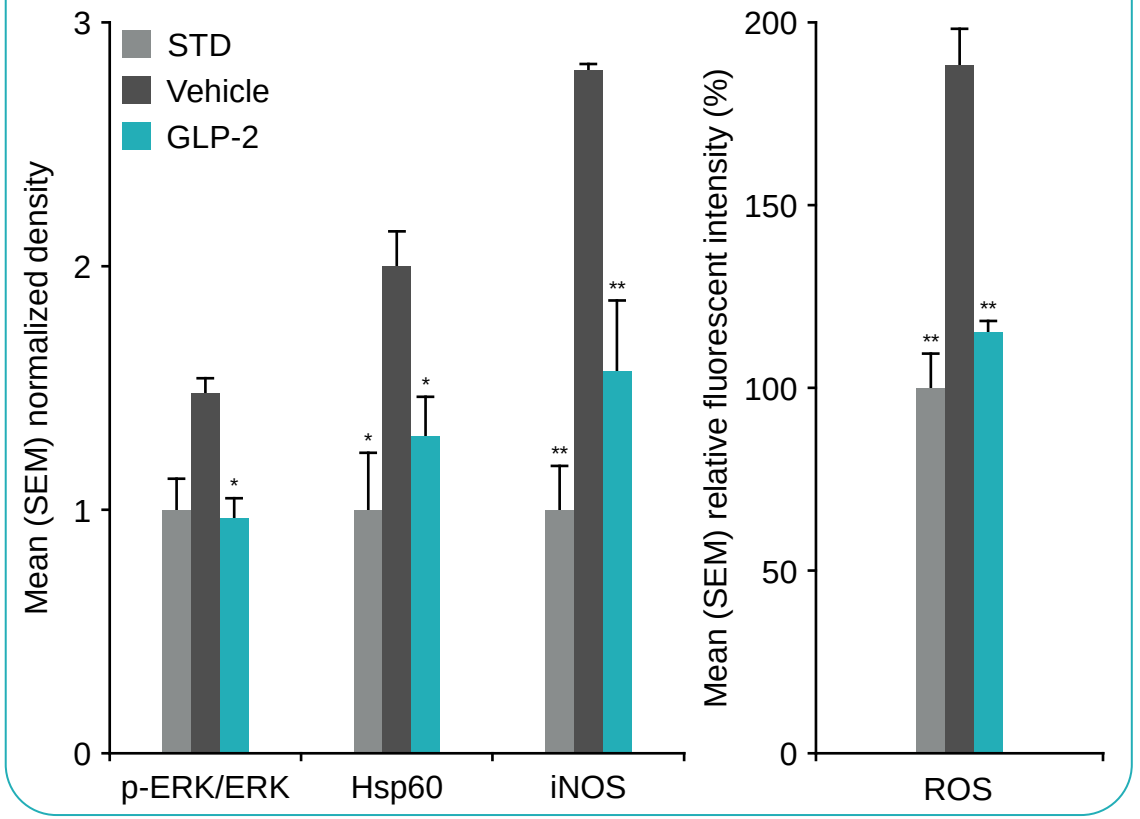
Expression of pro-inflammatory mediators in the brain



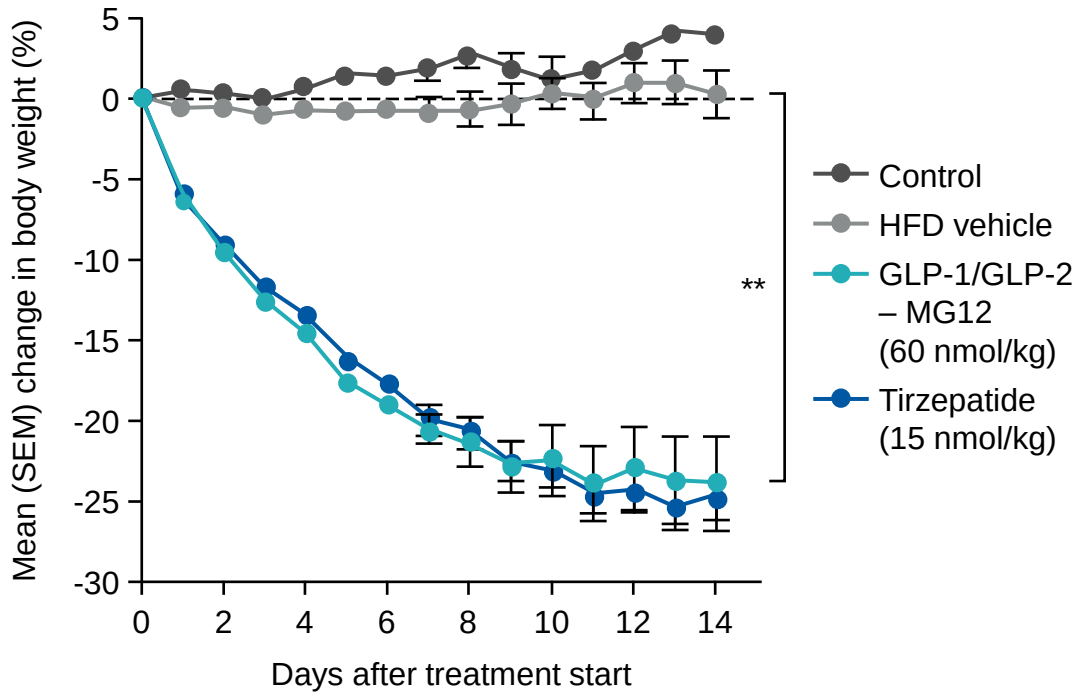
Expression of markers of oxidative stress



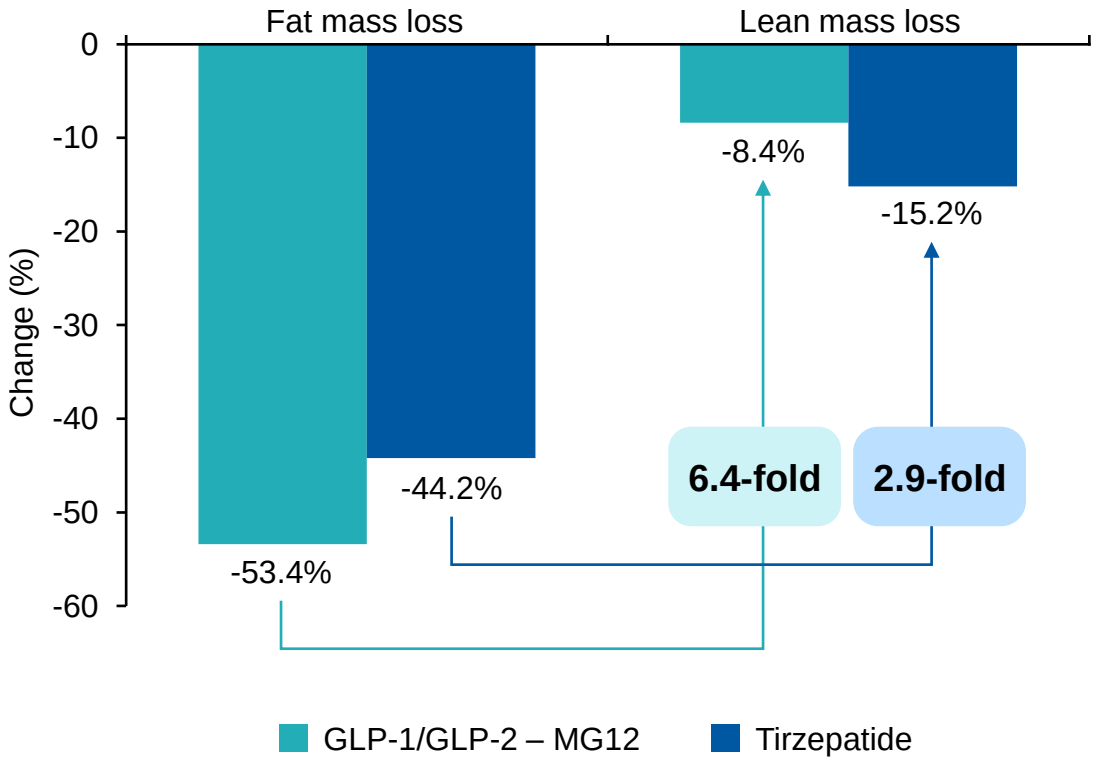
*p<0.05, **p<0.02 vs the vehicle group; n=6 per group. Studies were conducted in mouse brain tissue.
Source: Figures adapted from Nuzzo et al. Neurobiol Dis 2019;121:296–304, with permission from Elsevier conveyed through Copyright Clearance Center Inc.
GFAP=glial fibrillary acidic protein; GLP-2=glucagon-like peptide-2; IL-1β=interleukin 1 beta; IL-6=interleukin 6; IL-8=interleukin 8; iNOS=inducible nitric oxide synthase; NF-κB=nuclear factor kappa B; ROS=reactive oxygen species; SEM=standard error of the mean; STD=standard diet; TNFα=tumor necrosis factor alpha.

GLP-1R/GLP-2R dual agonist reduces body weight and improves body composition in DIO mice

Change in body weight



Change in fat and lean mass



**p<0.01 for MG-12 versus the vehicle.

Source: Figures adapted from Sae Won Kim et al. Dual agonism: two of us. Presentation at the 59th EASD Annual Meeting, October 2–6, 2023, Hamburg, Germany.

DIO=diet-induced obese; GLP-1R=glucagon-like peptide-1 receptor; GLP-2R=glucagon-like peptide-2 receptor; HFD=high-fat diet; SEM=standard error of the mean.

Strong scientific rationale for GLP-1 and GLP-2 receptor agonists to reduce weight and low-grade inflammation

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Obesity is associated with **low-grade inflammation**[1]

Established that GLP-1 and GLP-2 receptor agonists can help **reduce weight and low-grade inflammation**[2,3]

Data support the potential of GLP-1 and GLP-2 receptor agonists to **address cardiovascular, liver, and brain disease**[4-9]

Sources: 1. Calder et al. Br J Nutr 2011;106(Suppl 3):S5–S78; 2. Cani et al. Gut 2009;58(8):1091–1103; 3. Sae Won Kim et al. Dual agonism: two of us. Presentation at the 59th EASD Annual Meeting, October 2–6, 2023, Hamburg, Germany; 4. Drucker et al. J Clin Invest 2017;127(12):4217–4227; 5. Drucker. Cell Metab 2018;27(4):740–756; 6. Drucker. Cell Metab 2016;24(1):15–30; 7. Kim et al. Hepatology 2022;75(6):1523–1538; 8. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 9. Nuzzo et al. Neurobiol Dis 2019;121:296–304.
GLP-1=glucagon-like peptide-1; GLP-2=glucagon-like peptide-2.

Dapiglutide is a potential first-in-class GLP-1R/GLP-2R dual agonist

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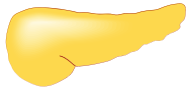
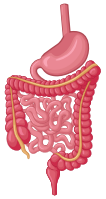
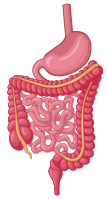
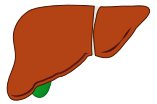
Design

- Derived from a GLP-2 peptide backbone with amino acid substitutions to 'dial in' GLP-1R activity
- Designed with higher potency towards the GLP-1R while retaining activity on the GLP-2R[1]
- Long-acting with a half-life (123–129 hours) that is suitable for once-weekly administration[2]

Dual activation of receptors

GLP-1 + **GLP-2**

GLP-1			GLP-2		
Pancreas	GI tract	Brain	GI tract	Liver	Brain
					
Improves glycemia[3]	Delays gastric emptying[3]	Reduces appetite[3]	Improves intestinal barrier function[4]	May reduce inflammation[5-7]	

Sources: 1. Reiner et al. JPEN J Parenter Enteral Nutr 2022;46(5):1107–1118; 2. Data presented by Agersnap at the 82nd ADA Scientific Sessions, June 3–7, 2022, New Orleans, LA; 3. Wang et al. Front Endocrinol (Lausanne) 2023;14:1085799; 4. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 5. Fuchs et al. Cell Mol Gastroenterol Hepatol 2023;16(5):847–856; 6. Kim et al. Hepatology 2022;75(6):1523–1538; 7. Nuzzo et al. Neurobiol Dis 2019;121:296–304.
GI=gastrointestinal; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; GLP-2=glucagon-like peptide-2; GLP-2R=glucagon-like peptide-2 receptor.

Dapiglutide showed dose-dependent mean weight loss of up to 4.3% over 4 weeks in healthy patients

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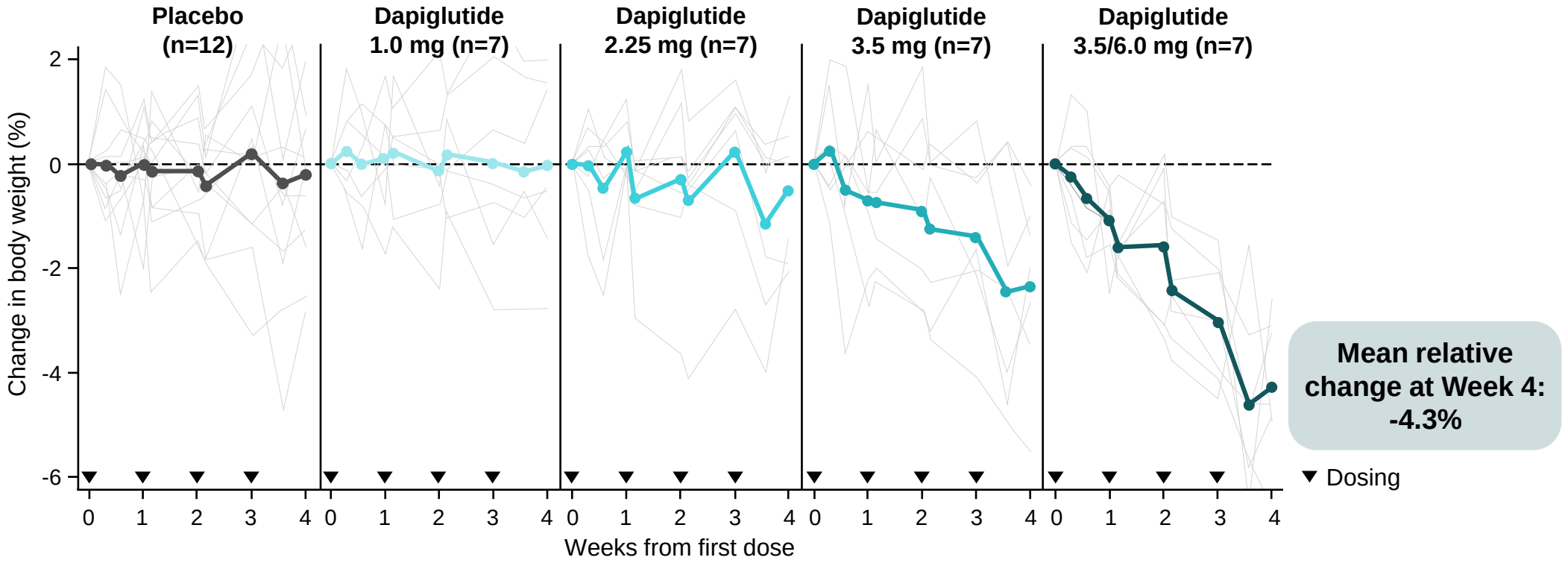
Phase 1 multiple ascending dose trial (n=40)



Dapiglutide was generally well-tolerated with no severe or serious AEs, no withdrawals due to AEs, and no observation of anti-drug antibodies

Source: Figures adapted from data presented by Agersnap at the 82nd ADA Scientific Sessions, June 3–7, 2022, New Orleans, LA.
AE=adverse event.

In H1 2024, results for dapiglutide are expected from the investigator-led DREAM trial

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DREAM is evaluating the effects of dapiglutide on body weight, gut permeability, and inflammation[1]

Population	N=54, men and women aged 18–75 years BMI ≥30 kg/m^2
Duration	12 weeks
Dose strengths	Similar to the doses evaluated in the previous 4-week MAD trial, thus up to 6.0 mg[2]
Endpoints	**Primary endpoint:** percentage change in body weight from baseline to Week 12 **Key secondary endpoints:** patients with a body weight reduction ≥5% and ≥10%; percentage change in fasting serum/plasma concentrations of biomarkers for gut permeability and inflammation

Sources: 1. ClinicalTrials.gov (NCT05788601), accessed November 2023; 2. Data presented by Agersnap at the 82nd ADA Scientific Sessions, June 3–7, 2022, New Orleans, LA.
BMI=body mass index; MAD=multiple ascending dose.

In H2 2024, results for dapiglutide are expected from the 13-week Phase 1b dose-titration trial

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The Phase 1b trial is evaluating higher doses of dapiglutide than the previous 4-week MAD trial and DREAM

Population	N=54, men and women aged 18–64 years BMI 27.0–39.9 kg/m^2
Duration	13 weeks
Dose strengths	Higher doses than the previous 4-week MAD trial and DREAM
Endpoints	**Primary endpoint:** incidence of TEAEs **Key secondary endpoints:** pharmacokinetics endpoints related to dapiglutide exposure; absolute and percentage change in body weight from baseline to Day 92

Source: ClinicalTrials.gov (NCT06000891), accessed November 2023.
BMI=body mass index; MAD=multiple ascending dose; TEAE=treatment-emergent adverse event.

Dapiglutide is a potential first-in-class GLP-1R/GLP-2R dual agonist targeting obesity and low-grade inflammation

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Weight loss – pursuing ≥20% weight loss

MoA – potential first-in-class GLP-1R/GLP-2R dual agonist

Safety and tolerability – similar to other GLP-1RA-based weight-loss medications[1]

Cardiovascular disease – potential cardioprotective benefits from GLP-1 agonism and additional anti-inflammatory effect from GLP-2 agonism[2-6]

Other comorbidities – evidence of the regenerative effects of GLP-2RAs and the potential to address organ damage associated with low-grade inflammation[5,7,8]

Sources: 1. Data presented by Agersnap at the 82nd ADA Scientific Sessions, June 3–7, 2022, New Orleans, LA; 2. Drucker et al. J Clin Invest 2017;127(12):4217–4227; 3. Drucker. Cell Metab 2018;27(4):740–756; 4. Drucker. Cell Metab 2016;24(1):15–30; 5. Kim et al. Hepatology 2022;75(6):1523–1538; 6. Drucker & Yusta. Annu Rev Physiol 2014;76:561–583; 7. Fuchs et al. Cell Mol Gastroenterol Hepatol 2023;16(5):847–856 8. Nuzzo et al. Neurobiol Dis 2019;121:296–304.
GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; GLP-1RA=glucagon-like peptide-1 receptor agonist; GLP-2R=glucagon-like peptide-2 receptor; GLP-2RA=glucagon-like peptide-2 receptor agonist; MoA=mechanism of action.

Questions?

Break

This meeting recommences
in 20 minutes at 2:50 pm

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Amylin: a next-generation weight-loss medication, representing an alternative to GLP-1 receptor agonists

Petrelintide

December 5th, 2023

GLP-1RA-based medications are effective at reducing weight but also associated with tolerability issues

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GLP-1RA-based medications are associated with GI side effects, including nausea and vomiting[1]

GLP-1RA-based medications

- Originally developed for T2DM but have shown **efficacy** as weight-loss medications[2]
- For many people who are overweight or have obesity, the strong efficacy has outweighed the **tolerability issues**[3]…

…because there have been **limited alternatives**

Emerging modalities

- There is a significant unmet need for non-incretin mechanisms that offer **improved tolerability** for a better patient experience and **high-quality weight loss**

1. Wang et al. Front Endocrinol (Lausanne) 2023;14:1085799; 2. Drucker et al. J Clin Invest 2017;127(12):4217–4227; 3. Wilding et al. N Engl J Med 2021;384(11):989–1002.
GI=gastrointestinal; GLP-1RA=glucagon-like peptide-1 receptor agonist; T2DM=type 2 diabetes mellitus.

Native amylin is a non-incretin peptide that increases satiety in contrast to GLP-1, which reduces appetite

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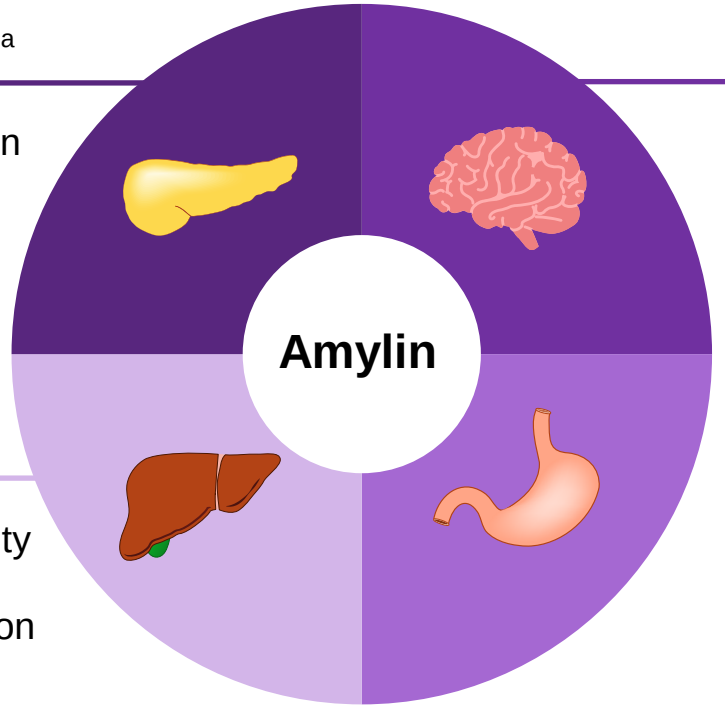
Mechanism of action

A 37-amino acid peptide hormone, produced mainly in the pancreatic beta cells and co-secreted with insulin in response to ingested nutrients

Proposed physiological effects of amylin receptor activation[1]



Pancreas (indirect)[a]
- ↓ Insulin secretion
- ↓ Glucagon secretion

Liver and adipose tissue
- ↑ Insulin sensitivity
- ↓ Fat accumulation

CNS
- ↑ Leptin sensitivity[2]
- ↑ Satiety
- ↑ Energy expenditure
- ↓ Body weight

Via the vagal nerve

GI tract
- ↓ Gastric emptying

[a]Mediated by the effect of amylin on the CNS.

Sources: 1. Figure adapted from Mathiesen et al. Eur J Endocrinol 2022;186(6):R93–R111, with permission from Oxford University Press; 2. Roth et al. Proc Natl Acad Sci U S A 2008;105(20):7257–7262.

CNS=central nervous system; GI=gastrointestinal; GLP-1=glucagon-like peptide-1.

The short-acting amylin analog, pramlintide, showed weight-loss potential in people with obesity

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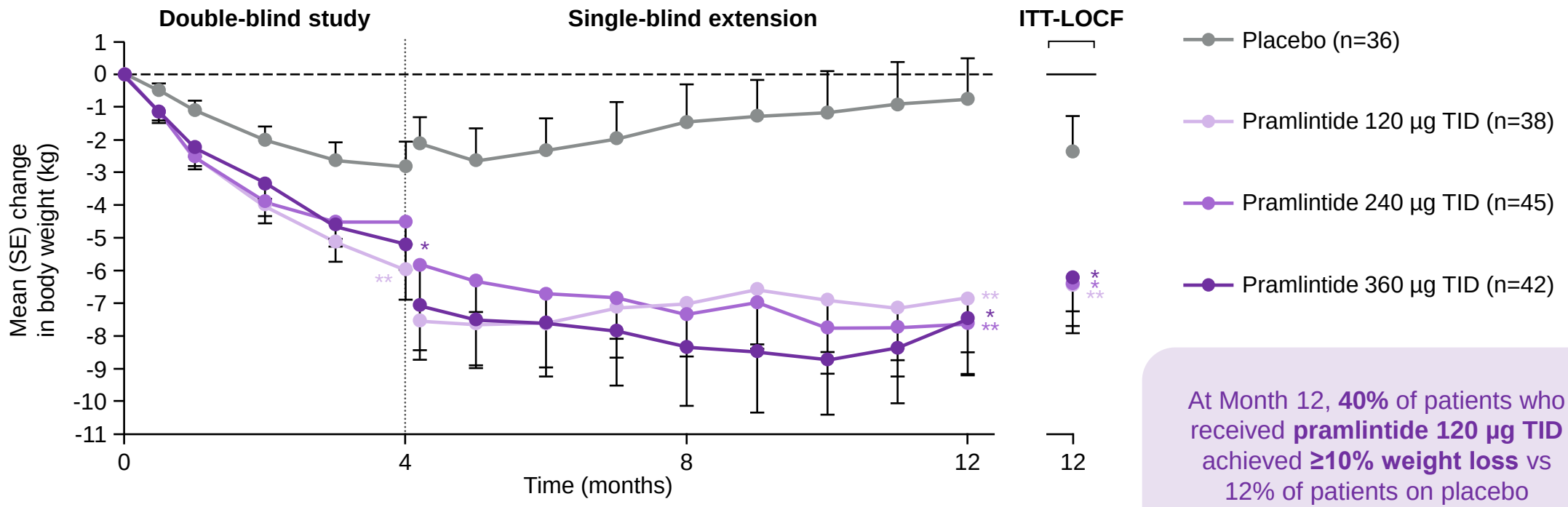
Phase 2b trial with pramlintide in people with obesity



At Month 12, **40%** of patients who received **pramlintide 120 µg TID** achieved **≥10% weight loss** vs 12% of patients on placebo

*p<0.05, **p<0.01 vs placebo.
N-values are at baseline.
Mean body weight at baseline was ~106 kg.
Source: Figure adapted from Smith et al. Diabetes Care 2008;31(9):1816–1823, and material from this publication has been used with the permission of the American Diabetes Association. Copyright and all rights reserved.
ITT=intention-to-treat; LOCF=last observation carried forward; SE=standard error; TID=three times daily.

Clinical data with cagrilintide demonstrate the weight-loss potential of long-acting amylin analogs

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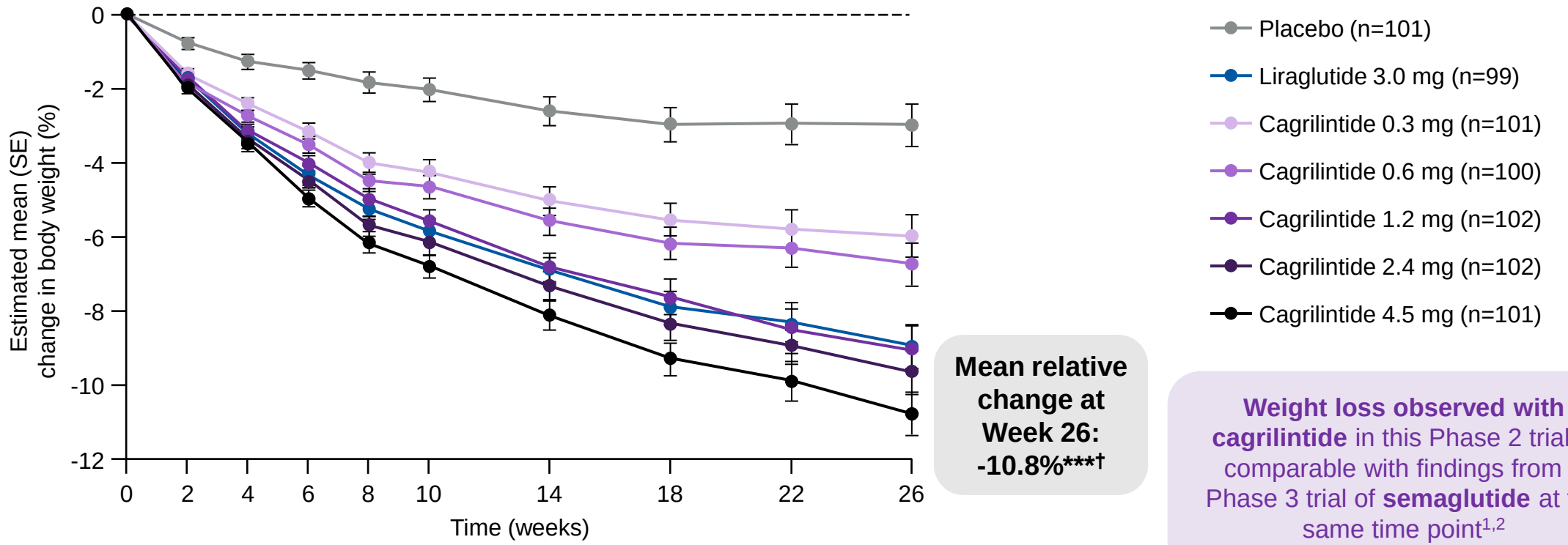
Phase 2 trial of cagrilintide in people with obesity or overweight[a] without T2DM[1]



Mean relative change at Week 26: -10.8%*†**

Weight loss observed with cagrilintide in this Phase 2 trial is comparable with findings from a Phase 3 trial of **semaglutide** at the same time point[1,2]

***p<0.001 vs placebo; †p<0.05 vs liraglutide 3.0 mg.
[a]BMI ≥27 kg/m^2 with hypertension or dyslipidemia.
Treatment efficacy was evaluated using the trial product estimand.[1] N-values are at baseline.
Sources: 1. Figure adapted from Lau et al. Lancet 2021;398(10317):2160–2172, with permission from Elsevier conveyed through Copyright Clearance Center Inc.; 2. Wilding et al. N Engl J Med 2021;384(11):989–1002.
BMI=body mass index; SE=standard error; T2DM=type 2 diabetes mellitus.

Amylin agonism has the potential to facilitate weight loss in people with and without T2DM

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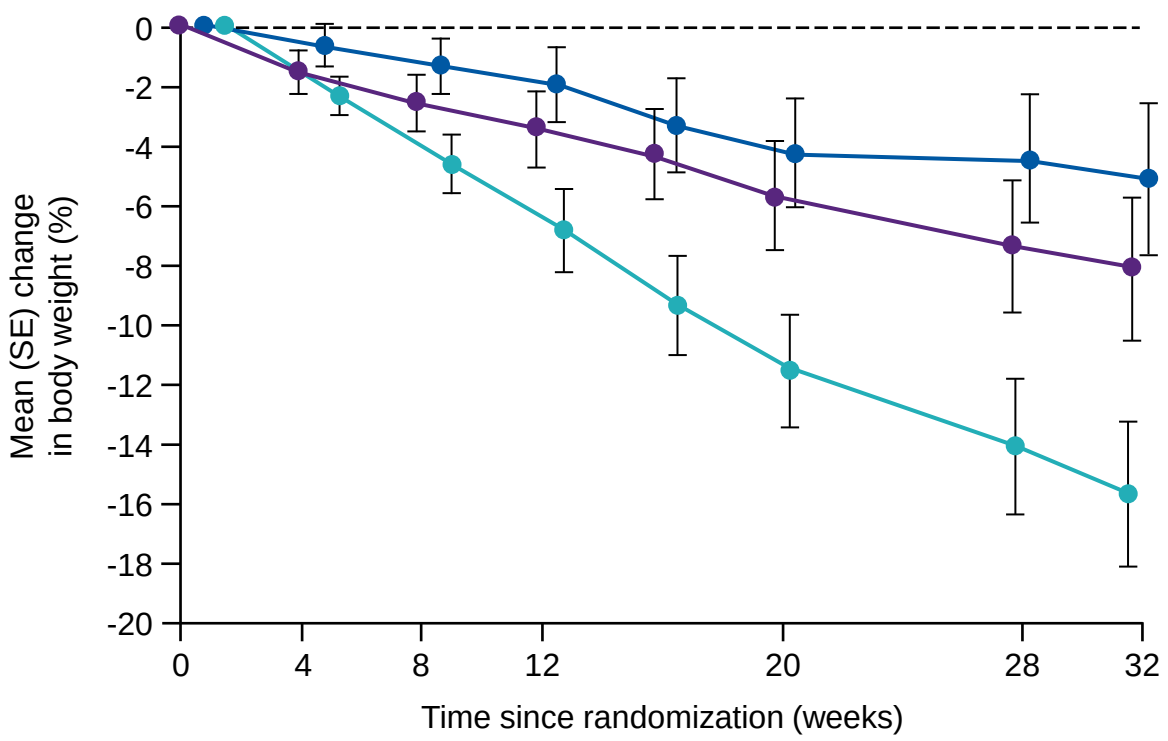
Phase 2 trial in people with T2DM of CagriSema vs cagrilintide or semaglutide



Mean relative change at Week 32

-5.1%

-8.1%

-15.6%

- Semaglutide 2.4 mg (n=31)
- Cagrilintide 2.4 mg (n=30)
- CagriSema – cagrilintide 2.4 mg and semaglutide 2.4 mg (n=31)

Treatment efficacy was evaluated using the trial product estimand.
Source: Figure adapted from Frias et al. Lancet 2023;402(10403):720–730, with permission from Elsevier conveyed through Copyright Clearance Center Inc.
SE=standard error; T2DM=type 2 diabetes mellitus.

Amylin analogs have the potential for better tolerability compared with GLP-1RAs

Conceptually, **increasing satiety** could lead to a **better patient experience** during weight loss compared to reducing appetite

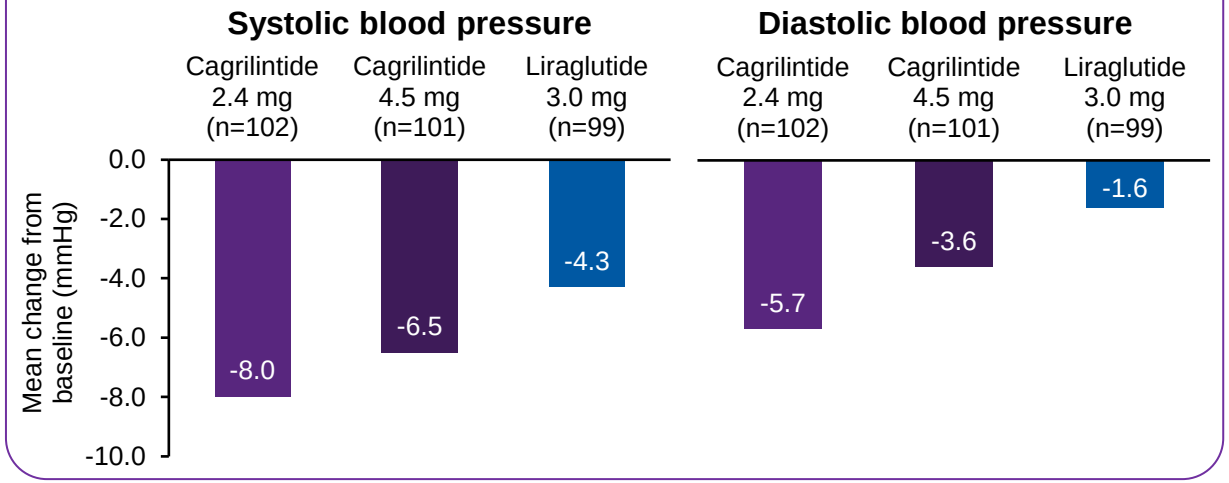
Clinical data for the **short-acting amylin analog, pramlintide**, demonstrated a benign tolerability profile **comparable to placebo**[1,2]

Clinical data with the **long-acting amylin analog, cagrilintide**, demonstrated a **more benign tolerability profile compared to liraglutide**, including less vomiting[3]

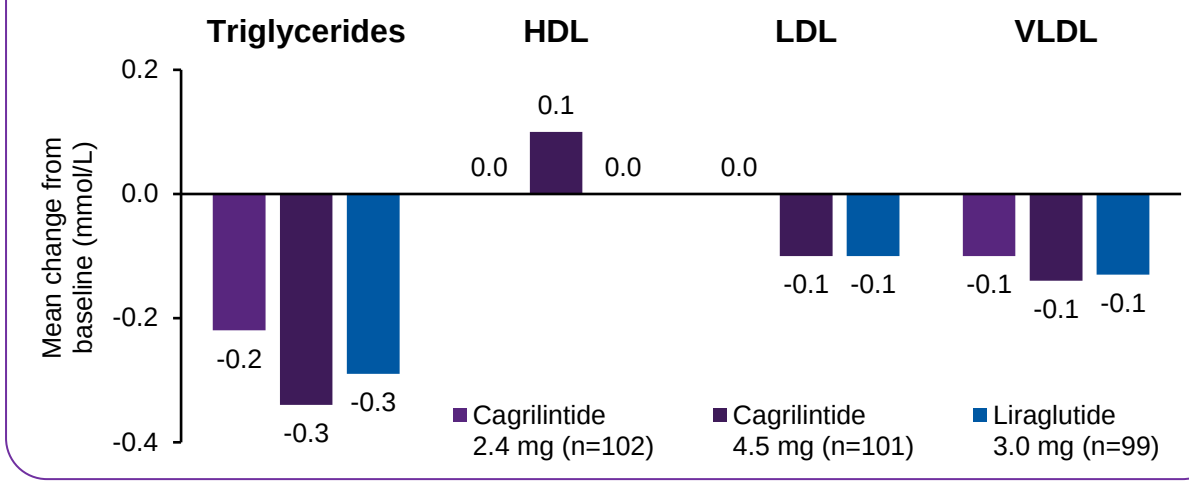
Sources: 1. Smith et al. Diabetes Care 2008;31(9):1816–1823; 2. Smith et al. Am J Physiol Endocrinol Metab 2007;293(2):E620–E627; 3. Lau et al. Lancet 2021;398(10317):2160–2172.
GLP-1RA=glucagon-like peptide-1 receptor agonist.

In the Phase 2 trial in people with obesity/overweight without T2DM, cagrilintide reduced CV risk markers

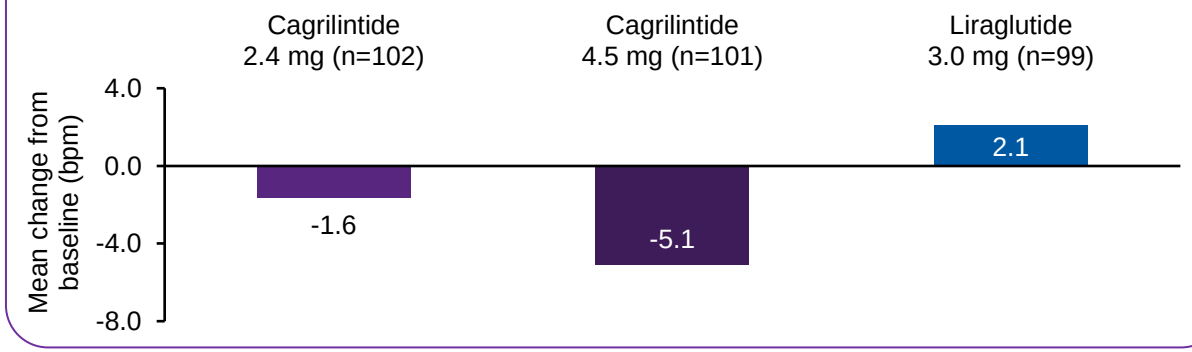
Absolute change in blood pressure at Week 26



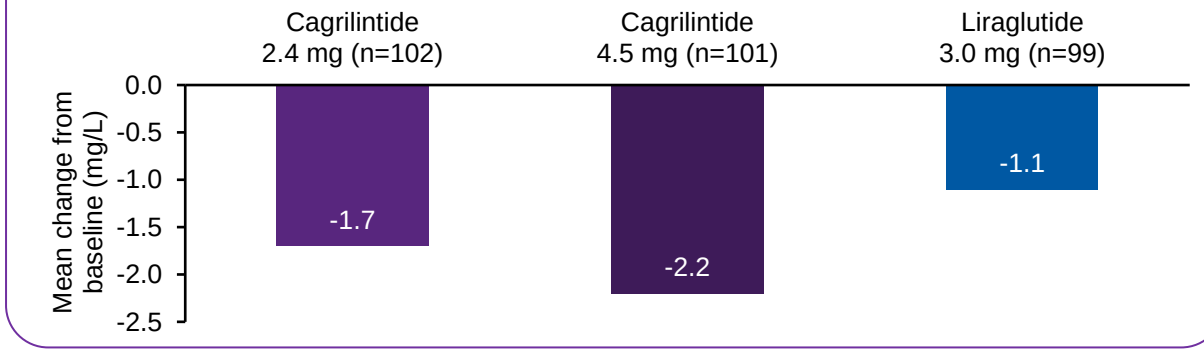
Absolute change in lipid profile at Week 26



Absolute change in heart rate at Week 26



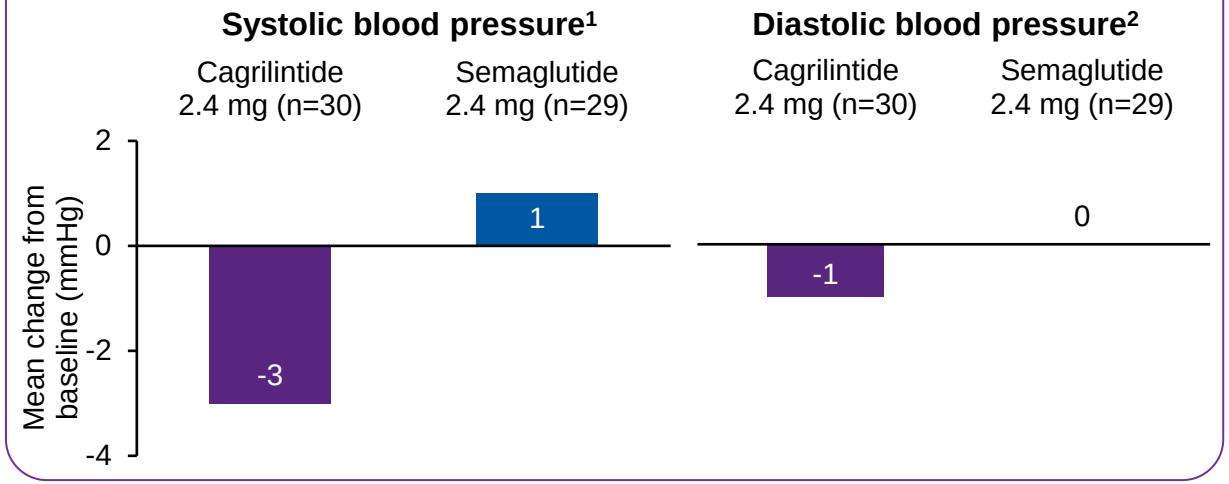
Absolute change in hsCRP at Week 26



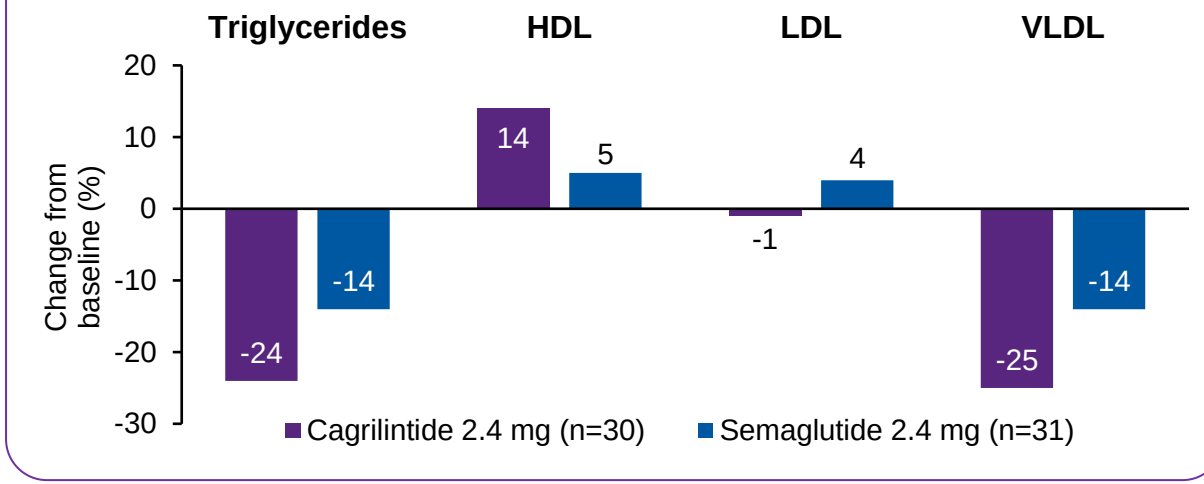
Source: Figures adapted from Lau et al. Lancet 2021;398(10317):2160–2172.
CV=cardiovascular; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; LDL=low-density lipoprotein; T2DM=type 2 diabetes mellitus; VLDL=very low-density lipoprotein.

In the Phase 2 trial in people with T2DM, cagrilintide also reduced CV risk markers

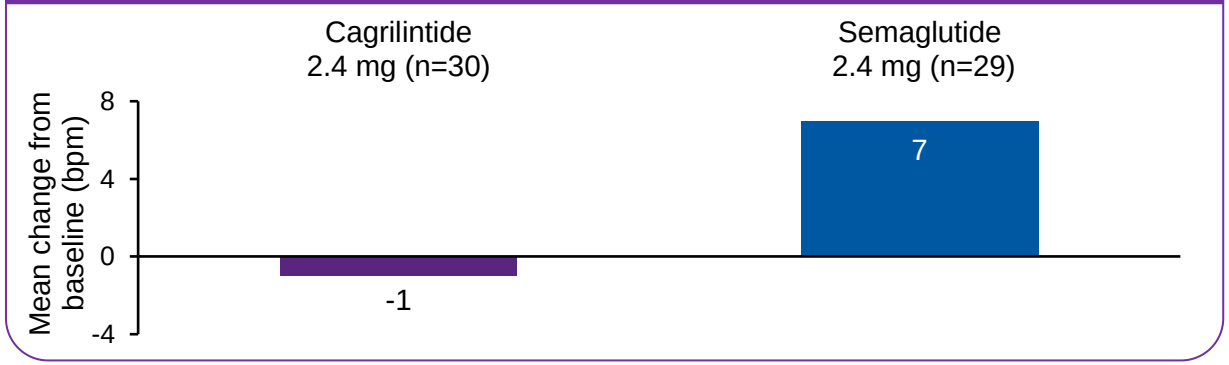
Absolute change in blood pressure at Week 32



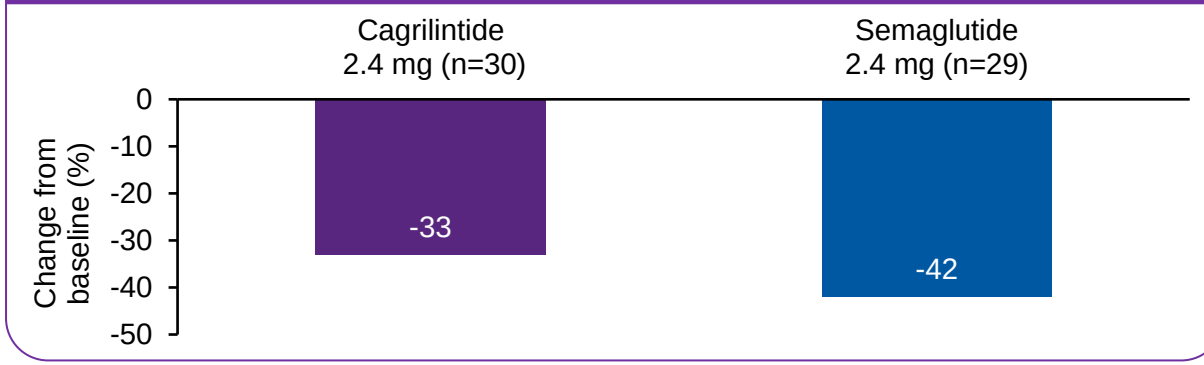
Relative change in lipid profile at Week 32[1]



Absolute change in heart rate at Week 32[1]



Relative change in hsCRP at Week 32[2]



Sources; 1. Figures adapted from Frias et al. Lancet 2023;402(10403):720–730; 2. Frias et al. Oral presentation (53-OR) at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA.
CV=cardiovascular; HDL=high-density lipoprotein; hsCRP=high-sensitivity C-reactive protein; LDL=low-density lipoprotein; T2DM=type 2 diabetes mellitus; VLDL=very low-density lipoprotein.

Data suggest that amylin agonism may facilitate fat mass loss and relative preservation of lean mass

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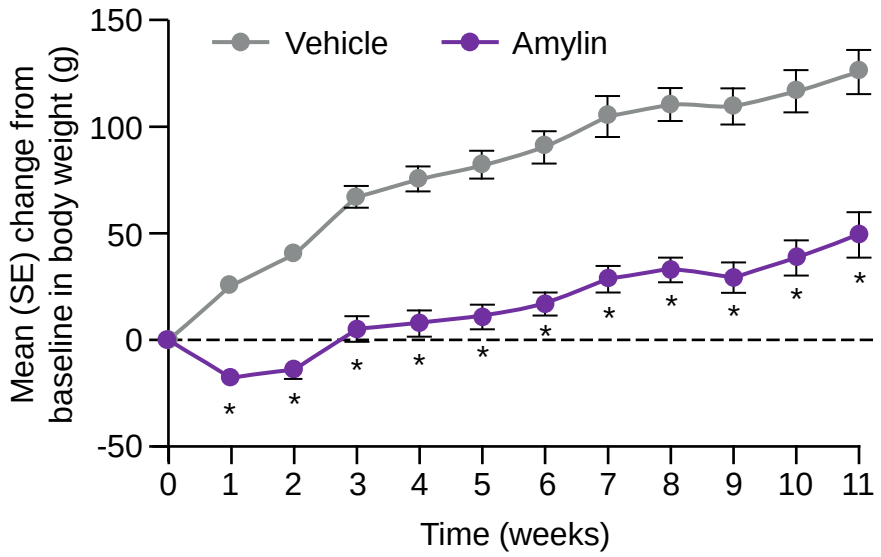
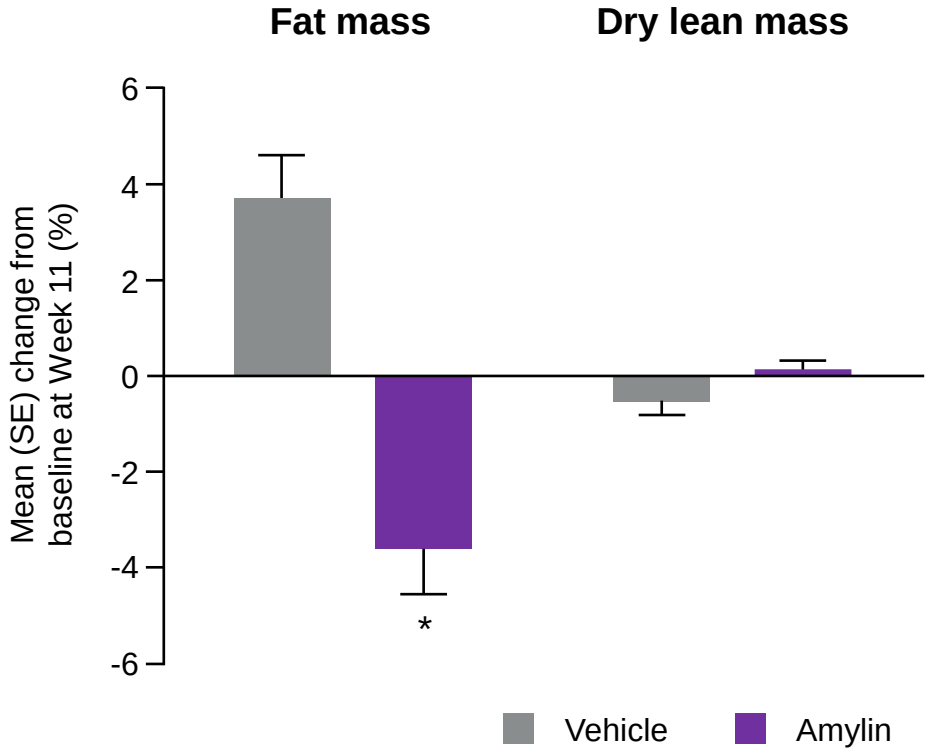
Change in body weight in rats



Main effect of treatment ($p<0.05$)
Treatment-by-week interaction ($p<0.05$)

Cumulative body weight change in rats who **self-selected between a high-fat or a low-fat diet** during 11 weeks of subcutaneous infusion with a **vehicle or amylin**

Change in body composition in rats



*$p<0.05$ vs the vehicle group; n=7–8 per group.
Source: Figures adapted from Mack et al. Am J Physiol Regul Integr Comp Physiol 2007;293(5):R1855–R1863.
SE=standard error.

This fat-specific weight loss has been demonstrated in a number of pre-clinical studies

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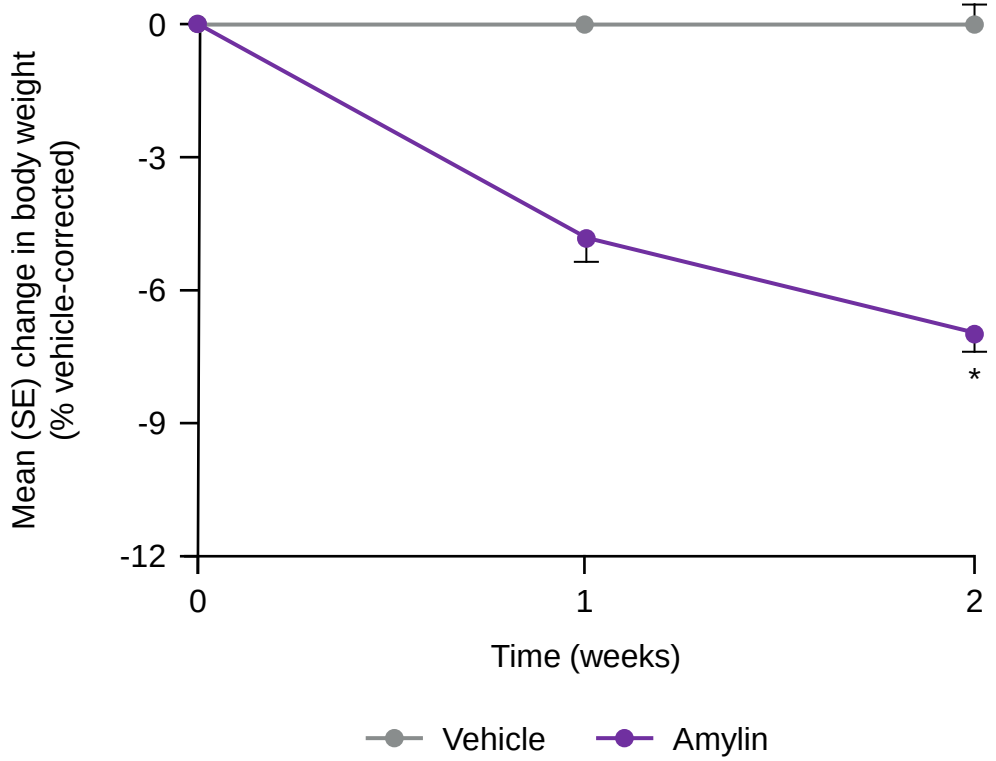
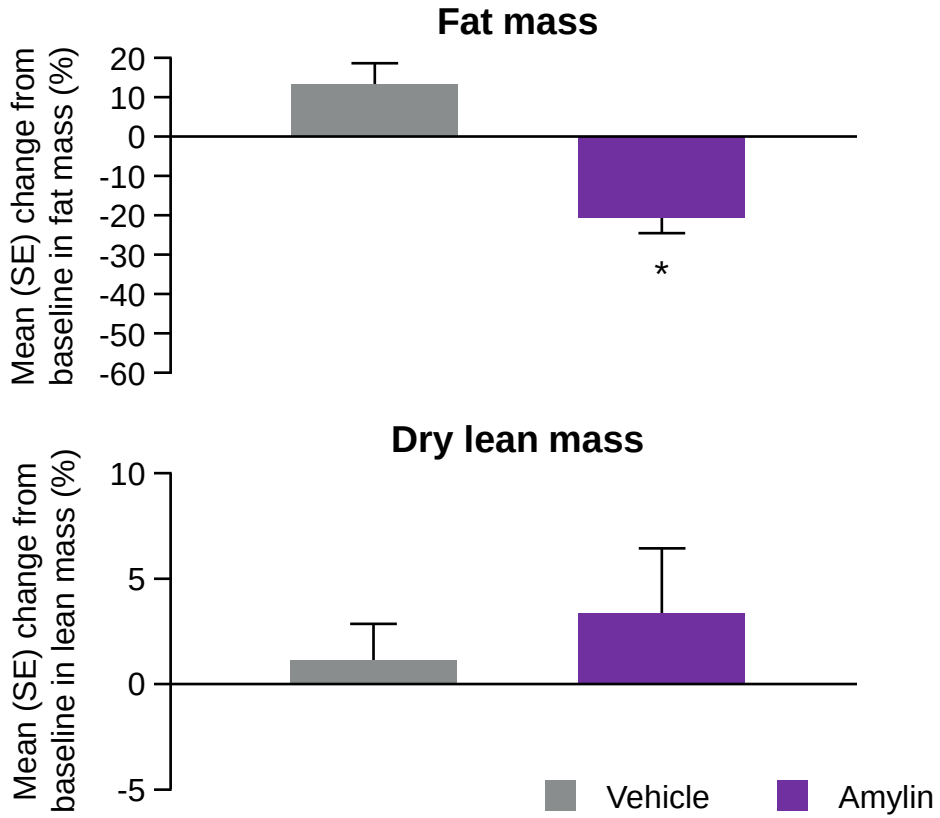
Change in body weight in DIO rats



Change in body composition in DIO rats



*p<0.05 vs the vehicle group; n=7–8 per group.
Source: Figures adapted from Roth et al. Int J Obes (Lond) 2008;32(8):1201–1210, with permission from Springer Nature conveyed through Copyright Clearance Center Inc.
DIO=diet-induced obese; SE=standard error.

Amylin analogs hold potential as future stand-alone weight-loss medications

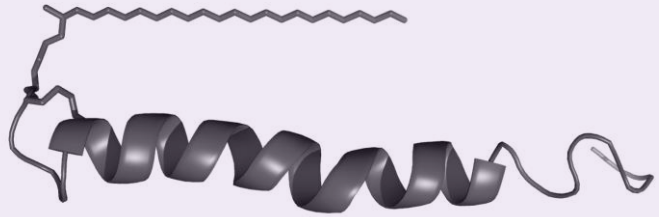
ZEALAND PHARMA

- Potential for **GLP-1RA-like weight loss**[1-3]
- Non-incretin MoA with **potential for improved tolerability**[1,4,5]
- Potential to **reduce CVD risk**[1,3]

Sources: 1. Lau et al. Lancet 2021;398(10317):2160–2172; 2. Wilding et al. N Engl J Med 2021;384(11):989–1002; 3. Frias et al. Lancet 2023;402(10403):720–730; 4. Smith et al. Diabetes Care 2008;31(9):1816–1823; 5. Smith et al. Am J Physiol Endocrinol Metab 2007;293(2):E620–E627.
CVD=cardiovascular disease; GLP-1RA=glucagon-like peptide-1 receptor agonist; MoA=mechanism of action.

Petrelintide is a long-acting, potential best-in-class amylin analog designed with stability at neutral pH

Petrelintide (ZP8396) is a 36-amino-acid acylated peptide, based on the peptide sequence of **human amylin**

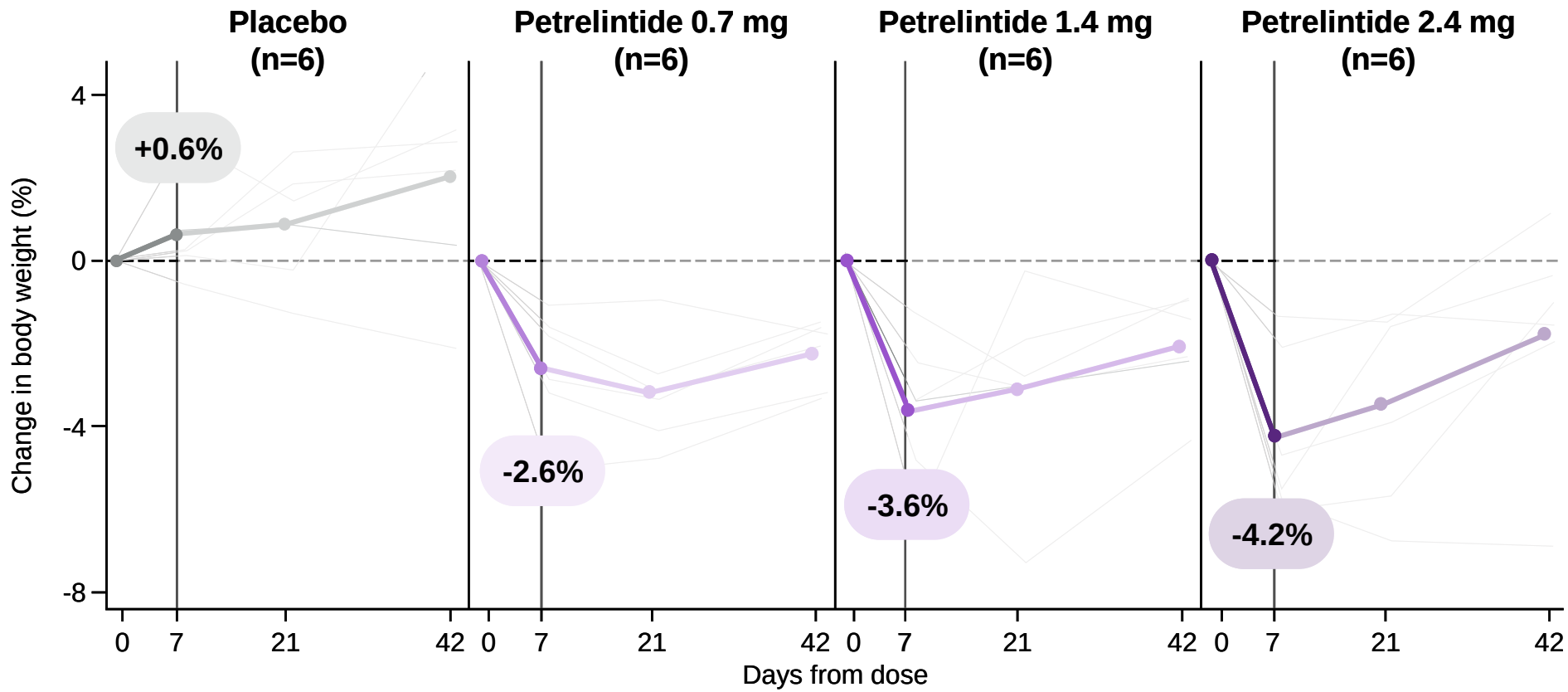


- **Long-acting** amylin analog (half-life of 10 days)[1] due to acylation, suitable for **once-weekly administration**
- **Chemical and physical stability** at neutral pH, **minimizing fibrillation** and allowing for **co-formulation** with other peptides[2]
- **Potent agonistic effects** on **amylin and calcitonin receptors**[3]

Sources: 1. Olsen et al. Poster 92-LB. Presented at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA; 2. Skarbaliene et al. Poster 1406-P. Presented at ADA 82nd Scientific Sessions, June 3–7, 2022, New Orleans, LA; 3. Eriksson et al. Presentation at ObesityWeek, November 1–4, 2022, San Diego, CA.

A single subcutaneous dose of petrelintide 2.4 mg resulted in average weight loss of 4.2% at Day 7

Change in body weight in Phase 1a SAD trial of petrelintide



Source: Figure adapted from Olsen et al. Poster 92-LB. Presented at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA.
SAD=single ascending-dose.

Six, once-weekly, low doses of petrelintide resulted in average weight loss above 5%

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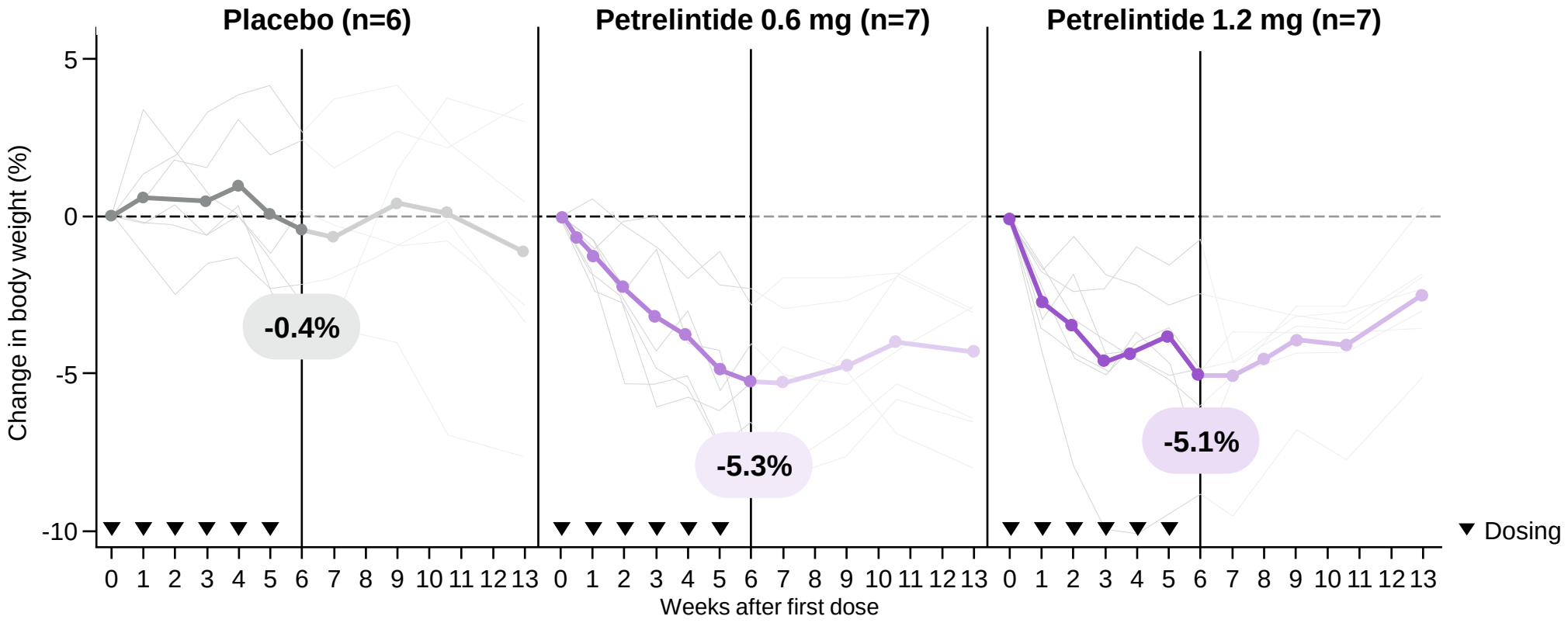
Part 1 of the Phase 1b MAD trial of petrelintide



Source: Figure adapted from Olsen et al. Poster presented at ObesityWeek, October 14–17, 2023, Dallas, TX.
MAD=multiple ascending dose.

In Part 1 of the MAD trial, petrelintide was well-tolerated with no serious or severe TEAEs and no withdrawals

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TEAEs in Part 1 of the Phase 1b MAD trial with petrelintide

Number of participants (events)	Placebo (n=6)	Petrelintide 0.6 mg (n=7)	Petrelintide 1.2 mg (n=7)
Total AEs	**5 (28)**	**6 (23)**	**7 (29)**
Mild	5 (24)	6 (23)	7 (29)
Moderate	3 (4)	0	1 (2)
Severe	0	0	0
Serious	**0**	**0**	**0**
Metabolism and nutrition disorders	**1 (1)**	**6 (9)**	**6 (8)**
GI disorders	**3 (7)**	**2 (6)**	**5 (9)**

- Nausea occurred in **three participants** on petrelintide, with one also reporting vomiting; no other participants reported vomiting
- **No injection-site reactions** were reported, and **no participants developed anti-drug antibodies**

Source: Table adapted from Olsen et al. Poster presented at ObesityWeek, October 14–17, 2023, Dallas, TX.
AE=adverse event; GI=gastrointestinal; MAD=multiple ascending dose; TEAE=treatment-emergent adverse event.

Results from Part 2 of the trial, exploring higher doses of petrelintide over 16 weeks, are expected in H1 2024

ZEALAND PHARMA

We are investigating significantly **higher doses** of petrelintide…

…over a **longer duration** of 16 weeks…

…using a **dose-escalation** scheme…

…in **48 people** who are overweight or have obesity

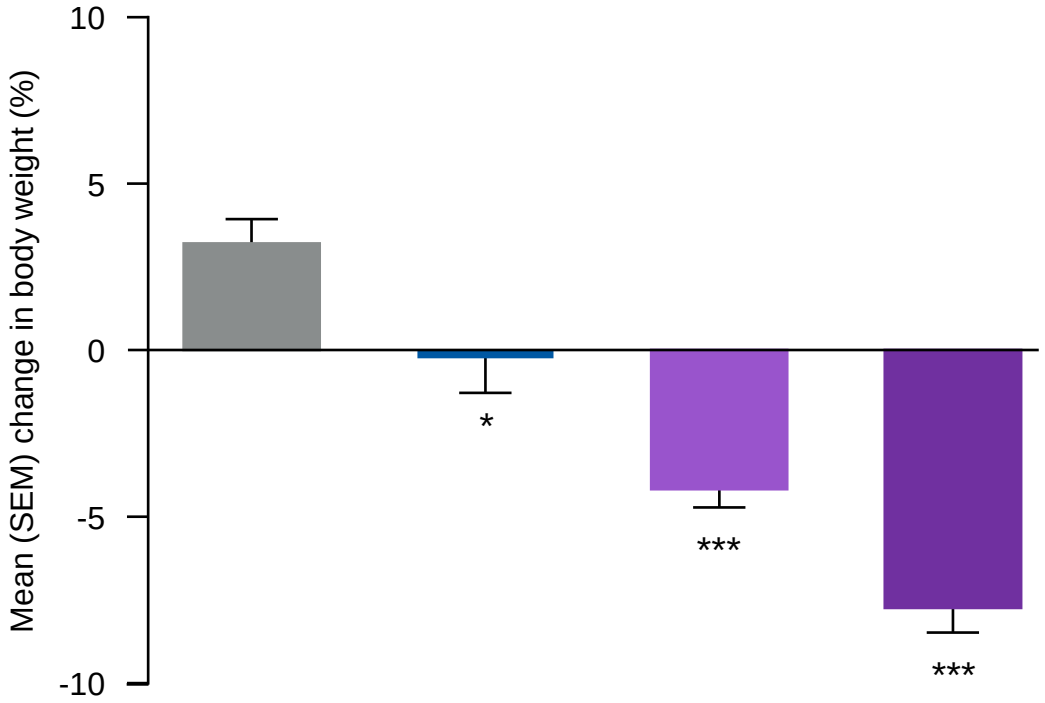
The next step in the development of petrelintide will be a comprehensive Phase 2 program to be initiated in H2 2024

Source: ClinicalTrials.gov (NCT05613387), accessed November 2023.

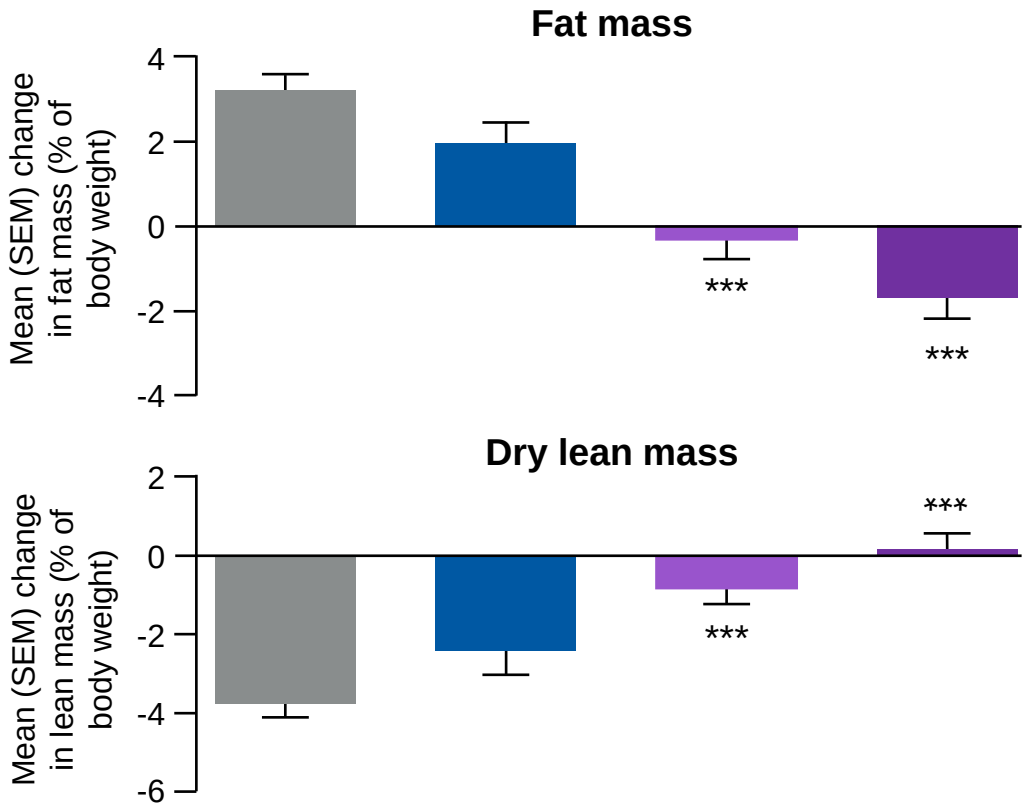
Petrelintide significantly reduced fat mass while preserving lean mass in DIO rats

Unpublished data

Change in body weight at Day 30



Change in body composition at Day 30



Vehicle | Liraglutide 5 nmol/kg BID | Petrelintide 2 nmol/kg Q2D | Petrelintide 10 nmol/kg Q4D

*p<0.05, ***p<0.001 vs vehicle.
Source: Figures adapted from Data on file.
BID=twice daily; DIO=diet-induced obese; Q2D=every 2 days; Q4D=every 4 days; SEM=standard error of the mean.

Petrelintide is a potential best-in-class amylin analog for GLP-1-like weight loss with better tolerability

ZEALAND PHARMA

Weight loss – potential for ~15% reduction in body weight as monotherapy, with high-quality weight loss[1-4]

MoA – mechanism reduces food intake by restoring leptin sensitivity and increasing satiety[5]

Safety and tolerability – potential for better tolerability vs GLP-1RAs[1,2,6]

Cardiovascular disease – potential to reduce CVD risk (e.g., through effects on blood pressure, heart rate, lipids, and hsCRP)[2,7]

Sources: 1. Olsen et al. Poster presented at ObesityWeek, October 14–17, 2023, Dallas, TX; 2. Lau et al. Lancet. 2021;398(10317):2160–2172; 3. Wilding et al. N Engl J Med 2021;384(11):989–1002; 4. Data on file; 5. Roth et al. Proc Natl Acad Sci U S A 2008;105(20):7257–7262; 6. Olsen et al. Poster 92-LB. Presented at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA; 7. Frias et al. Lancet 2023;402(10403):720–730.
CVD=cardiovascular disease; GLP-1=glucagon-like peptide-1; GLP-1RA=glucagon-like peptide-1 receptor agonist; hsCRP=high-sensitivity C-reactive protein; MoA=mechanism of action.

Questions?

ZEALAND PHARMA

Targeting obesity and NASH with glucagon/GLP-1 receptor agonists

Survodutide

December 5th, 2023

Considering obesity as a neurological disease

Obesity is a set of diseases

Our focus is not on ‘weight loss’ but ‘health gain’

Source: Painting from Joseph Wright of Derby (1790).

Oxyntomodulin represents the scientific foundation for the investigation of survodutide

Oxyntomodulin (OM)

- A hormone with dual agonism at GCG and GLP-1 receptors that **reduces body weight by increasing energy expenditure and regulating appetite**[1]
- Clinical application is limited due to a short half-life[2]

Survodutide is a 29-amino-acid peptide **derived from the endogenous hormones GCG and GLP-1**[3]

Dual activation of receptors[3]

In human plasma assays, survodutide activates the **human GCGR and GLP-1R** with potencies of **8.3 nM** and **1.0 nM**, respectively

The extended half-life of survodutide is achieved by:[3]

- Integration of a **glycine–serine linker containing a C18 di-acid**, which mediates albumin binding and reduces renal clearance
- Integration of a synthetic amino acid (position 2), which provides resistance to DPP-4 proteolytic cleavage

Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.

Sources: 1. Wynne et al. Int J Obes (Lond) 2006;30(12):1729–1736; 2. Schjoldager et al. Eur J Clin Invest 1988;18(5):499–503; 3. Zimmermann et al. Mol Metab 2022;66:101633.

DPP-4=dipeptidyl peptidase 4; GCG=glucagon; GCGR=glucagon receptor; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; OM=oxyntomodulin.

Survodutide activates GCGR and GLP-1R, which are critical in controlling metabolic functions

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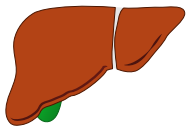
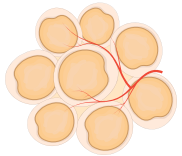
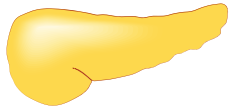
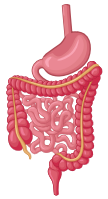
GCG/GCGR + GLP-1/GLP-1R[4]

↑ Energy expenditure (metabolic rate)

↑ Insulin secretion **↓ Food intake**

Liver (direct)	Adipose tissue (indirect)	Pancreas	GI tract	Brain
				
↑	↑	↑	↓	↓
Fatty acid oxidation[1] Glycogenolysis[2] Gluconeogenesis[2]	Lipolysis[3]	Glucose-dependent insulin secretion	Gastric emptying	Food intake/appetite (hypothalamic centers)

← GLP-1 has a glucagon-suppressive effect[4] →

Dual agonism of GCGR and GLP-1R is expected to provide **superior body weight reduction** vs selective GLP-1 analogs, with comparable glycemic control[5,6]

Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.

Sources: 1. Pégorier et al. Biochem J 1989;264(1):93–100; 2. Cherrington. Diabetes 1999;48(5):1198–1214; 3. Del Prato et al. Obes Rev 2022;23(2):e13372; 4. Flint et al. J Clin Invest 1998;101(3):515–520; 5. Tan et al. Diabetes. 2013;62(4):1131–1138; 6. Celga et al. Diabetes 2014;63(11):3711–3720.

GCG=glucagon; GCGR=glucagon receptor; GI=gastrointestinal; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor.

Agonism of the GCGR by survodutide in mouse hepatocytes is potentially relevant in humans

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mRNA sequence analysis from mouse hepatocytes suggests treatment with increasing doses of survodutide:

- ↓ Downregulates gene clusters upregulated in the progression of NASH fibrosis in humans
- ↑ Upregulates gene clusters downregulated in the progression of NASH fibrosis in humans

Consequent working hypothesis:

Survodutide → GCGR

Survodutide activation of GCGR causes transcriptional changes affecting multiple pathways

Cholesterol and bile acid metabolism	Epigenetics and transcriptional regulation	Oxidative phosphorylation	Protein, amino acid, and glucose metabolism
CYP7A1	IHH	GLS2	GNMT
CYP8B1	Osgin1	NOX4	NNMT
CYP17A1	Ung	Cox6b2	DDAH
		GOT1	SDS
			ASNS
			ASS1

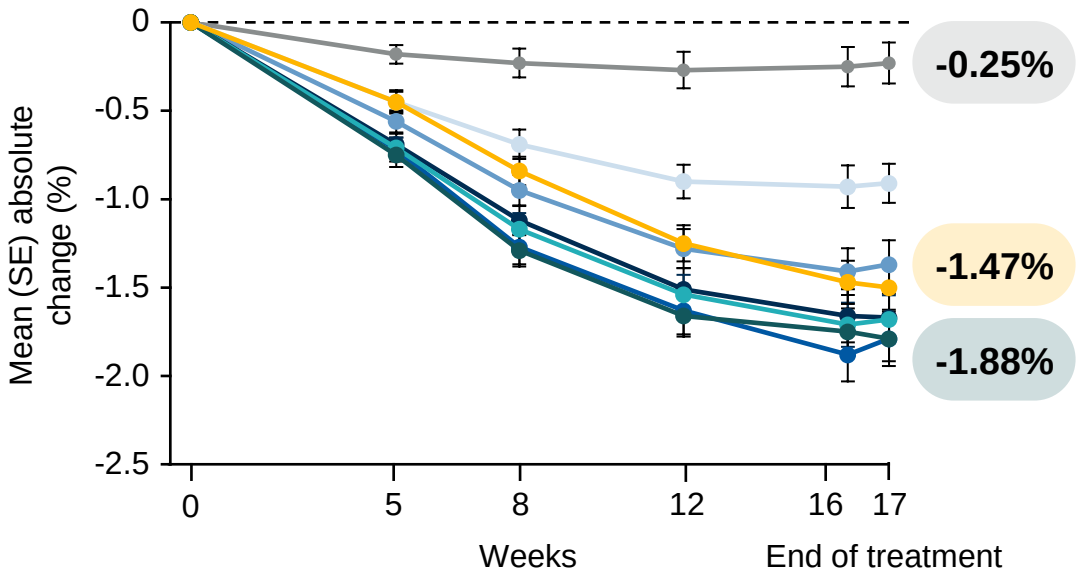
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.

Source: Figure adapted from Zimmermann et al. Mol Metab 2022;66:101633, used under the Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/). The figure has been reformatted. The publication is available at https://doi.org/10.1016/j.molmet.2022.101633

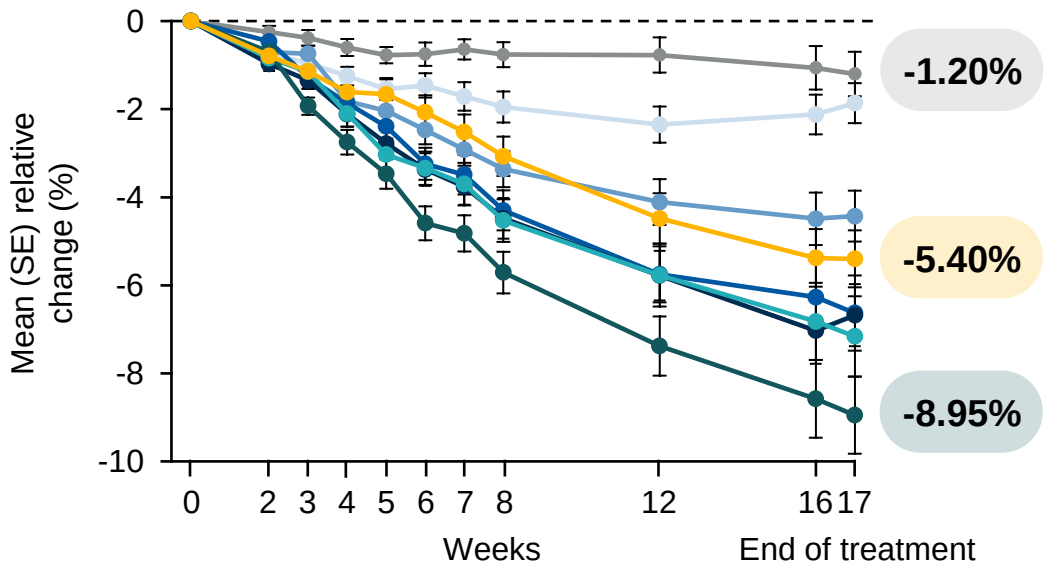
GCGR=glucagon receptor; mRNA=messenger ribonucleic acid; NASH=nonalcoholic steatohepatitis.

In a 16-week Phase 2 trial in T2DM, survodutide effectively reduced HbA1c and body weight

Change in HbA1c



Change body weight



- Placebo
- Survodutide 0.3 mg QW
- Survodutide 0.9 mg QW
- Survodutide 1.8 mg QW
- Survodutide 2.7 mg QW
- Survodutide 1.2 mg BIW
- Survodutide 1.8 mg BIW
- Semaglutide[a] 1.0 mg QW

The safety and tolerability profile was as expected and in line with increasing doses of GLP-1R agonists

[a]The semaglutide arm was open-label.
Body weight at baseline was 93.0–100.1 kg and HbA1c at baseline was 7.9–8.2%.
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Sources: Figures adapted from Rosenstock. Presentation at ObesityWeek, November 1–4, 2022, San Diego, CA.
BIW=twice-weekly; GLP-1R=glucagon-like peptide-1 receptor; HbA1c=hemoglobin A1c; QW=once-weekly; SE=standard error; T2DM=type 2 diabetes mellitus.

In a 46-week Phase 2 trial in obesity, survodutide dose-dependently reduced body weight by up to 18.7%

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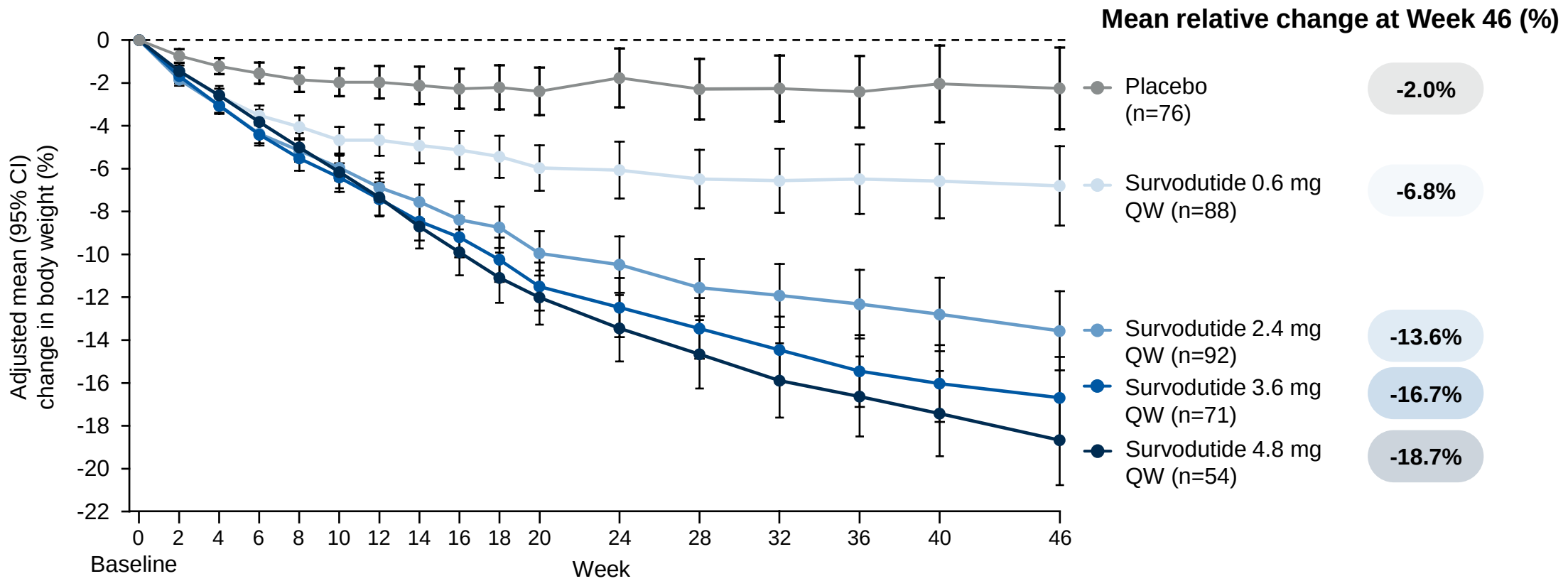
Phase 2 trial of survodutide in people who were overweight or had obesity



Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Source: Figure adapted from Le Roux et al. Oral presentation (51-OR) at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA.
Analysis based on dose reached at the end of treatment regardless of the dose assigned at randomization.
CI=confidence interval; QW=once-weekly.

Treatment with survodutide in the Phase 2 obesity trial showed no unexpected safety findings

- As expected, **GI disorders were the most frequent drug-related AEs**
- Most treatment discontinuations occurred during the **rapid dose escalation** phase (up to Week 20) and may be **mitigated with more gradual dose-escalation**

TEAE, n (%)[a]	Survodutide 0.6 mg (n=77)	Survodutide 2.4 mg (n=78)	Survodutide 3.6 mg (n=77)	Survodutide 4.8 mg (n=77)	Survodutide total (n=309)	Placebo (n=77)
Any TEAE	70 (90.9)	70 (89.7)	71 (92.2)	70 (90.9)	281 (90.9)	58 (75.3)
Nausea[b]	26 (33.8)	51 (65.4)	48 (62.3)	49 (63.6)	174 (56.3)	15 (19.5)
Vomiting[b]	7 (9.1)	23 (29.5)	26 (33.8)	27 (35.1)	83 (26.9)	4 (5.2)
Diarrhea[b]	14 (18.2)	22 (28.2)	18 (23.4)	15 (19.5)	69 (22.3)	8 (10.4)
Constipation[b]	9 (11.7)	17 (21.8)	19 (24.7)	20 (26.0)	65 (21.0)	4 (5.2)
Leading to treatment discontinuation	15 (19.5)	20 (25.6)	19 (24.7)	22 (28.6)	76 (24.6)	3 (3.9)
GI-related	5 (6.5)	13 (16.7)	13 (16.9)	20 (26.0)	51 (16.5)	1 (1.3)
Serious	1 (1.3)	2 (2.6)	6 (7.8)	4 (5.2)	13 (4.2)	5 (6.5)
Investigator defined, drug-related TEAE	47 (61.0)	66 (84.6)	62 (80.5)	62 (80.5)	237 (76.7)	29 (37.7)
Serious, drug-related TEAE	0 (0.0)	0 (0.0)	2 (2.6)	0 (0.0)	2 (0.6)	0 (0.0)

[a]Based on the treated set and presented according to planned treatment; [b]TEAEs listed according to preferred term and occurred in ≥15% patients in any treatment arm.
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Source: Table adapted from Le Roux et al. Oral presentation (51-OR) at ADA 83rd Scientific Sessions, San Diego, June 23–26, 2023.
AE=adverse event; GI=gastrointestinal; TEAE=treatment-emergent adverse event.

Survodutide reduced blood pressure by up to 8.6 mmHg (systolic) and up to 4.8 mmHg (diastolic) at Week 46

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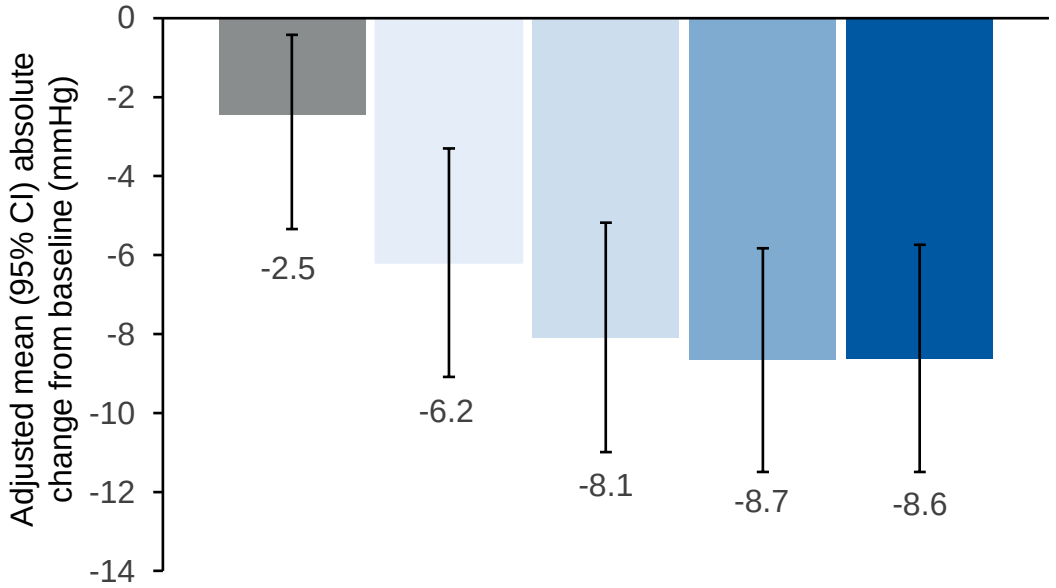
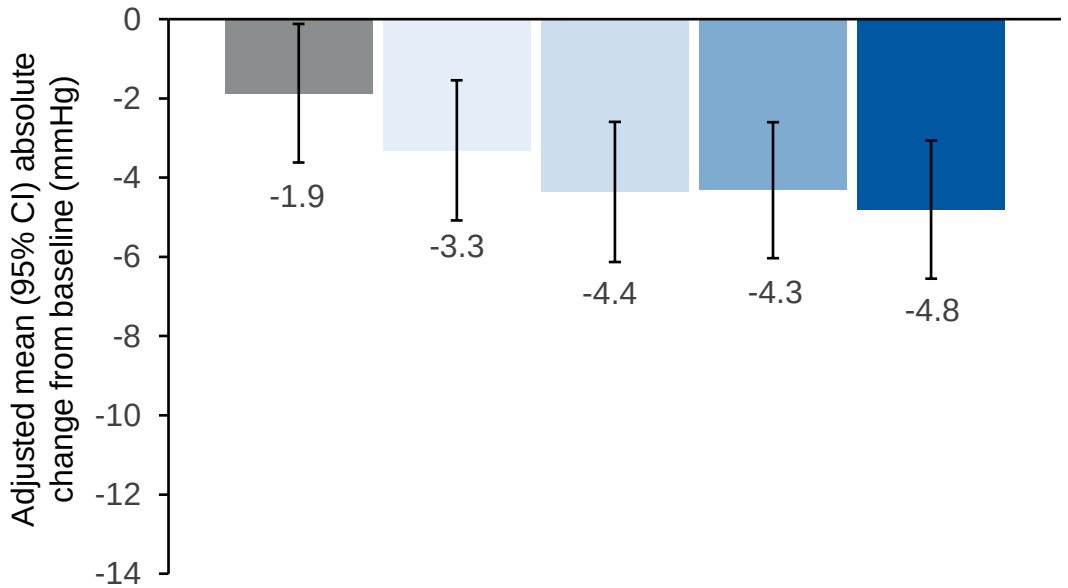
Systolic blood pressure



Diastolic blood pressure



Placebo | Survodutide 0.6 mg QW | Survodutide 2.4 mg QW | Survodutide 3.6 mg QW | Survodutide 4.8 mg QW

Mean blood pressure at baseline across cohorts: 122.6–127.5 mmHg for systolic blood pressure; 80.5–82.4 mmHg for diastolic blood pressure.
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Source: Figures adapted from Le Roux. Presentation at the 59th EASD Annual Meeting, October 2–6, 2023, Hamburg, Germany.
CI=confidence interval; QW=once-weekly.

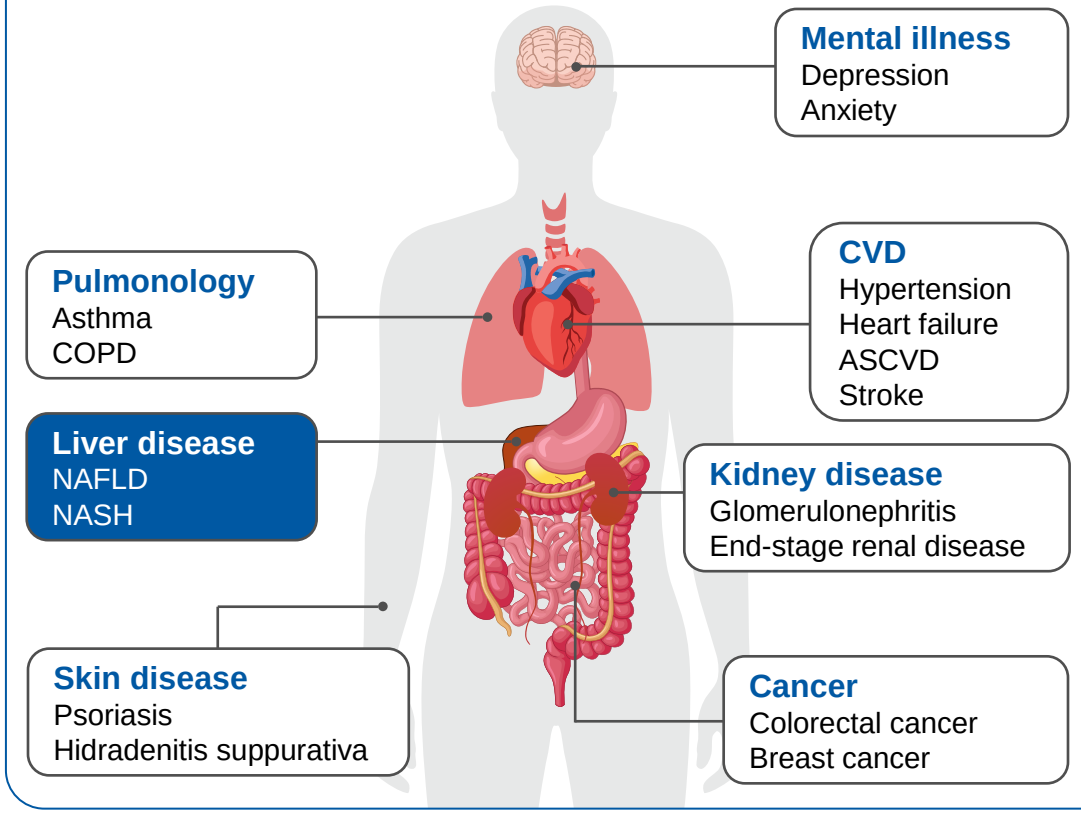
The Phase 3 program with survodutide in obesity, SYNCHRONIZE™, has been initiated

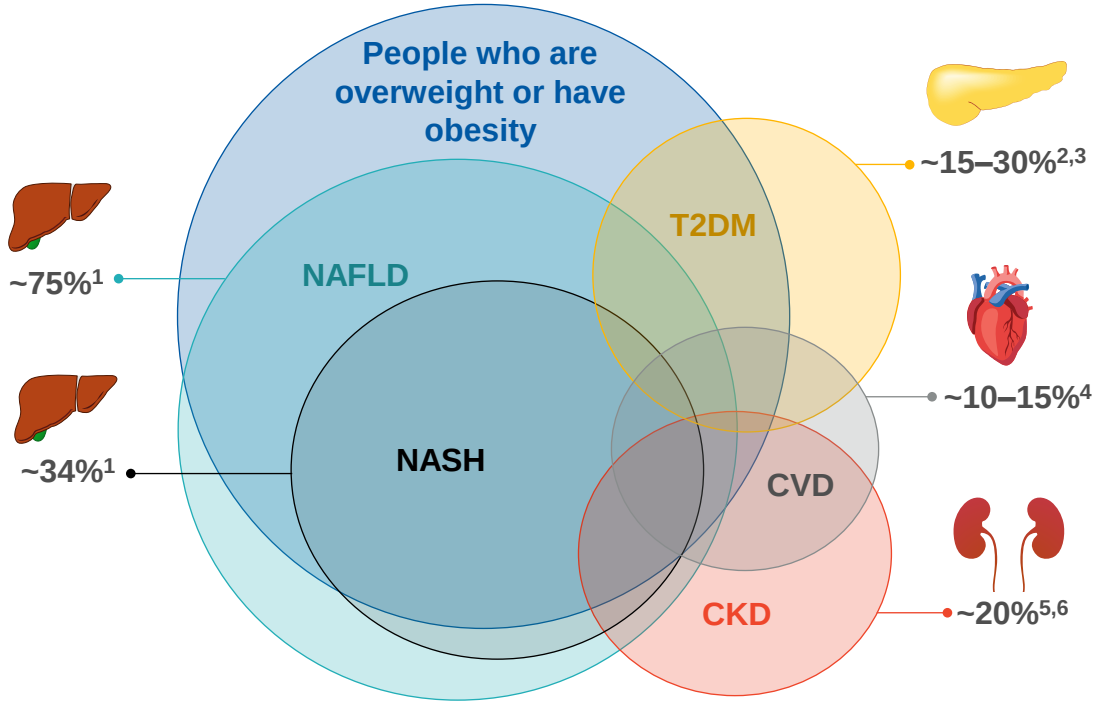
	Inclusion criteria	Study design	Primary endpoint
SYNCHRONIZE™-1[1] Efficacy and safety in patients with obesity without T2DM	• HbA1c <6.5% (no history of diabetes) • BMI ≥30 or BMI ≥27 with comorbidities[a]	• N=600 • 1:1:1 ratio (3.6 mg, 6.0 mg, or placebo) • Trial duration: 76 weeks	• Percentage change in body weight from baseline to Week 76 • Achievement of body weight reduction ≥5% from baseline to Week 76
SYNCHRONIZE™-2[2] Efficacy and safety in patients with obesity and T2DM	• HbA1c ≥6.5% and <10% • BMI ≥27 • T2DM managed with diet and exercise alone or with stable pharmacological treatment	• N=600 • 1:1:1 ratio (3.6 mg, 6.0 mg or placebo) • Trial duration: 76 weeks	• Percentage change in body weight from baseline to Week 76 • Achievement of body weight reduction ≥5% from baseline to Week 76
SYNCHRONIZE™-CVOT[3] Long-term CV safety in patients with obesity and established CVD/CKD or risk factors for CVD	• BMI ≥27 with CVD and/or at least two weight-related risk factors for CVD, or • BMI ≥30 with CVD/CKD and/or at least two weight-related factors for CVD	• N=4,935 • 1:1:1 ratio (3.6 mg, 6.0 mg or placebo) • Trial duration: up to 114 weeks	• Time to first occurrence of any of five major adverse cardiac events (5P-MACE) to demonstrate non-inferiority

[a]Comorbidities comprise dyslipidemia, hypertension, obstructive sleep apnea, and others.
Inclusion criteria for all three trials include age ≥18 years. 5P-MACE includes cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, ischemia-related coronary revascularization or heart failure.
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Sources: 1. SYNCHRONIZE-1. ClinicalTrials.gov (NCT06066515), accessed November 2023; 2. SYNCHRONIZE-2. ClinicalTrials.gov (NCT06066528), accessed November 2023; 3. SYNCHRONIZE-CVOT. ClinicalTrials.gov (NCT06077864), accessed November 2023.
BMI=body mass index; CKD=chronic kidney disease; CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcomes trial; HbA1c=hemoglobin A1c; T2DM=type 2 diabetes mellitus.

There is a significant overlap between obesity and liver disease

Obesity is associated with severe comorbidities, for which there are significant unmet medical needs





Estimates of overlap of comorbidities are not available in literature; approximation in figure is based on individual prevalence estimates.
Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Sources: 1. Quek et al. Lancet Gastroenterol Hepatol 2023;8(1):20–30; 2. Vinciguerra et al. Acta Diabetol 2013;50(3):443–449; 3. Pantalone et al. BMJ Open 2017;7(11):e017583; 4. Schienkiewitz et al. BMC Public Health 2012;12:658; 5. Arinsoy et al. J Ren Nutr 2016;26(6):373–379; 6. Yim & Yoo. Clin Exp Pediatr 2021;64(10):511–518.
ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; T2DM=type 2 diabetes mellitus.

Phase 2 results from the NASH trial with survodutide are expected in H1 2024

Men and women 18–80 years with NASH and fibrosis (NAS ≥4 and F1–F3) and BMI ≥25 kg/m²

N=295 — R

- **Survodutide dose group 1 QW**
- **Survodutide dose group 2 QW**
- **Survodutide dose group 3 QW**
- **Placebo QW**

Primary endpoint:
Histological improvement of NASH without worsening of fibrosis after 48 weeks of treatment

Secondary endpoints:
- LFC reduction of ≥30% from baseline
- Absolute and relative change of LFC from baseline
- ≥1 stage decrease in fibrosis stage (liver biopsy)
- Absolute change in NAS (liver biopsy)

Screening (imaging and biopsy) — 0 — Dosing — Week 48 (imaging and biopsy) — End of study

Survodutide was co-invented by Boehringer Ingelheim and Zealand Pharma. Boehringer Ingelheim is responsible for clinical development and commercialization.
Source: ClinicalTrials.gov (NCT04771273), accessed November 2023.
BMI=body mass index; LFC=liver fat content; NAS=NAFLD activity score; NASH=nonalcoholic steatohepatitis; QW=once-weekly.

Survodutide holds potential as a leading GLP-1-containing weight-loss medication in the 2030s

ZEALAND PHARMA

- **Weight loss** – potential for ~20–25% weight loss,[1] and improved glycemic control[2]
- **MoA** – novel GCGR/GLP-1R dual agonist designed with bias towards GLP-1R[3]
- **Safety and tolerability** – similar to other GLP-1RA-based weight-loss medications[1,4-7]
- **Cardiovascular disease** – potential cardioprotective benefits driven by GLP-1RA, further supported by blood pressure reductions in the Phase 2 obesity trial[8]
- **Other comorbidities** – potential for important benefit in NASH with direct effect of glucagon on the liver[9,10]

Sources: 1. Le Roux et al. Oral presentation (51-OR) at ADA 83rd Scientific Sessions, June 23–26, 2023, San Diego, CA; 2. Rosenstock. Presentation at ObesityWeek, November 1–4, 2022, San Diego, CA; 3. Zimmermann et al. Mol Metab 2022;66:101633; 4. Wilding et al. N Engl J Med 2021;384(11):989–1002; 5. O'Neil et al. Lancet 2018;392(10148):637–649; 6. Frias et al. Lancet 2018;392(10160):2180–2193; 7. Nauck et al. Diabetes Care 2016;39(2):231–241; 8. Le Roux. Presentation at the 59th EASD Annual Meeting, October 2–6, 2023, Hamburg, Germany; 9. Pégorier et al. Biochem J 1989;264(1):93–100; 10. Cherrington. Diabetes 1999;48(5):1198–1214.
GCGR=glucagon receptor; GLP-1=glucagon-like peptide-1; GLP-1R=glucagon-like peptide-1 receptor; GLP-1RA=glucagon-like peptide-1 receptor agonist; MoA=mechanism of action; NASH=nonalcoholic steatohepatitis.

Questions?

We are starting to develop the keys that could help address the greatest healthcare challenge of our time

300,000 years

50 years[1]

3 million deaths[2]

- Dapiglutide
- Petrelintide
- Survodutide

Sources: 1. World Health Organization (WHO). Fact sheet. Obesity and overweight. 9 June 2021. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight, accessed December 2023; 2. World Health Organization (WHO). Fact sheet. Obesity. 9 June 2021. https://www.who.int/news-room/facts-in-pictures/detail/6-facts-on-obesity, accessed December 2023.

Multiple catalysts across the obesity pipeline in 2024

H1 2024

Dapiglutide
Topline results from DREAM trial

Petrelintide
Topline results from MAD Part 2

Survodutide
Topline results from Phase 2 trial in NASH

H2 2024

Dapiglutide
Topline results from 13-week dose-titration trial

Petrelintide
Initiation of Phase 2b trial

MAD=multiple ascending dose; NASH=nonalcoholic steatohepatitis.

Thank you for attending