William Blair

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Industry Report

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Shaping the Future: Innovations and Trends in Obesity Treatment

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Introduction

In the past three years, investors' perception of the obesity space has drastically transformed. Obesity was previously viewed as a condition that was unamenable to therapeutic intervention, primarily due to suboptimal tolerability and modest efficacy. However, the commercial success of Novo Nordisk's Wegovy and Eli Lilly's Zepbound has propelled the obesity space into a secular growth opportunity that could last until the next decade. Taking into account obesity and its associated comorbidities, we estimate that anti-obesity medication could reach over $100 billion in global sales, pending a more accommodative reimbursement landscape.

Beyond the substantial weight loss magnitude achieved with recently approved obesity drugs (which has tripled or quadrupled that of previous-generation Saxenda), Wegovy also demonstrated a 20% reduction in cardiovascular mortality, stroke, and heart attacks. The beneficial outcomes establish GLP-1 receptor agonism as cardioprotective independent of insulin sensitivity. Eli Lilly is on track to release cardiovascular outcomes results around midyear for Mounjaro in the type 2 diabetes population, which we view as a pertinent data point supporting the addition of glucose-dependent insulinotropic peptide (GIP) receptor agonism (on top of GLP-1). The corresponding cardiovascular outcomes study in obesity is slated to read out in 2027.

We believe both investor and big pharma interest, as evidenced by the recent M&A activity, collaboration agreements, and fundraising activities, will drive continued innovation in the field. There are three directions in which the obesity field could advance: 1) rational combination of multi-agonism—the success of retatrutide (also referred to as triple G) validates the potential to combine multiple mechanisms to achieve maximal weight loss potential; 2) longer treatment interval—once-monthly or quarterly administration could offer a material improvement in patient convenience while alleviating supply chain pressure by decreasing the amount of required drug substance; and 3) expansion to modalities that could increase energy expenditure as opposed to appetite suppression.

In this report, we aim to offer investors a comprehensive collection of clinical data presented to date across all relevant modalities in the obesity space. To help investors navigate through the rapidly evolving space, we have devised a simple scoring algorithm that incorporates the velocity of weight loss and adverse event profile to better assess the competitiveness of investigational agents. ***Based on our analysis, we are most bullish on Viking (our top pick for 2025), Skye, Structure, and Corbus. We believe that Altimmune, BioAge, Terns, and Zealand, while intriguing, exhibit less obvious degrees of differentiation.***

In the private space, we are intrigued by OrsoBio and Rivus, which leverage mitochondrial uncouplers as a means to increase energy expenditure. In parallel, Kailera ($400 million series A), Metsera ($275 million IPO), and Verdiva ($411 million series A) will undoubtedly garner investor interest given the prolific fundraising activities in the past year. We conclude the report with several high-profile catalysts that are expected in the next two years.

We have compiled and analyzed data generated from both approved and investigational agents in the obesity field. Our aim is to establish this industry primer as an all-encompassing information source for investors to conduct due diligence. In exhibit 1, we have summarized relevant clinical parameters of approved and investigational therapeutics for weight loss management. In particular, we have outlined placebo-adjusted weight loss magnitude at week 4, week 12, and end-of-trial, along with gastrointestinal adverse events (GI AEs) of interest (namely, nausea, vomiting, and diarrhea). To represent each agent's clinical profile that encompasses both efficacy and tolerability, we calculated a combined score for comparative purposes. We explain the details of our proposed obesity therapy scoring function in the next section.

The final column of the table lists William Blair's combined efficacy and safety score for each asset.

Exhibit 1
Shaping the Future: Innovations and Trends in Obesity Treatment
Overview of Efficacy, Safety, and Dosage of Select Assets in Overweight or Obesity

Drug	Dosage	Frequency of Dose	Administration Mode	Study ID	Weight Loss at 4 Weeks	Weight Loss at 12 Weeks	Weight Loss at 48-72 Weeks or End of Trial (if earlier)	GI AEs (% of participants)	Notes	WB Combined Efficacy and Safety Score
GLP-1 RA										
Wegovy (semaglutide)	2.4 mg	weekly	subQ	Phase III STEP 1 NCT03548935	1%	4%	12% (68 wks.)	N 27% V 18% D 16%	A	3.72
semaglutide	50 mg	daily	oral	Phase III OASIS 1 NCT05035095	2%	3%	13% (68 wks.)	N 37% V 20% D 10%	A	2.73
orforglipron	45 mg	daily	oral	Phase II NCT05051579	4%	6%	12% (36 wks.)	N 32% V 23% D 6%	A, B, C	5.76
	36 mg	daily	oral	Phase II NCT05051579	4%	5%	11% (36 wks.)	N 31% V 22% D -7%	A, B, C	4.92
danuglipron	200 mg	2x daily	oral	Phase II NCT04707313	2%	5%	9% (26 wks.)	N up to 73% V up to 47% D up to 25%	B >50% discontinuation rate due to AEs	-0.28
	160 mg	2x daily	oral	Phase II NCT04707313	2%	5%	10% (26 wks.)	N up to 73% V up to 47% D up to 25%	B >50% discontinuation rate due to AEs	-0.28
GLP-1/GIP RA										
Zepbound (tirzepatide)	15 mg	weekly	subQ	Phase III SURMOUNT 1 NCT04184622	3%	7%	18% (72 wks.)	N 22% V 11% D 16%	A, D	7.00
	10 mg	weekly	subQ	Phase III SURMOUNT 1 NCT04184622	3%	7%	16% (72 wks.)	N 24% V 9% D 14%	A, D	7.04
VK2735	15 mg	weekly	subQ	Phase II VENTURE NCT06068946	3%	13% (13 wks.)	Trial was 13 wks. long	N 43% V 29% D 2%	B	11.14
	10 mg	weekly	subQ	Phase II VENTURE NCT06068946	4%	11% (13 wks.)	Trial was 13 wks. long	N 17% V 17% D 11%	B	3.98
RG6640 (CT-388)	22 mg	weekly	subQ	Phase I NCT04838405	4%	13%	18% (24 wks.)	N 63% V 65% D 34%	E	5.32
	8 mg	weekly	subQ	Phase I NCT04838405	4%	9%	This dose was administered for 12 wks. only	N 22% V 15% D 30%	E	8.78
GLP-1/GCG RA										
pemvidutide	2.4 mg	weekly	subQ	Phase II MOMENTUM NCT05295875	3%	6%	13% (48 wks.)	N 40% V 24% D 13%	A, E	5.18
	1.8 mg	weekly	subQ	Phase II MOMENTUM NCT05295875	3%	6%	9% (48 wks.)	N 48% V 24% D 5%	A, E	5.18
survodutide	4.8 mg	weekly	subQ	Phase II NCT04667377	2%	6%	16% (46 wks.)	N 44% V 30% D 10%	A	4.92
	3.6 mg	weekly	subQ	Phase II NCT04667377	2%	6%	14% (46 wks.)	N 42% V 29% D 13%	A	4.94
efinopegdutide	10 mg	weekly	subQ	Phase II NCT03486392	3%	7%	10% (26 wks.)	N 60% V 55% D 15%	B	2.00
	7.4 mg	weekly	subQ	Phase II NCT03486392	3%	6%	8% (26 wks.)	N 61% V 40% D 15%	B	3.12
mazdutide	6 mg	weekly	subQ	Phase II NCT04904913	2%	8%	12% (24 wks.)	N 36% V 25% D 17%	E	7.14
	4.5 mg	weekly	subQ	Phase II NCT04904913	2%	7%	11% (24 wks.)	N 19% V 17% D 16%	E	6.91

Notes applicable to the entire table: 1) with the exception of the bimagrumab study, only data from obese subjects not diagnosed with T2D are used; 2) weight loss and adverse events are placebo-adjusted unless otherwise indicated; 3) weight loss and adverse effects are rounded to the nearest percentage; 4) where multiple doses were used in the study, the highest and second highest doses are given unless otherwise indicated; 5) unless otherwise indicated, weight loss given is treatment estimand; 6) gastrointestinal adverse events (GI AEs) are N=nausea, V=vomiting, and D=diarrhea; 7) where more than one titration schedule was used for a given dosage, data are from the fastest titration schedule if published results are broken out for each schedule; 8) only trials lasting at least 12 weeks are included.

Notes applicable to specific trials: A) includes diet and exercise counseling; B) efficacy estimand used for all weight loss values due to public unavailability of treatment estimand; C) published data combined multiple titration schedules for weight loss while adverse event figures are given here for the fastest titration schedules; D) efficacy estimand used for interim weight loss values due to unavailability of treatment estimand but treatment estimand used for final weight loss values; E) data made available do not specify whether treatment estimand or efficacy estimand was used.

CB1R=Cannabinoid receptor 1. DACRA=Dual amylin and calcitonin receptor agonist. GCG=Glucagon. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1. RA=Receptor agonist.
Sources: Company documents, clinicaltrials.gov.

Exhibit 1 (Continued)
Shaping the Future: Innovations and Trends in Obesity Treatment
Overview of Efficacy, Safety, and Dosage of Select Assets in Overweight or Obesity

Drug	Dosage	Frequency of Dose	Administration Mode	Study ID	Weight Loss at 4 Weeks	Weight Loss at 12 Weeks	Weight Loss at 48-72 Weeks or End of Trial (if earlier)	GI AEs (% of participants)	Notes	WB Combined Efficacy and Safety Score
GLP-1/GIP/GCG RA										
retatrutide	12 mg	weekly	subQ	Phase II NCT04881760	4%	10%	22% (48 wks.)	N 35% V 18% D 4%	A, B	9.85
	8 mg	weekly	subQ	Phase II NCT04881760	4%	8%	22% (48 wks.)	N 49% V 25% D 9%	A, B	7.04
GLP-1 RA and GIP antagonist										
MariTide (maridebart cafraglutide)	420 mg	every 4 wks.	subQ	Phase II NCT05669599	Not yet available	Not yet available	16% (52 wks.)	Not yet available	B	
	280 mg	every 4 wks.	subQ	Phase II NCT05669599	Not yet available	Not yet available	18% (52 wks.)	Not yet available	B	
Amylin RA										
Symlin (pramlintide)	360 mg	3x daily	subQ	Phase II NCT00112021 NCT00189514	1%	3%	6% (52 wks.)	N 27% V 2 % D 1%	A, B	3.28
	360 mg	2x daily	subQ	Phase II NCT00112021 NCT00189514	2%	3%	7% (52 wks.)	N 22% V 3% D 2%	A, B	3.49
DACRA										
cagrilintide	4.5 mg	weekly	subQ	Phase II NCT03856047	2%	6%	8% (26 wks.)	N 29 % V 5% D -2 %	A	6.23
	2.4 mg	weekly	subQ	Phase II NCT03856047	2%	5%	7% (26 wks.)	N 13% V 6% D 9%	A	5.26
DACRA + GLP1RA										
CagriSema (cagrilintide + semaglutide)	cagri 4.5 mg sema 2.4 mg	weekly	subQ	Phase I NCT03600480	4%	4%	7% (20 wks.)	N 40% V 23% D -38%	E Placebo group received semaglutide	4.12
	cagri 2.4 mg sema 2.4 mg	weekly	subQ	Phase I NCT03600480	3%	5%	7% (20 wks.)	N 50% V 62% D -21%	E Placebo group received semaglutide	2.21
Amycretin	100 mg	daily (50 mg b.i.d.)	oral	Phase I NCT05369390	NA	12%	Trial was 12 wks. long	N 67% V 56% D 19%	E	6.48
	50 mg	daily	oral	Phase I NCT05369390	NA	9%	Trial was 12 wks. long	N 23% V 38% D 6%	E	8.10
CB1R antagonist and/or inverse agonist										
Acomplia (rimonabant)	20 mg	daily	oral	Phase II RIO-N America NCT00029861	1%	3%	5% (52 wks.)	N 5% V n/a D 0%	A, B	3.55
	5 mg	daily	oral	Phase II RIO-N America NCT00029861	0%	0%	1% (52 wks.)	N 1% V n/a D 2%	A, B	0.57
monlunabant	10 mg (lowest dose)	daily	oral	Phase II NCT05891834	NA	NA	6% (16 wks.)	not available	B Weight loss at higher doses was "limited."	
Activin type II receptor antagonist										
bimagrumab	10mg/kg	every 4 wks.	IV	Phase II NCT03005288	NA	NA	6% (48 wks.)	N 11% V n/a D 30%	A, E	
Mitochondrial protonophore										
HU6	450 mg	daily	oral	Phase II HuMAIN NCT05284617	1%	1%	3% (19 wks.)	N n/a V n/a D 12%	B Patients had HFpEF	1.48

Notes applicable to the entire table: 1) with the exception of the bimagrumab study, only data from obese subjects not diagnosed with T2D are used; 2) weight loss and adverse events are placebo-adjusted unless otherwise indicated; 3) weight loss and adverse effects are rounded to the nearest percentage; 4) where multiple doses were used in the study, the highest and second highest doses are given unless otherwise indicated; 5) unless otherwise indicated, weight loss given is treatment estimand; 6) gastrointestinal adverse events (GI AEs) are N=nausea, V=vomiting, and D=diarrhea; 7) where more than one titration schedule was used for a given dosage, data are from the fastest titration schedule if published results are broken out for each schedule; 8) only trials lasting at least 12 weeks are included.

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Sources: Company documents, clinicaltrials.gov.

Although 2024 was not an outstanding year for biotech deals as measured by volume, there have been a number of transactions in the obesity space. Most of the contracts have involved licensing, but there have also been some acquisitions, along with three initial public offerings consummated and another announced. Notably, a number of the licensing agreements involved rights to use advanced information technology. There has been speculation that more transactions will occur this year, given large cash stockpiles at companies like Eli Lilly and Novo Nordisk, which have existing obesity franchises. Naturally, much will depend on the overall economic and regulatory environments. A review of these financing deals is presented in exhibits 2 and 3. In addition, a graphical

depiction of funds raised by companies in the obesity space is presented in exhibit 4. Exhibit 4 depicts an increase in the total dollar volume of venture capital investments in 2024; this was attributable to larger deal size, on average, rather than an increase in the number of deals.

Exhibit 2
Shaping the Future: Innovations and Trends in Obesity Treatment
Notable Mergers and Acquisitions, Partnership/Licensing Deals, and IPOs Involving Obesity-Related Assets During 2024 and 2025

Acquiror/Licensee/ Partner	Target/Licensor/ Partner	Date Announced or Closed	Deal Value (M&A or IPO) (millions)	Upfront (millions)	Potential Milestones (millions)	Royalties? (Licensing/ Partnership)	Details
Mergers & Acquisitions							
Johnson & Johnson	Ambrx	January 2024	$2,000	$2,000	NA	NA	Ambrx specializes in antibody-drug conjugates but has done some work on treatments for obesity-related diseases
Roche	Carmot	January 2024 (closed)	$3,100	$2,700	$400	NA	Carmot is developing therapeutics for metabolic diseases, including obesity and diabetes
Novo Nordisk	Catalent	February 2024	$11,000	NA	NA	NA	Novo agreed to acquire three manufacturing sites used to produce GLP-1 drugs from Catalent for $11 billion, in connection with its acquisition of the company for $16.5 billion
AstraZeneca	Amolyt Pharma	March 2024	$1,050	$800	$250	N/A	Amolyt focuses on endocrine diseases
AstraZeneca	Six Peaks	May 2024	$80 (option, with deal value to be agreed)	NA	NA	NA	AstraZeneca paid $80 million for a two-year option to acquire Six Peaks, whose lead candidate is a bispecific antibody that targets activin type IIA and IIB receptors, if an IND is submitted for the drug
Licensing and Partnerships							
Rhythm Pharmaceuticals	LG Chem Life Sciences	January 2024	$305	$60 (closing) $40 (after 18 months)	$205	Yes	Rhythm agreed to acquire the global rights to the oral small-molecule melanocortin-4 receptor (MC4R) agonist LB54640
Novo Nordisk	EraCal Therapeutics	January 2024	Up to $256	Yes	Yes	Yes	EraCal entered a collaboration and license agreement with Novo Nordisk to develop and commercialize EraCal's oral, small-molecule program for obesity and other metabolic diseases
Kailera	Jiangsu Hengrui Pharmaceuticals	May 2024	Amount not disclosed	Not disclosed	Not disclosed	Not disclosed	Kailera acquired exclusive rights to a portfolio of four obesity-related assets outside Greater China from Jiangsu Hengrui Pharmaceuticals
HK Inno.n Corp.	Hangzhou Sciwind Biosciences	May 2024	Amount not disclosed	Not disclosed	Not disclosed	Yes	Licensing and partnership agreement for ecnoglutide injection (XW003), GLP-1 analog for the treatment of type 2 diabetes, obesity, and MASH, in South Korea
5 Prime Sciences	Lilly	May 2024	Amount not disclosed	Yes	Yes	Yes	5 Prime Sciences is a biotechnology data analytics company, and the partnership is intended to advance discovery and development in cardio-metabolic diseases, including diabetes, obesity, and related conditions
Novo Nordisk	Metaphore Biotechnologies	May 2024	Up to $600	Yes	Yes	Yes	Metaphore, which designs novel therapeutics by combining machine learning and molecular mimicry, entered a research collaboration with Novo to develop up to two next-generation therapeutics for obesity management
Lilly	HAYA Therapeutics	September 2024	Up to $1,000	Yes	Yes	Yes	This collaboration will use HAYA's regulatory genome discovery platform, which enables the identification of tissue-, disease- and cell-specific long non-coding RNA targets and the development of RNA-targeting therapies, to support preclinical drug discovery efforts in obesity and related metabolic conditions
Novo Nordisk	Ascendis Pharma	November 2024	$285	Yes	Yes	Yes	Ascendis granted Novo an exclusive worldwide license to its TransCon technology platform to develop, manufacture, and commercialize Novo's proprietary products in metabolic diseases (including obesity and type 2 diabetes)
Merck	Hansoh Pharma	December 2024	$2,012	$112	$1,900	Yes	Hansoh Pharma granted Merck an exclusive global license to develop, manufacture, and commercialize HS-10535, an investigational preclinical oral small-molecule GLP-1 receptor agonist
Corxel Pharmaceuticals	Suzhou Vincentage Pharma Co.	December 2024	Amount not disclosed	Not disclosed	Not disclosed	Not disclosed	Corxel acquired global rights, excluding Greater China, to VCT220 (to be renamed CX11), a small-molecule GLP-1 agonist developed by Vincentage Pharma
Verdiva Bio	Hangzhou Sciwind Biosciences	January 2025	$2,470	$70	Up to $2,400	Yes	The parties entered a licensing and collaboration agreement for the global development and commercialization of a portfolio of metabolic disease therapies in territories outside Greater China and South Korea, with the portfolio including oral ecnoglutide, an oral amylin receptor agonist, and a subcutaneous injectable amylin receptor agonist
Initial Public Offerings							
BioAge	NA	September 2024	$240	NA	NA	NA	BioAge is developing therapeutic product candidates for metabolic diseases, such as obesity, by targeting the biology of human aging
Metsera	NA	January 2025	$275	NA	NA	NA	Metsera is developing injectable and oral drugs to treat obesity
Aardvark Therapeutics	NA	February 2025	$94	NA	NA	NA	Aardvark is developing small molecule therapies to inhibit hunger and treat metabolic diseases

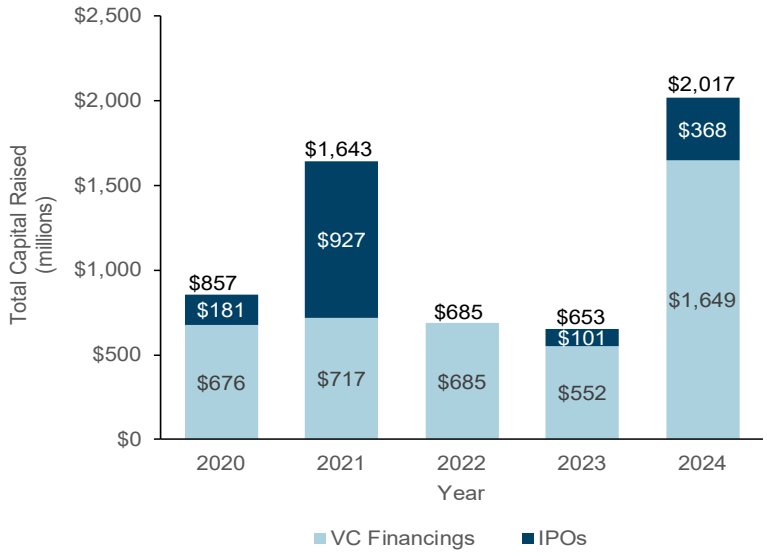
IPO=Initial public offering. M&A=Mergers and acquisitions.
Sources: Company documents

Exhibit 3
Notable Private Equity Financings Involving Obesity-Related Assets During 2024 and 2025

Company	Investors	Date Completed	Deal Value (millions)	Equity or Debt	Equity Series	Details
Venture Capital Investments						
Resalis Therapeutics	Sunstone Life Science Ventures, Claris Ventures, Angel Investors	January 2024	$11	Equity	A	Resalis Therapeutics is developing a microRNA-based treatment for metabolic disorders
Ji Xing Pharmaceuticals (Shanghai) Co. Ltd.	Leaps by Bayer, RTW Investments L.P.	January 2024	$162	Equity	D	Ji Xing develops and commercializes therapeutics to treat cardiovascular and ophthalmic diseases
BioAge Labs	Sofinnova Investments Inc., Longitude Capital, RA Capital Management L.P., Cormorant Asset Management, RTW Investments L.P., SV Health Investors LLP, Orbimed Advisors LLC, Sands Capital Ventures, Pivotal Bioventure Partners, Osage University Partners, Lilly Ventures, Amgen Ventures, Andreessen Horowitz (a16z)	February 2024	$170	Equity	D	The funding will be used to support Phase II clinical development of BioAge's lead compound azelaprag, an oral apelin receptor agonist, in combination with Lilly's Zepbound and other incretins for treatment of obesity
Metsera	ARCH Venture Partners, F-Prime Capital Partners, GV, Mubadala Capital Ventures, Newpath Partners, SoftBank Group, Undisclosed Investors	April 2024 August 2024	$240 $32	Equity	A A-1	Metsera is developing injectable and oral drugs to treat obesity
Aardvark Therapeutics	Decheng Capital, Cormorant Asset Management, Surveyor Capital, SymBiosis, Tetragon Financial Group Ltd., Walleye Capital, Laurion Capital Management L.P., LG Technology Ventures, Cantor Fitzgerald, Silver Arc Capital, Prader-Willi Syndrome Association – USA, Vickers Venture Partners, Foundation for Prader-Willi Research	May 2024	$85	Equity	C	Aardvark intends to use the proceeds to advance its lead asset, ARD-101, for the treatment of hyperphagia in patients with Prader-Willi Syndrome and to advance other pipeline programs
CinRx Pharma LLC	Existing Investors, Undisclosed investors	May 2024	$73	Uncharacterized	Uncharacterized	CinRx Pharma has multiple portfolio companies in medical areas that address metabolic, gastrointestinal and oncology needs
Orion Biotechnology Canada	Keiretsu Forum, Undisclosed investors	July 2024	$0.7	Equity	A	Orion is focused on drugging G protein-coupled receptors in obesity and metabolic diseases and its lead candidates target GPR75
Confo Therapeutics N.V.	Ackermans & van Haaren, Driehaus Capital Management, Quest for Growth, BioGeneration Ventures, Fund+, MINTS, Perceptive Advisors, Qbic Fund, PMV, V-Bio Ventures, VIB, Wellington Partners	July 2024	$65	Equity	B	Proceeds will be used to advance two programs through Phase 1 and two additional programs to IND approval, including molecules targeting GPR75 for obesity
Click Therapeutics Inc.	Undisclosed	August 2024	$8	Debt	NA	Click develops digital therapeutics (mobile software applications) for a variety of indications including obesity.
OrsoBio Inc.	Ascenta Capital, Woodline Partners L.P., Samsara Biocapital, Longitude Capital, Enavate Sciences, NuevaBio, Eli Lilly and Co.	September 2024	$67	Equity	B	Proceeds from the financing will be used to accelerate development of OrsoBio's mitochondrial protonophore portfolio for the treatment of obesity and associated metabolic disorders
Ji Xing Pharmaceuticals (Shanghai) Co. Ltd.	Apeloa Pharmaceutical Co. Ltd.	September 2024	$2.8	Equity	D	Ji Xing develops and commercializes therapeutics to treat cardiovascular and ophthalmic diseases
Model Medicines Inc.	Undisclosed, but at least 43 investors	September 2024	$15	Equity	Undisclosed	Model Medicines integrates diverse data inputs, advanced modeling algorithms, and drug design to identify promising drug candidates in multiple areas of biology
Kailera Therapeutics	Atlas Venture, Bain Capital Life Sciences, RTW Investments L.P., Lyra Capital Pte Ltd.	October 2024	$400	Equity	A	Kailera develops injectable and oral therapies for obesity and related conditions using agonists to receptors for GLP-1, GIP, and glucagon that are licensed from Jiangsu Hengrui Pharmaceuticals
Metsera	Wellington Management, Venrock Healthcare Capital Partners, Fidelity Management & Research Co., Janus Henderson Investors, T. Rowe Price Associates Inc., Viking Global Investors, Deep Track Capital, RA Capital Management L.P., Arch Venture Partners, Alpha Wave Ventures, GV, Softbank Vision Fund 2, Newpath Partners, SymBiosis, Undisclosed Investors	November 2024	$215	Equity	B	Metsera is developing injectable and oral drugs to treat obesity
Antag Therapeutics	Versant Ventures, Novo Holdings A/S, SR One, Dawn Biopharma, Pictet Asset Management, Longview Ventures, Export and Investment Fund of Denmark	December 2024	$84	Equity	A	The funds will support the clinical development of AT-7687, a once-weekly subcutaneous antagonist of the glucose-dependent insulinotropic polypeptide receptor (GIPR), and support expansion of Antag's pipeline of monthly injectable therapies.
Verdiva Bio Ltd.	Forbion, General Atlantic, RA Capital Management L.P., Orbimed Advisors LLC, Logos Capital, Lilly Asia Ventures, Lyfe Capital	January 2025	$411	Equity	A	The funds will be used to advance obesity drugs licensed from Hangzhou Sciwind Biosciences and potentially to acquire rights to additional products

Sources: Company documents.

Exhibit 4
Funding (Venture Capital and Initial Public Offerings) Raised by Obesity-Related Companies, 2020-2024



Sources: Company reports.

A Scoring Function for Investigational Weight Management Agents

Given the rapid pace of innovation in the obesity field, coupled with expanding investigational agents in the pipeline, we believe it could be overwhelming for investors to digest and compare emerging data. As such, we aim to offer investors a simple calculator to quickly assess the relative clinical profile of investigational anti-obesity agents. The score calculates a positive number for efficacy, which is then reduced to reflect the severity of certain adverse effects; thus, a higher score is better.

More specifically, the rationale for the score is as follows:

Efficacy contribution: While we acknowledge that the ultimate arbiter for efficacy is maximum weight loss (which typically plateaus shortly after one year of treatment), weight loss velocity has emerged in the investment community as the alternative surrogate efficacy measurement in the absence of long-term data. To eliminate the intrinsic noise from short-term Phase I studies that typically enroll single digits per arm, we believe the placebo-adjusted weight loss at 12 weeks (WL12) serves as a reasonable time point for assessment.

Tolerability offset: While the titration schedule is not explicitly included in the scoring function, by accounting for adverse events, namely, vomiting, diarrhea, and nausea, the scoring function balances efficacy with tolerability parameters. Among these three adverse events, vomiting is particularly troublesome for patients, and we applied a double weighting over diarrhea and nausea.

Among agents with Phase III results available, Zepbound demonstrated the lowest placebo-adjusted frequency across vomiting (11%), diarrhea (16%), and nausea (22%). This results in a "tolerability liability" of 0.6, calculated as [(0.11×2) + 0.16 + 0.22]. Since all other approved or

investigational agents have relatively worse tolerability, the relative difference to Zepbound is used to quantify the tolerability liability (the correction constant). Lastly, to account for the non-linear relationship between adverse event frequency and the patient's perception of tolerability, we incorporated a multiplier for agents with exceedingly high adverse event rates (up to 0.40: 1×; 0.41-0.80: 2×; 0.81-1.20: 3×; 1.21 or above: 4×) (the penalty factor).

Thus, the scoring function equals:

$$WL12 - [(Vomiting\% \times 2) + Diarrhea\% + Nausea\% - Correction\ Constant] \times Penalty\ Factor$$

As a base case, Zepbound has a score of 7.0 (7% weight loss at week 12 with no adjustments (since it represents the floor and the bracketed number would be zero). In comparison, despite Roche's CT-388 demonstrating a more rapid placebo-adjusted weight loss of 12% at week 12, high placebo-adjusted adverse event frequencies (65% vomiting, 63% nausea, and 34% diarrhea) reduced CT-388's score to 5.32.

Background on GLP-1 and GIP Receptor Agonists

GLP-1, or glucagon-like peptide 1, is a 30-amino-acid cleavage derivative of proglucagon, the shared precursor molecule for both GLP-1 and glucagon. Endocrine epithelial L cells of the intestinal mucosa and α cells located in the pancreatic islets of Langerhans produce proglucagon, as do a small group of neurons localized to the nucleus of the brain stem's solitary tract. Proglucagon is processed differently depending on the organ system. In the pancreas, the prohormone convertase PC2 cleaves proglucagon into glicentin-related pancreatic peptide (GRPP), major proglucagon fragment (MPGF), intervening peptide-1 (IP-1), and glucagon itself. In the gut and brain, prohormone convertase PC3 cleaves proglucagon into glicentin, intervening peptide 2 (IP-2), GLP-1, and GLP-2. The chemical structures of five endogenous peptides that regulate energy homeostasis and glucose metabolism including amylin, GLP-1, GIP, peptide tyrosine-tyrosine 3-36 (peptide YY_{3-36}), and glucagon are presented in exhibit 5.

Exhibit 5
Structures of Endogenous GLP-1, GIP, Amylin, Peptide YY_{3-36}, and Glucagon

GLP-1=Glucagon-like peptide 1. GIP=Glucose insulinotropic peptide. Peptide YY=Peptide tyrosine tyrosine.
Sources: Holst, Nat Metab 2024.

GLP-1 is secreted following a meal, regardless of the specific macronutrients ingested, by endocrine L cells in the gastrointestinal tract localized from the jejunum to the rectum. L cells in the proximal region of the gastrointestinal tract—that is, closer to the stomach—are believed to be responsible for the observed GLP-1 increase in the bloodstream following a meal. During fasting, circulating GLP-1 concentration remains low, approaching the lower limit of detection of quantifying assays.

Investigators initially identified GLP-1 based on the molecule's insulinotropic ability to potently prime glucose-mediated insulin production while having no impact on insulin secretion without the presence of glucose. This insulinotropic capacity of GLP-1 is shared by a handful of molecules in the large glucagon-secretin peptide family, including vasoactive intestinal polypeptide (VIP), peptide histidine isoleucine (PHI), glucagon, and glucose-dependent insulinotropic polypeptide, also called gastric inhibitory polypeptide (GIP). What makes GLP-1 stand out from other molecules, though, is its ability to reduce heightened blood glucose levels by both stimulating insulin secretion, which sequesters glucose into intracellular glycogen, and inhibiting glucagon secretion in the liver, which in turn reduces hepatic glucose production.

Blood glucose levels then decrease, but since the effects of GLP-1 are glucose-dependent, blood glucose levels decrease at a less steep rate as less glucose is present in the bloodstream. After identifying this ability, researchers dubbed GLP-1 as an "incretin," or a hormone produced following introduction of oral and intra-intestinal glucose that is able to promote insulin secretion to a greater degree compared with intravenous infusion of glucose at similar blood glucose levels. GIP was also established as an incretin, and both GLP-1 and GIP are believed to be the main source of the incretin effect allowing for rapid normalization of blood glucose levels following ingestion of glucose-containing foods.

The effects of GLP-1 and GIP are limited by dipeptidyl peptidase-4 (DPP-4), which inactivates these incretins. DPP-4 accomplishes this by slicing alanine and proline from the N-terminal ends of GLP-1 and GIP. DPP-4, in turn, can be pharmacologically inhibited.

GLP-1 also has profound impacts on the gastrointestinal tract itself. Infusions of GLP-1 may completely inhibit the emptying of stomach contents into the proximal small intestine as well as inhibit the progression of food through the rest of the gastrointestinal tract and exocrine secretion in the stomach and pancreas. It is thought that this increase in gastric accommodation is driven by GLP-1 activation of vagal afferents (Camilleri & Lupianez-Merly, Amer. J. Gastroent. 2024). The vagus nerves are the main nerves of the parasympathetic nervous system that regulate body functions including digestion, heart rate, and the immune system.

Because of the inhibition of gastric emptying, GLP-1 also lowers the difference in glucose concentration between before and after a meal, also known as postprandial glucose excursions. Based on these properties, GLP-1 is believed to be one of the hormones responsible for limiting upper-gastrointestinal functions that follow nutrient stimulation of the distal small intestine. It is thought that this mechanism signals an abundance of nutrients that in turn stops a person from eating more food.

In studies of the effects of GLP-1 infusions, researchers observed a dose-dependent inhibitory effect of GLP-1 infusion on hunger and food intake and a dose-dependent enhancement of satiety between meals. As the rate of infusion of GLP-1 increased, so did the degree of food intake inhibition. During these experiments, investigators noted the potential of GLP-1 administration to induce nausea and vomiting in a manner similar to glucagon, inferring a limit to the quantity and rate of GLP-1 that can be given safely.

GLP-1 offered promising therapeutic potential in patients with type 2 diabetes.

Briefly, patients with type 2 diabetes have impaired pancreatic β cell function, leading to a failure to produce insulin adequately in response to glucose ingestion, dysregulated blood glucose levels, and a host of resulting systemic complications. In fact, patients with type 2 diabetes almost completely lack the incretin effect mentioned earlier. The profile of GLP-1 stimulating the glucose-dependent release of insulin sequestered in granules as well as increasing the rate of insulin synthesis and protecting pancreatic β cells from glucose-, fatty acid-, and cytokine-driven apoptosis offered researchers an encouraging potential way to improve blood glucose regulation in type 2 diabetes. Furthermore, GLP-1 inhibits the secretion of glucagon, which is typically elevated in patients with type 2 diabetes, contributing heavily to hyperglycemia. Researchers later identified that chronic GLP-1 administration led to increased insulin sensitivity.

Patients with type 2 diabetes received GLP-1 or GIP infusions, and investigators observed that GIP was marginally effective on its own, while GLP-1 infusion resulted in significant enhancement in insulin secretion. Moreover, constant administration of GLP-1 over four hours to patients with long-standing type 2 diabetes brought fasting glucose to normal levels, promoted insulin secretion, and limited glucagon secretion.

Later studies then homed in on the impacts of GIP and GLP-1 on early- and late-phase insulin secretion; early phase begins in response to increased blood glucose levels within about two minutes of eating and lasts 10 to 15 minutes. Late phase is the sustained, gradual release of de novo insulin-containing vesicles that are activated independent of blood glucose level; this late phase of insulin secretion plateaus at about two to three hours following a meal. When given to patients with type 2 diabetes, GIP was revealed to stimulate early-phase insulin secretion to a similar extent as GLP-1; however, GIP had no effect on late-stage insulin secretion. Conversely, GLP-1 infusion increased

late-phase insulin secretion to a greater degree in patients with type 2 diabetes than did glucose alone in the non-diabetic control group. At the same time, the effects of GLP-1 are attenuated in patients with type 2 diabetes compared with healthy individuals.

A proof-of-concept study in which patients with type 2 diabetes were administered subcutaneous GLP-1 continuously over six weeks revealed antidiabetic effects of GLP-1, including reduced glycated hemoglobin (HbA_{1c}), improved β-cell function, restored early-phase insulin response, and significant body weight loss without observable adverse events (Zander, et al. Lancet 2002). In part, these results accelerated the research-and-development efforts surrounding stabilized, long-acting GLP-1 receptor agonists (RAs).

Obesity is thought to be linked to dysregulated secretion of GLP-1 following a meal, with weight loss tied to higher GLP-1 levels and higher responses to oral glucose intake.

Studies on the role of incretin hormones in the underlying pathology of type 2 diabetes identified deficient insulinotropic functions of GIP in particular and to a lesser extent GLP-1 as the primary cause for dysregulated or entirely defective incretin effect. However, questions remained as to what extent GLP-1 and GIP contributed to the pathophysiology of obesity; studies investigating the question, such as the ADDITION-PRO cohort study, identified an inverse relationship between GLP-1 responses to oral glucose tolerance tests and the magnitude of obesity in patients. In the 1,462-individual Phase III ADDITION-PRO study, GLP-1 levels were quantified during fasting and 30 minutes and 120 minutes following an oral glucose tolerance test. Investigators reported that patients with overweight or obesity demonstrated about 20% decreased GLP-1 responses independent of their respective glucose tolerance, with GLP-1 responses inversely correlated with the magnitude of obesity.

A study of 35 monozygotic (identical) and 75 dizygotic (fraternal) twin pairs found that poor GLP-1 responses were closely linked to acquired obesity in young adults. Investigators found that overall GLP-1 response heritability was 67% and that impaired GLP-1 responses could be found in the heavier co-twins compared with the leaner monozygotic co-twins who had non-identical body mass index (BMI), liver fat, and insulin sensitivity. Since monozygotic twins are nearly genetically identical, or concordant, acquired obesity in one twin and not the other may be due in part to nongenetic causes. However, the authors concluded that further investigation was required to determine whether metabolically unhealthy obesity observed in the study was an acquired condition not linked to genetics or resulted from underlying genetic susceptibility to obesity and environmental stimuli.

Research into the mechanisms behind the anti-obesity effect of GLP-1 RAs indicates that interactions with appetite-reducing regions in the central nervous system lead to reduced food intake.

While poor GLP-1 responses were found to be linked to obesity in previous studies, investigators were puzzled to find that mice with total deletion of the gene encoding GLP-1 receptor did not become obese. This finding led to the question of whether GLP-1 physiologically regulated appetite and food intake. To answer this question, researchers additionally investigated the relationships between food intake and gastric bypass surgery, exendin 9-39, a truncated form of exendin-4 and a potent GLP-1R antagonist (i.e., a drug that blocks the effects of agonists and inverse agonists, but produces no effect on its own), and peptide tyrosine-tyrosine (peptide YY, or PYY). PYY, like GLP-1, is a gut hormone that is released following a meal and that has appetite-reducing capabilities. PYY is initially made in the form of PYY_{1-36}, and that form dominates in circulation in the fasted state. Cleavage of two amino acids by DPP-4 produces PYY_{3-36}, which is the major circulating form postprandially. The two forms of PYY have different receptor selectivity (DeSilva & Bloom, Gut & Liver

2012). Administration of long-acting formulation of exendin 9-39 to obese mice revealed weight loss and diabetes-protective effects of endogenous GLP-1, as obese mice receiving daily exendin 9-39 exhibited significantly greater food intake, body weight, and glucose intolerance.

To test if a similar impact of exendin 9-39 could be observed in humans, investigators performed two studies. In the first study, researchers measured food intake, appetite, and appetite-impacting hormones like GLP-1 and PYY in nine patients before and three months after Roux-en-Y gastric bypass (RYGB) surgery with and without exendin 9-39. In the second study, investigators examined patients who had received RYGB and randomized them into a placebo-controlled, crossover-enabled trial on four experimental days with either exendin 9-39, the DPP-4 inhibitor sitagliptin (to inhibit formation of active PYY_{3-36}), combined exendin 9-39 and sitagliptin, or placebo. Researchers found that exendin 9-39 increased food intake before RYGB in the first study but failed to increase food intake following RYGB; this could be explained by increased plasma levels of both GLP-1 and PYY following surgery and after exendin 9-39 administration (Svane, et al. Int'l J. Obesity 2016).

Even though exendin 9-39 inhibited GLP-1R in this setting, the increased levels of PYY offset the effects of GLP-1R antagonism and kept patient appetite from increasing. It is thought that this phenomenon may be due to paracrine negative feedback in the intestine, in which GLP-1 antagonism leads, in turn, to increased secretion of and response to PYY. While administration of the DPP-4 inhibitor sitagliptin could attenuate the formation of active PYY3-36 to reduce the peptide's impact on appetite, DPP-4 inhibition also significantly increases GLP-1 levels, which in turn also has suppressive effects on appetite. In the combined regimen cohort of sitagliptin and exendin 9-39, in which both GLP-1R and the formation of active PYY3-36 were inhibited, patients in the second study exhibited a 20% significant increase in food intake, lending weight to the hypothesis that both PYY and GLP-1 play roles in regulating food intake.

The only molecularly characterized receptor for GLP-1 is GLP-1 receptor (GLP-1R), expressed in most organ systems, including the cardiovascular and digestive systems, the central nervous system (CNS), and the peripheral nervous system. Because of the rapid degradation of GLP-1 following entry into circulation, researchers in the field question if GLP-1 receptors expressed in the CNS interact primarily with GLP-1 generated locally in brain stem neurons known as preproglucagon neurons. Preproglucagon neurons extend widely throughout the CNS, and the GLP-1 they produce could interact with these CNS GLP-1 receptors. Of note, radiolabeled or fluorescently tagged GLP-1 has not been reported to enter circumventricular structures or other brain sites in animals that do not express GLP-1R. Circumventricular organs are structures on the periphery of the brain that lack a blood–brain barrier. This allows polypeptide hypothalamic hormones to exit the brain while leaving the blood–brain barrier intact and simultaneously allows circulating molecules that cannot cross the blood–brain barrier to effect changes in the brain. This exclusion of circulating GLP-1 from the CNS may also extend to exogenous GLP-1 RAs, as it was found that infusions of liraglutide in patients did not detectably impact liraglutide concentrations in cerebral spinal fluid even though the concentration of circulating liraglutide in plasma was 30 nM.

However, GLP-1 in the bloodstream appears to interact with GLP-1 receptors of the circumventricular organs (such as the area postrema). In conditions such as following exceptionally large meals or rapid diarrhea or gastric emptying, GLP-1 levels may attain high enough circulating concentrations to stimulate circumventricular GLP-1 receptors and affect appetite. Furthermore, investigators have shown that intraperitoneal injections of liraglutide and exendin-4 result in the activation of afferent, or signaling to centers in the brainstem, forebrain, and sensory nerves, including the vagus nerves.

In a mouse model, GLP-1 receptors in the CNS and visceral nervous system, which relay information between the CNS and visceral organs, appear to be important for mediating changes in food intake while not being required for blood glucose regulation. In animals with CNS or visceral

nerve-specific deletion of GLP-1R, administration of liraglutide lowered blood glucose levels but did not impact food intake or body weight. In other experiments, researchers have identified that GLP-1 effects on appetite and food intake appear to implicate interactions with CNS glutamatergic neurons instead of GABAergic neurons. Regarding interactions with GLP-1R on vagal sensory nerves and how they mediate the effects of GLP-1, researchers have described two parallel circuits that form parts of the system relaying satiety signals through vagal nerves. These include the *Glp1r*-expressing vagal sensory neurons, which act independently of the nucleus of the solitary tract, a region in the brainstem's medulla oblongata that regulates internal homeostasis, as well as mechanosensitive oxytocin-receptor vagal sensory nerves, which are the primary drivers of central GLP-1 mediated meal termination.

In summary, the impacts of GLP-1 on food intake and appetite entail the activation of afferent nerves that signal via a "relay" in the nucleus of the solitary tract to regions in the brain that regulate appetite. Exogenous GLP-1 and GLP-1 RAs may reach high enough concentrations in the bloodstream to directly trigger GLP-1R–expressing neurons in the circumventricular organs. These activated circumventricular neurons then may stimulate neurons in brain nuclei, or nerve clusters, including the central amygdala, parabrachial nucleus, the bed nucleus of the stria terminalis, and the paraventricular nucleus, which are all brain regions known to regulate appetite and/or feeding behavior.

Early Development of GLP-1 Receptor Agonists

Early peptide-based GLP-1 RAs exenatide and liraglutide had longer circulating half-lives compared with GLP-1 through decreased degradation by DPP-4 and more limited renal elimination.

An issue that investigators had to address in developing therapeutics targeting the GLP-1 receptor was the short 1.5- to 2.0-minute half-life of endogenous GLP-1 in plasma. This attenuated timespan resulted mainly from the degradation of GLP-1 by the enzyme dipeptidyl peptidase-4 (DPP-4) and the rapid elimination of GLP-1 by the kidneys.

To lengthen the half-life of GLP-1 RAs in the bloodstream, researchers initially took inspiration from a 39-amino-acid peptide called exendin-4, derived from the saliva of the Gila monster. The sequence similarity of exendin and GLP-1 was uncovered in the 1990s by a researcher who was intrigued by previous studies showing that venom from Gila monsters caused enlargement of the pancreas, suggesting overstimulation of that organ (NIH website). Exenatide, under the brand name Byetta, was the first GLP-1 RA to reach the market, in 2005, after development efforts by Amylin Pharmaceuticals and Eli Lilly. It is a synthetic exendin-4 with C-terminal amidation to promote the molecule's stability. Exenatide stimulates insulin production via GLP-1 receptor agonism in a similar manner to endogenous GLP-1, resists degradation by DPP-4, and is eliminated renally only by glomerular filtration. In turn, the half-life of Byetta was extended to two to three hours in circulation (PubChem listing). The available chemical structures, dosing regimens, and half-lives of peptide-based therapeutics with high sequence homology to endogenous GLP-1, including lixisenatide, exenatide, liraglutide, dulaglutide, and semaglutide, are presented in exhibit 6.

Exhibit 6
Structures of Endogenous GLP-1, Lixisenatide, Exenatide, Liraglutide, Dulaglutide, and Semaglutide

Dark blue=Amino acids with homology to GLP-1 sequence. Light blue=Amino acids that differ from GLP-1's sequence. Green=Amino acids unique to lixisenatide. Gray=Spacer amino acids.

C16=16 carbons long. C18=18 carbons long. Fc=Fragment crystallizable. GLP-1=Glucagon-like peptide 1. IgG4=Immunoglobulin G4. T2DM=Type 2 diabetes mellitus.

Sources: Holst, Nat Metab 2024, Global Substance Registration System, Company documents.

The registrational AMIGO-1, AMIGO-2, and AMIGO-3 trials demonstrated that exenatide had relevant anti-diabetic hyperglycemic effects and induced weight loss. For example, the AMIGO-2 trial of twice-daily 5 µg or 10 µg exenatide versus placebo preceding main meals with ongoing sulfonylurea therapy in poorly controlled type 2 diabetes demonstrated significant reductions in HbA1c, fasting glucose concentrations in the 10 µg arm, and a mean weight loss of 1.6 kg in the 10 µg arm with mild to moderate gastrointestinal adverse events after 30 weeks on treatment. Extended-release exenatide was approved in 2013 following development by Amylin Pharmaceuticals, Alkermes plc, and Eli Lilly, under the brand name Bydureon, which had a half-life of roughly two weeks, allowed once-weekly dosing, and had marginally improved efficacy on both diabetic hyperglycemia and weight loss metrics.

After exenatide, the next GLP-1 RA that was also a GLP-1 analog to be commercialized was liraglutide in 2010 under the Novo Nordisk brand name Victoza in overweight or obesity with type 2 diabetes. It received regulatory approval based on the results of the Phase III LEAD trials. Liraglutide is a natural GLP-1 peptide with a palmitic acid modification attached via a glutamic acid spacer to the lysine residue at position 26 and a substitution of a lysine with an arginine residue at position 34 of the GLP-1 precursor peptide. The molecule's modifications allowed liraglutide to bind to circulating albumin to avoid degradation by DPP-4 and renal elimination, granting a circulating half-life of 12 hours to enable constant GLP-1 receptor agonism with daily subcutaneous infusions (PubChem listing).

To increase the GLP-1 RA dose that could be safely administered, investigators had to address treatment-related gastrointestinal adverse events through dose titration.

Researchers noted that gastrointestinal adverse events were limiting the dose of GLP-1 RAs that could be safely administered in clinical trials and in tandem the potential efficacy of the drugs. One of the earlier indications of this dose-limiting aspect of adverse events linked to GLP-1 RA administration was detailed in the mid-1990s (Ritzel, et al. *Diabetologia* 1995). Healthy individuals received 0.17, 0.5, 1.5, and 4.5 ng/kg GLP-1 subcutaneous infusions, and the majority of patients experienced paresthesia, vertigo, hyperhidrosis, chills, and, at elevated doses, nausea and vomiting during peak GLP-1 concentration in the bloodstream. In addition, a 2001 study (Larsen et al. *Diabetes Care* 2001) in moderate type 2 diabetes demonstrated that GLP-1 continuous intravenous infusions for one week at 4, 8, 16, and 24 ng/kg/min elicited intolerable side effects including vomiting at the 16 ng/kg/min and 24 ng/kg/min doses, resulting in researchers not including details on these doses in the final publication. The 4 ng/kg/min and 8 ng/kg/min dose levels were infused successfully over the trial term but still resulted in reports of dizziness, nausea, and vomiting, which were elevated in the 8 ng/kg/min dose cohort.

A key example of the effectiveness of gradual GLP-1 RA titration at mitigating on-target gastrointestinal adverse events is presented in the registrational studies (NCT01336023) for the drug IDegLira, the combination of liraglutide and the long-acting insulin degludec in long-standing type 2 diabetes, which entered the market under the Novo Nordisk brand name of Xultophy in 2016. In the study, patients received the drug over a two-week titration according to fasting blood glucose levels, which is typical for insulin therapy. Patients received either IDegLira or insulin degludec alone or liraglutide alone. Patients receiving the combined regimen demonstrated comparable adverse events to patients receiving insulin degludec alone, in which group researchers reported nearly no gastrointestinal adverse events.

Based on the results of this study and others, investigators realized that higher tolerable dose levels and greater therapeutic efficacy might be achieved using slower up-titration time frames for the treatment of not only type 2 diabetes patients but also otherwise healthy patients with obesity. Novo Nordisk sponsored a 20-week Phase II trial testing 1.2 mg, 1.8 mg, 2.4 mg, or 3.0 mg once-daily liraglutide compared with placebo in obese individuals. Results published in *The Lancet* in 2009 (Astrup, et al. *Lancet* 2009) demonstrated a dose-dependent impact on weight loss; liraglutide dosing resulted in mean weight loss from baseline of around 5 kg (1.2 mg dose), 6 kg (1.8 mg), 6 kg (2.4 mg), and 7 kg (3.0 mg), with 7 kg representing around 8% of baseline body weight. Furthermore, while clinicians observed negligible efficacy in about 25% of patients at the 1.2 mg dose, nearly all participants who received the highest doses of liraglutide lost weight.

Novo Nordisk then sponsored the four Phase III SCALE trials testing once-daily 3.0 mg liraglutide, with results published between 2013 and 2016; the results of these trials ultimately led to FDA approval for liraglutide (under the brand name Saxenda) in overweight and obesity. The trials included SCALE 1, enrolling 3,731 patients with obesity, of which 61% were pre-diabetic; SCALE 2, enrolling patients with obesity and type 2 diabetes; a third maintenance study that began treatment of obese, non-diabetic individuals with liraglutide following diet-induced weight loss; and a fourth study testing liraglutide in patients with sleep apnea and obesity. SCALE 1 patients saw around 8 kg in body weight loss after roughly one year of treatment, with three years of follow-up to allow for assessment of weight loss durability and potential mitigation of incident diabetes. In the study, the rate of incident diabetes decreased by 79%. In the maintenance trial, patients lost about 6% of their body weight in the lead-in low-calorie diet and then another roughly 6% in the year after on liraglutide therapy, representing a total of 12-13 kg.

Lixisenatide is a 44-amino-acid peptide based on the GLP-1 analog exendin-4. Marketed by Sanofi in the United States as Adlyxin, it was approved by the FDA in 2016 as a once-daily injection to improve glycemic control in adults with type 2 diabetes. Lixisenatide has been found to be effective for weight loss in type 2 diabetes patients (Vosoughi, et al., *eClinicalMedicine* 2021). However, Sanofi decided to discontinue its availability in the U.S. in 2023. Nevertheless, it remains available

in Europe under the name Lyxumia. It is interesting to note that a recent trial suggested that it may be associated with less progression of motor disability in participants with early Parkinson's disease, although it was associated with gastrointestinal side effects (Meissner, et al. *NEJM* 2024).

Development of Improved GLP-1 Receptor Agonists

The next generation of obesity assets comprises the peptide-based blockbuster drugs semaglutide and tirzepatide. They induce improved insulin secretion, decreased food intake, elongated half-lives, and improved dosing regimens. Investigators sought to alter the characteristics of earlier-generation GLP-1 RAs such as albumin binding, resistance to DPP-4 cleavage, and linker optimization to achieve greater weight loss efficacy and more optimal dosing methods, including once-weekly subcutaneous dosing schedules. Oral versions of semaglutide and tirzepatide that can be approved by the FDA for treatment of obesity (as opposed to diabetes) are also in trials.

While semaglutide is solely a GLP-1 RA, tirzepatide combines a GLP-1 RA with a GIP receptor agonist (GIP RA). It has been shown that dual GIPR/GLP-1R agonism can result in greater weight loss than GLP-1R agonism alone (Jastreboff et al., *NEJM* 2022). Furthermore, GIPR agonism may alleviate some GLP-1–linked gastrointestinal adverse events when used in combination with GLP-1 RAs (Knop et al., *Diabetes Obes Metab* 2024). The available chemical structures, dosing regimens, and half-lives of peptide-based therapeutics with high sequence homology to endogenous GLP-1, GIP, and glucagon, including tirzepatide, retatrutide, pemvidutide, and survodutide, are presented in exhibit 7.

Exhibit 7
Structures of Endogenous GLP-1, GIP, Glucagon, Tirzepatide, Retatrutide, Pemvidutide, and Survodutide

Gray=Spacer amino acids.

Ac4c=1-aminocyclobutane-1-carboxylic acid. AEEA=Aminodiethoxyacetyl. Aib=α-aminoisobutyric acid. C18=18 carbons long. C20=20 carbons long. GIP=Glucose insulinotropic peptide. GLP-1=Glucagon-like peptide 1. MeL=α-methyl-L-leucine.

Sources: Holst, Nat Metab 2024, Chavda et al., Molecules 2022, Coskun et al, Cell Metab 2022, Bailey et al., Peptides 2023, Global Substance Registration System, Company documents

Novo Nordisk's Semaglutide

Semaglutide, marketed under brand names of Ozempic for type 2 diabetes and Wegovy for weight management, is a peptide-based GLP-1 receptor mono-agonist with a once-weekly dosing schedule. Data from the Phase III SUSTAIN 1, SUSTAIN 2, and SUSTAIN 6 trials supported FDA approval of once-weekly injections of 0.5 mg or 1.0 mg semaglutide (starting with a dose level of 0.25 mg and increasing to 0.5 mg after four weeks) in Ozempic for type 2 diabetes in December 2017, with a higher dose of 2.0 mg added in March 2022.

Regarding Wegovy, the FDA weighed data from the Phase III STEP 1, STEP 2, STEP 3, STEP 4, and SUSTAIN 6 trials to support its approval of 1.7 mg or 2.4 mg semaglutide (starting with a dose level of 0.25 mg and increasing to 0.5 mg after four weeks) in Wegovy for weight management in June 2021. A detailed summary of the Phase III STEP 1, STEP 2, STEP 3, STEP 4, STEP 5, STEP-HFpEF, and SELECT trial results of Wegovy are presented in exhibit 8.

Exhibit 8
Phase III STEP Trial Series Results of Wegovy in Patients With Obesity or Overweight With or Without Type 2 Diabetes

Sponsor					Novo Nordisk A/S			
Mechanism of Action					GLP-1 receptor agonist			
Trial	**Disease**	**Study Arms**	**Enrollment**	**Baseline Patient Characteristics**	**Change in Body Weight at Week 68**	**Patients Reaching ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss**	**TEAEs Affecting ≥5% of Patients**	**Serious TEAE Frequency (Discontinuation Rate)**
Phase III STEP 1 (NCT03548935)	BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related risk factor* without type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly	1,961 patients (2:1 randomization)	BMI=38 kg/m² Male=24%-27%% HbA1c=5.7%	**-15%** (p <0.001) Placebo-adjusted: -12%	86%; 69%; 51%; 32% (all p <0.001 except 20% weight loss, which was not tested)	Nausea 44% Diarrhea 32% Vomiting 25% Constipation 23%	10% (7%)
		placebo			**-2%**	**32%**, 12%, 5%, 2%	Nausea 17% Diarrhea 16% Constipation 10% Vomiting 7%	6% (3%)
Phase III STEP 2 (NCT03552757)	BMI ≥27 kg/m² with type 2 diabetes (HbA1c ≥ 7% and ≤ 10%) without renal impairment**	2.4 mg Ozempic once weekly	1,210 patients (1:1:1 randomization)	BMI=35-36 kg/m² Male=45%-53% HbA1c=8.1%	**-10% p<0.0001** **Placebo-Adjusted: -6%**	**69%**, 46%, 26%, 13% (all p <0.0001 except 20% weight loss, which was not tested)	Nausea 34% Vomiting 22% Diarrhea 21% Constipation 17%	10% (6%)
		1.0 mg Ozempic once weekly			**-7% p<0.0001** **Placebo-Adjusted: -4%**	**57%**, 29%, 14%, 5%	Nausea 32% Diarrhea 22% Vomiting 13% Constipation 13%	8% (5%)
		placebo			**-3%**	**29%**, 8%, 3%, 2%	Diarrhea 12% Nausea 9% Constipation 6% Vomiting 3%	9% (4%)
Phase III STEP 3 (NCT03611582)	BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related risk factor* without type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly + 1,000-1,200 kcal/day diet and exercise[1] for 8 weeks ↓ 2.4 mg Wegovy once weekly + 1,000-1,200 kcal/day diet and exercise[1]	611 patients (2:1 randomization)	BMI=38 kg/m² Male=12%-23% HbA1c=5.7%-5.8%	**-16% p<0.001** **Placebo-Adjusted: -10%**	**87%** 75%, 56%, 36% (all p <0.001)	Nausea 58% Constipation 37% Diarrhea 36% Vomiting 27%	9% (6%)
		placebo + 1,000-1,200 kcal/day diet and exercise[1] for 8 weeks ↓ placebo + 1,000-1,200 kcal/day diet and exercise[1]			**-6%**	**48%**, 27%, 13%, 4%	Constipation 25% Nausea 22% Diarrhea 22% Vomiting 11%	3% (3%)
Phase III STEP-4 (NCT03548987)	BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related risk factor* without type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly for 20 weeks (lead-in) ↓ 2.4 mg Wegovy once weekly for 48 weeks (randomization)	803 patients (2:1 randomization)	BMI at screening=38 kg/m² BMI at randomization=34-35 kg/m² Male=20%-24% HbA1c at screening=5.7% HbA1c at randomization=5.4%	-8% p<0.001 (weeks 20-68) placebo-adjusted: -15% (weeks 20-68) -17% (weeks 1-68) placebo-adjusted: -12% (weeks 1-68)	89%, 79%, 64%, 40%	Randomization: Diarrhea 14% Nausea 14% Constipation 12% Vomiting 10%	Randomization: 8% (2%)
		2.4 mg Wegovy once weekly for 20 weeks (lead-in) ↓ placebo (randomization)			**+7%** (weeks 20-68) -5% (weeks 1-68)	48%, 20%, 9%, 5%	Randomization: Diarrhea 7% Constipation 6% Nausea 5% Vomiting 3%	Randomization: 6% (2%)

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.
**Renal impairment is defined as an estimated glomerular filtration rate less than 30 mL/min/1.73 m² or less than 60 mL/min/1.73 m² for patients treated with sodium-glucose cotransporter 2 inhibitors
[1]At randomization, patients were prescribed 100 minutes of exercise per week (spread across 4-5 days), which increased by 25 minutes every 4 weeks to reach 200 min/week.
For each trial, Wegovy was administered utilizing a 16-weeks-long dose-escalation titration period beginning at 0.25 mg once weekly and increasing to 0.5 mg at week 4, 1.0 mg at week 8, and 1.7 mg at week 12 to attain a maintenance dose of 2.4 mg once weekly by week 16.
BMI=Body mass index. GLP-1=Glucagon-like peptide-1. HbA1c=Glycated hemoglobin. NS=Not significant.
Sources: Company reports, clinicaltrials.gov, Wilding et al., NEJM 2021, Davies et al., The Lancet 2021, Wadden et al., JAMA 2021, Rubino et al., JAMA 2021.

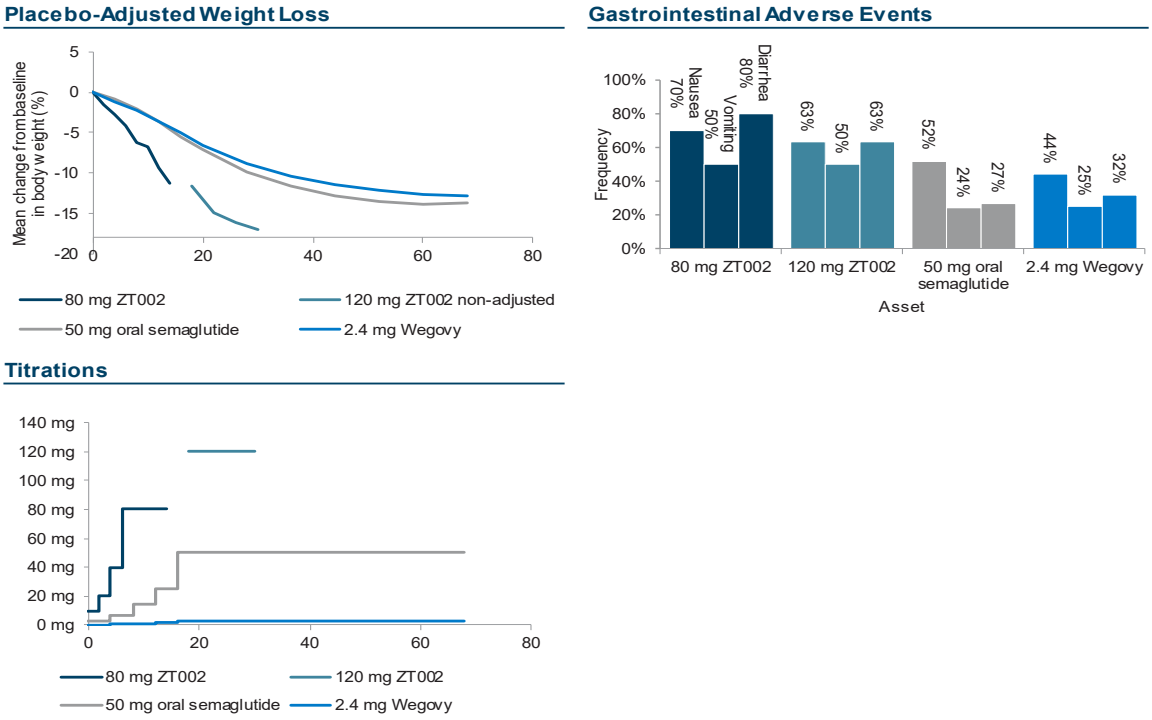
Exhibit 8 (Continued)
Phase III STEP Trial Series Results of Wegovy in Patients With Obesity or Overweight With or Without Type 2 Diabetes

Sponsor					Novo Nordisk A/S				
Mechanism of Action					GLP-1 receptor agonist				
Trial	**Disease**	**Study Arms**	**Enrollment**	**Baseline Patient Characteristics**	**Change in Body Weight at Week 104**	**Patients Reaching ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss**	**Placebo-Adjusted Reduction in the Risk of Progression to Type 2 Diabetes**	**TEAEs Affecting ≥5% of Patients**	**Serious TEAE Frequency (Discontinuation Rate)**
Phase III STEP 5 (NCT03693430)	BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related risk factor* without type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly for 104 weeks	304 patients (1:1 randomization)	BMI=39 kg/m² Male=19%-26% HbA1c=5.7%	-15% p<0.0001 placebo-adjusted: -13%	**77%**, 62%, 52%, 36% (all *p* <0.0001 except 20% weight loss, which was not tested)		Nausea 53% Diarrhea 35% Constipation 31% Vomiting 30%	8% (6%)
		placebo			-3%	**34%**, 13%, 7%, 2%		Diarrhea 24% Nausea 22% Constipation 11% Vomiting 5%	12% (5%)
Trial	**Disease**	**Study Arms**	**Enrollment**	**Baseline Patient Characteristics**	**Change in Body Weight at Week 52**	**Change in KCCQ-CSS (Placebo-Adjusted) at Week 52**	**Placebo-Adjusted Reduction in the Risk of Progression to Type 2 Diabetes**	**TEAEs in Safety Focus Areas Affecting ≥5% of Patients**	**Serious TEAE Frequency (Discontinuation Rate)**
Phase III STEP-HFpEF (NCT04788511)	BMI ≥ 30 kg/m² NYHA Class II through IV LVEF ≥ 45% without type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly for 52 weeks	529 patients (1:1 randomization)	BMI=37 kg/m² Male=43%-44% LVEF=57% KCCQ-CSS=58-59 points	-13% p<0.001 placebo-adjusted: -11%	+17 points p<0.001 placebo-adjusted: +8 points		COVID-19-related event 15% Serious cardiovascular disorder 7% Heart failure event <1%	13% (13%)
		placebo			**-3%**	**+9 points**		COVID-19-related event 17% Serious cardiovascular disorder 15% Heart failure event 5%	27% (5%)
Trial	**Disease**	**Study Arms**	**Enrollment**	**Baseline Patient Characteristics**	**Change in Body Weight at Week 104**	**Percent Meeting the Primary Cardiovascular Composite Endpoint[1]**	**Placebo-Adjusted Reduction in the Risk of Progression to Type 2 Diabetes (at Week 156)**	**Serious TEAEs Affecting ≥5% of Patients**	**Serious TEAE Frequency (Discontinuation Rate)**
Phase III SELECT (NCT03574597)	BMI ≥27 kg/m² Cardiovascular disease** without NYHA IV heart failure or type 2 diabetes (HbA1c < 6.5%)	2.4 mg Wegovy once weekly for a mean duration of 145 weeks	17,604 patients (1:1 randomization)	BMI=33 kg/m² Male=72%-73% HbA1c=5.8%	-9% placebo-adjusted: -9%	7% HR=0.80, p<0.001 placebo-adjusted: -2%	73% *p* <0.0001 Baseline HbA1c < 5.7%: 67%	Cardiac disorders 12% *p* <0.001 Infections and infestations 7% *p* =0.001 Nervous system disorders 5% *p* =NS Surgical and medical procedures 5% *p* <0.001 Neoplasms 5% *p* =NS	33% *p* <0.001 (17% *p* <0.001)
		placebo			-1%	**8%**		Cardiac disorders 14% Infections and infestations 8% Surgical and medical procedures 6% Nervous system disorders 6% Neoplasms 5%	36% (8%)

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.
**Patients had at least one of the following: prior myocardial infarction, prior ischemic or hemorrhagic stroke, and/or symptomatic peripheral arterial disease.
[1]The primary efficacy endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The hazard ratio, 95% confidence interval, and P value were adjusted for the group sequential design with the use of likelihood-ratio ordering, and the nominal two-sided significance level was 0.046.
For each trial, Wegovy was administered utilizing a 16-weeks-long dose-escalation titration period beginning at 0.25 mg once weekly and increasing to 0.5 mg at week 4, 1.0 mg at week 8, and 1.7 mg at week 12 to attain a maintenance dose of 2.4 mg once weekly by week 16.
BMI=Body mass index. GLP-1=Glucagon-like peptide-1. HbA1c=Glycated hemoglobin. HR=Hazard ratio. KCCQ-CSS=Kansas City Cardiomyopathy Questionnaire Clinical Summary Score. LVEF=Left ventricular ejection fraction. NS=Not significant. NYHA=New York Heart Association.
Sources: Company reports, ClinicalTrials.gov, Garvey et al., Nat Med 2022, Kosiborod et al., NEJM 2023, Lincoff et al., NEJM 2023, Kahn et al., Diabetes Care 2024.

Semaglutide is a peptide measuring 31 amino acids long with high sequence homology to endogenous human GLP-1 (amino acids 1 and 7-37), with several key modifications. These consist of two amino acid substitutions of alanine at the eighth position with αaminoisobutyric acid and of lysine at position 34 with arginine. In addition, to increase the half-life of the molecule, semaglutide features a conjugation of octadecanoic di-acid (a fatty acid with 18 carbon molecules) to the side chain of lysine at position 26 via a polyethylene glycol spacer and a γ-glutamic acid linker. (Amino acid position numbers refer to native GLP-1.) The usage of a fatty di-acid and a longer spacer component provides enhanced albumin binding and reduced renal clearance, which contributes to semaglutide's longer half-life and greater therapeutic efficacy compared with the earlier-generation liraglutide (Mahapatra, et al. *Rev. Endocrin. Metab. Disord.* 2022). Semaglutide has a half-life of 160 hours, or roughly one week. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of peptide-based GLP-1 RAs including ZT002, Wegovy, and oral semaglutide is presented in exhibit 9.

Exhibit 9
Combined Weight Loss, Adverse Events, and Titration Curves of Peptide-Based GLP-1 Receptor Agonists



GLP-1=Glucagon-like peptide 1.
Sources: Company documents.

Phase II trial of Wegovy

In results published in 2018, once-daily injections of 0.4 mg demonstrated 14% weight loss in patients with obesity over one year of dosing. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT02453711).

Efficacy. In results published in 2018 once-daily Wegovy administered with a 4-week titration demonstrated generally dose-dependent placebo-adjusted weight loss up to 12% in obesity at 1 year, compared with 6% for once-daily Saxenda (in the intent-to-treat population). In addition, Wegovy given with a faster 2-week titration demonstrated dose-dependent placebo-adjusted weight loss up to 15% at 1 year.

Safety and tolerability. Treatment with Wegovy led to up to 54% nausea (dose-dependent; in the second-highest 2-week titration group), 38% diarrhea (dose-dependent; at the highest 4-week titration dose), and 23% vomiting (dose-dependent; at the third-highest 4-week titration dose). Serious treatment-emergent adverse events did not exhibit a dose-dependent relationship in the Wegovy arms, occurring at up to 13% in the lowest and highest 4-week titration dose groups, a rate that was greater compared with the Saxenda and placebo arms. In addition, the Wegovy discontinuation rate occurred in the range of 4% to 17%, compared to 9% for Saxenda and 3% for placebo.

The results of this trial indicated that higher doses of Wegovy could be safely administered in obese patients and could achieve greater weight loss compared with placebo or Saxenda, forming the basis of the STEP trials for obesity to come (O'Neil et al., *Lancet* 2018).

Phase III STEP 1 trial of Wegovy
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03548935).

Efficacy. In results released in 2021, once-weekly Wegovy achieved around 12% placebo-adjusted weight loss at 68 weeks in the intent-to-treat population. In addition, roughly 86% of patients receiving Wegovy experienced at least 5% body weight reduction, compared with nearly 32% in the placebo arm.

Safety and tolerability. Treatment with Wegovy led to up to 44% nausea, 32% diarrhea, and 25% vomiting. Serious treatment-emergent adverse events were slightly elevated in the Wegovy arm, at 10%, with more frequent gastrointestinal disorders, compared with the placebo arm. In addition, the discontinuation rate was higher in the Wegovy arm, with a low- to high-single-digit rate in both arms.

The results of this trial further validated the potential for Wegovy dosed weekly in patients with obesity and indicated that higher doses of Wegovy could be safely administered, with more rapid titrations, than had been observed previously (Wilding et al., *NEJM* 2021).

Phase III STEP 4 trial of Wegovy
In results published in 2021, once-weekly injections demonstrated around 17% weight loss at 16 months in obesity without type 2 diabetes. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03548987).

Efficacy. In the intent-to-treat population, patients who had received Wegovy in the initial 20-week run-in period demonstrated nearly 11% body weight loss from baseline; patients who continued Wegovy treatment lost a further 8% of their body weight, whereas patients who switched to placebo gained roughly 7% of their body weight, relative to patient weight at week 20. In addition, a significantly lower proportion of patients gained weight on Wegovy, at about 15%, compared with patients who switched to placebo, at roughly 82% (p<0.001).

In the 68-week trial, patients receiving Wegovy experienced roughly 17% body weight loss from baseline, compared with 5% for patients who switched to placebo at week 20. Investigators also reported a higher proportion of patients who lost weight on Wegovy compared with placebo.

Safety and tolerability. Treatment with Wegovy led to up to 14% nausea, 14% diarrhea, and 10% vomiting. Serious treatment-emergent adverse events in the Wegovy arm, at 8%, were roughly balanced with the placebo arm. In addition, the discontinuation rate was the same in both arms, in the low single digits.

Following this study, 2.4 mg Wegovy once weekly was approved by the FDA for the treatment of obesity in June 2021 (FDA press release). STEP 4 also highlighted the potential cardiovascular benefits of Wegovy administration, as seen with the improvements in circulating lipid profiles and glucose metabolism in patients receiving Wegovy.

The cardiovascular benefits of Wegovy would be further explored in the following Phase III STEP-HFpEF (heart failure with preserved ejection fraction) study (Rubino et al., *JAMA* 2021). Novo hopes to obtain FDA approval of Wegovy for treatment of heart failure.

Phase III STEP-HFpEF trial of Wegovy

In results released in August 2023, once-weekly injections demonstrated around 11% placebo-adjusted weight loss and a nearly 8-point placebo-adjusted change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) in patients with obesity-related heart failure with preserved ejection fraction (HFpEF) over roughly one year of dosing. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04788511).

Efficacy. In the intent-to-treat population, Wegovy administration achieved significant mean weight loss of roughly 13%, compared with body weight loss of about 3% for the placebo group at one year (p<0.001). In addition, a higher proportion of patients in the Wegovy arm lost weight compared with patients receiving placebo. Patients receiving Wegovy furthermore demonstrated a significantly greater improvement in KCCQ-CSS compared with placebo, indicating a more pronounced effect on heart-failure-linked symptoms, quality of life, social function, and physical function.

Patients also experienced significant improvements in the confirmatory secondary endpoints of 6-minute walk distance and in levels of the inflammatory C-reactive protein (CRP) at week 52 (p<0.001). Moreover, patients receiving Wegovy demonstrated improvements in the secondary endpoints of systolic blood pressure, waist circumference, and KCCQ overall summary score compared with those in the placebo arm.

Safety and tolerability. Treatment with Wegovy led to reduced cardiac disorders, infections, and infestations, compared with the placebo arm. The rate of serious treatment-emergent adverse events in the Wegovy arm, at 13%, was roughly half the placebo arm rate, mainly driven by more frequent cardiovascular disorders in the placebo arm. However, the discontinuation rate due to adverse events was roughly 13% in the Wegovy arm, compared to 5.3% for placebo.

Next steps. Novo aims to resubmit to U.S. regulators in the first half (Kosiborod et al., *NEJM* 2023).

Phase III SELECT trial of Wegovy

In results published in November 2023, once-weekly Wegovy demonstrated clinically meaningful and consistent cardioprotective effects in overweight/obese patients with preexisting cardiovascular disease but without type 2 diabetes. The benefits are particularly impressive given that most patients were already receiving statins, blood thinners, or beta blockers. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03574597).

Efficacy. Wegovy demonstrated a nearly 20% reduction in the risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke (hazard ratio=0.80; p<0.001), compared with patients in the placebo arm. In addition, Wegovy reduced the risk of all-cause mortality by around 19% (hazard ratio=0.81). Furthermore, the risk associated with the heart failure composite endpoint (defined as death or hospitalization from cardiovascular events or urgent medical visit resulting from heart failure) was reduced by 18% in the Wegovy arm (hazard ratio=0.82).

Patients on Wegovy also demonstrated a greater reduction in body weight after 2 years of treatment at a roughly 9% reduction, compared with a nearly 1% reduction for the placebo group (in the intent-to-treat population).

Moreover, the asset demonstrated improved (decreased) total cholesterol, triglycerides, and systolic and diastolic blood pressure. In addition, Wegovy increased heart rate by about 4 beats per minute, compared with an increase of only about 1 beat per minute for placebo. There was also a large proportion of patients who transitioned from pre-diabetes to normal HbA1c levels.

Safety and tolerability. Treatment with Wegovy led to slightly fewer cardiac disorders, infections and infestations, and nervous system disorders compared with the placebo arm. Serious treatment-emergent adverse events were slightly reduced in the Wegovy arm, at 33%, with the most common adverse events of cardiac disorders, infections and infestations, and nervous system disorders. In addition, the discontinuation rate was roughly double in the Wegovy arm, at a midteens percentage, mostly driven by more frequent gastrointestinal disorders.

From a public health perspective, the SELECT trial represents the first cardiovascular outcomes trial (CVOT) that demonstrated Wegovy (or a GLP-1 RA in general) as a weight management therapeutic could reduce major adverse cardiac event (MACE) outcomes and provide a cardioprotective effect (Lincoff et al., *NEJM* 2023).

In March 2024, Novo Nordisk removed the BMI limitations from Wegovy's label (March 2024 version). The previous version said that the drug was indicated for adult patients with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) and for pediatric patients aged 12 years and older with an initial BMI at the 95th percentile or greater for age and sex (obesity) (July 2023 version). This will provide doctors with more flexibility to prescribe the medication in cases where BMI may not be an appropriate sole measure of obesity.

Phase III FLOW trial of Ozempic

In results published in May 2024, once-weekly Ozempic offered significant protection to patients with type 2 diabetes and chronic kidney disease from major kidney disease events. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03819153).

Efficacy. Ozempic demonstrated a roughly 24% reduction in the risk of major kidney disease events (defined as a composite of the onset of kidney failure, at least a 50% reduction in the estimated glomerular filtration rate [eGFR] from baseline, or death from kidney-related or cardiovascular causes; hazard ratio=0.76; p=0.0003), compared with placebo. Roughly 19% of patients in the Wegovy arm met the primary endpoint, compared with around 23% of patients in the placebo arm; most patients who experienced an event experienced a persistent reduction in eGFR, indicating poorer kidney function. In addition, around 12% of Ozempic arm patients met the composite of kidney-related component parts of the primary endpoint, compared with 15% of patients in the placebo arm.

Furthermore, patients receiving Ozempic demonstrated about 5% placebo-adjusted weight loss at 2 years in the intent-to-treat population. Patients receiving Ozempic also demonstrated significantly reduced rates of major cardiovascular events and any-cause mortality, as well as improved kidney function by eGFR, compared with placebo arm patients.

Safety and tolerability. Treatment with Ozempic led to slightly less cardiovascular disorders, heart failure, and acute kidney failure. Serious treatment-emergent adverse events were slightly reduced in the Ozempic arm, at 50%, with the most common events of diabetic retinopathy,

Covid-19-related disorder, and cardiovascular disorder. In addition, the discontinuation rate was higher in the Ozempic arm, driven by gastrointestinal disorders, with rates in the low 10s in both arms.

Following the publication of these results, Novo Nordisk submitted a label extension application for Ozempic in patients with type 2 diabetes and chronic kidney disease, which was accepted for review by the FDA in June 2024 (Perkovic et al., *NEJM* 2024; Novo Nordisk June 2024 press release).

Phase IIIa OASIS-1 trial of oral semaglutide

Oral versions of weight loss drugs will likely be an important addition to injectables for reasons including greater flexibility for patients. To that end, Novo Nordisk explored an oral version of the GLP-1 RA semaglutide. Top-line results from the trial in obesity or overweight were announced in May 2023; following positive results from the study (with weight loss comparable to what was demonstrated by Wegovy in the Phase III STEP 1 trial), Novo Nordisk filed for regulatory approval in 2023 in Europe.

For context, oral semaglutide was approved by the FDA in September 2019 under the brand name Rybelsus as a second-line adjunct to diet and exercise to improve glycemic control in type 2 diabetes. In January 2023, the FDA approved a label update for Rybelsus allowing its use as a first-line treatment for type 2 diabetes. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05035095).

Efficacy. In the treatment policy estimand, including patients regardless of treatment adherence, Rybelsus demonstrated around 13% placebo-adjusted weight loss at 68 weeks in the intent-to-treat population. In addition, a greater proportion of patients receiving Rybelsus experienced weight loss compared with the placebo arm. Furthermore, Rybelsus demonstrated reductions (improvements) in HbA1c, fasting blood sugar, and systolic and diastolic blood pressure compared with placebo.

Safety and tolerability. Treatment with oral semaglutide led to 52% nausea, 27% diarrhea, and 24% vomiting. Serious treatment-emergent adverse events were slightly elevated in the oral semaglutide arm, at 10%. In addition, the discontinuation rate was slightly higher in the oral semaglutide arm, occurring in the midsingle digits in both arms. A detailed summary of the Phase IIIa OASIS-1 trial results of oral semaglutide in obesity is presented in exhibit 10 (Knop et al., *The Lancet* 2023).

Exhibit 10
Novo Nordisk A/S
68-Week Results of Oral Semaglutide in Obesity Without Type 2 Diabetes

Phase IIIa OASIS-1 Trial (NCT05035095)

Sponsor	Novo Nordisk A/S	
Mechanism of Action	GLP-1 receptor agonist	
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%	
Baseline Patient Characteristics	Age=49 years Male=26% Body weight=105 kg BMI=37 kg/m² HbA1c=5.6% Prediabetes=40%	Age=50 years Male=29% Body weight=106 kg BMI=38 kg/m² HbA1c=5.6% Prediabetes=39%
Study Arms	50 mg oral semaglutide once daily	placebo
Enrollment	334 patients	333 patients
Titration Schedule	3 mg for 4 weeks; 7 mg for 4 weeks; 14 mg for 4 weeks; 25 mg for 4 weeks; 50 mg for 52 weeks	
Change in Body Weight at Week 68	**-15% *p* <0.0001** **placebo-adjusted: -13%**	**-2%**
Patients Reaching ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss	**85%**, 69%, 54%, 34% (all *p* <0.0001)	**26%**, 12%, 6%, 3%
TEAE Frequency	92%	86%
TEAEs Affecting ≥20% of Patients	Nausea 52% COVID-19 36% Constipation 28% Diarrhea 27% Vomiting 24%	15% 35% 15% 17% 4%
Serious TEAE Frequency	10%	9%
TEAEs Leading to Discontinuation	Overall: 6% (4% gastrointestinal)	Overall: 4% (2% gastrointestinal)

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.

Sources: Company reports, Knop et al., The Lancet 2023, clinicaltrials.gov.

Next steps. The Phase III OASIS 2 and OASIS 4 studies tested 50 mg oral semaglutide in patients of East Asian descent with obesity or overweight with at least one weight-related comorbidity (including type 2 diabetes) and 25 mg oral semaglutide in patients with obesity or overweight with at least one weight-related comorbidity (excluding type 2 diabetes), respectively. According to clinicaltrials.gov, these studies had primary completion dates in July 2023 and April 2024, respectively. Results from these studies have not been disclosed yet (NCT05132088; NCT05564117).

The ongoing Phase III OASIS 3 study is examining 50 mg oral semaglutide in patients of Chinese descent with obesity or overweight with at least one weight-related comorbidity (including type 2 diabetes); according to clinicaltrials.gov, this trial has a primary completion date in February (NCT05890976).

Eli Lilly's Tirzepatide

Tirzepatide, marketed under the brand names of Mounjaro for type 2 diabetes and Zepbound for weight management, is a peptide-based dual agonist of the GLP-1 and GIP receptors. Data from the Phase III SURPASS-1, SURPASS-2, SURPASS-3, SURPASS-4, and SURPASS-5 trials and two other trials conducted in Japan supported FDA approval in May 2022 of once-weekly injections of 5.0 mg, 7.5 mg, 10.0 mg, 12.5 mg, or 15.0 mg tirzepatide (starting with a dose level of 2.5 mg and increasing to 5.0 mg after four weeks) in Mounjaro for type 2 diabetes.

Regarding the weight management indication, the FDA based its November 2023 approval for once-weekly injections of 2.5 mg, 5.0 mg, 7.5 mg, 10.0 mg, 12.5 mg, or 15.0 mg tirzepatide (starting with a dose level of 2.5 mg and increasing to 5.0 mg after four weeks) in Zepbound on data from the Phase III SURMOUNT-1 and SURMOUNT-2 trials. A detailed summary of the Phase III SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, SURMOUNT-4, and SURMOUNT-5 trial results and the designs of the Phase III SURMOUNT-MMO and SURMOUNT-MAINTAIN studies of Zepbound are presented in exhibit 11.

Exhibit 11
Phase III SURMOUNT Trial Series Results of Zepbound in Patients With Obesity or Overweight With or Without Type 2 Diabetes

Sponsor				Eli Lilly and Company					
Mechanism of Action				Dual receptor agonist of GLP-1 and GIP					
Trial	**Disease**	**Study Arms**	**Enrollment**	**Baseline Patient Characteristics**	**Change in Body Weight at Week 72**	**Patients Reaching ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss**	**Placebo-Adjusted Reduction in the Risk of Progression to Type 2 Diabetes (at Week 176)**	**Select Gastrointestinal Adverse Events Affecting ≥5% of Patients**	**Serious TEAE Frequency (Discontinuation Rate)**
Phase III SURMOUNT-1 (NCT04184622)	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* without type 2 diabetes (HbA1c < 6.5%)	5 mg Zepbound once weekly	2,539 patients (1:1:1:1 randomization)	BMI=37-38 kg/m² Male= 32%-33% HbA1c=5.6% Prediabetes=39%-42%	-15% (p<0.001) placebo-adjusted: -12%	85%; 69%; 48%; 30% (all *p* <0.001)	93% *p* <0.0001	Nausea 25% Diarrhea 19% Constipation 17% Vomiting 8%	6% (4%)
		10 mg Zepbound once weekly			-20% *p* <0.001 placebo-adjusted: **-16%**	**89%;** 78%; 67%; 50% (all *p* <0.001)		Nausea 33% Diarrhea 21% Constipation 17% Vomiting 11%	7% (7%)
		15 mg Zepbound once weekly			-21% *p* <0.001 placebo-adjusted: **-18%**	**91%;** 84%; 71%; 57% (all *p* <0.001)		Nausea 31% Diarrhea 23% Vomiting 12% Constipation 12%	5% (6%)
		placebo			-3%	**35%;** 19%; 9%; 3%		Nausea 10% Diarrhea 7% Constipation 6% Vomiting 2%	7% (3%)
Phase III SURMOUNT-2 (NCT04657003)	BMI ≥ 27 kg/m² with type 2 diabetes (HbA1c ≥7% and ≤ 10%)	10 mg Mounjaro once weekly	938 patients (1:1:1 randomization)	BMI=36-37 kg/m² Male=49%-50% HbA1c=7.9%-8.1%	-13% *p* <0.0001 placebo-adjusted: **-10%**	**79%;** 61%; 40%; 22% (all *p* <0.0001)		Diarrhea 20% Nausea 20% Vomiting 11% Constipation 8%	6% (4%)
		15 mg Mounjaro once weekly			-15% *p* <0.0001 placebo-adjusted: **-12%**	**83%;** 65%; 48%; 31% (all *p* <0.0001)		Diarrhea 22% Nausea 22% Vomiting 13% Constipation 9%	9% (7%)
		placebo			-3%	**32%;** 9%; 3%; 1%		Diarrhea 9% Nausea 6% Constipation 4% Vomiting 3%	7% (4%)
Phase III SURMOUNT-3 (NCT04657016)	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one of weight-related comorbidity* without type 2 diabetes (HbA1c < 6.5%)	Intensive diet and exercise over 12 weeks (lead-in) ↓ if 5%+ weight loss achieved, 10 mg or 15 mg Zepbound once weekly over 72 weeks + Intensive diet and exercise (randomization)	579 patients (1:1 randomization, post-lead-in)	BMI at screening=38-39 kg/m² BMI at randomization=36 kg/m² Male=37% HbA1c=5.5%	**Randomization:** -18% *p* <0.001 placebo-adjusted: **-21%**	**Randomization: 88%;** 77%; 65%; 45% (all *p* <0.001)		Randomization: Nausea 40% Diarrhea 31% Constipation 23% Vomiting 18%	Randomization: 6% (11%)
		Intensive diet and exercise over 12 weeks (lead-in) ↓ if 5%+ weight loss achieved, placebo once weekly over 72 weeks + Intensive diet and exercise (randomization)			**Randomization:** +3%	**Randomization: 17%;** 9%; 4%; 2%		Randomization: Nausea 14% Diarrhea 9% Constipation 7% Vomiting 1%	Randomization: 5% (2%)
Phase III SURMOUNT-4 (NCT04660643)	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* without type 2 diabetes (HbA1c < 6.5%)	10 mg or 15 mg Zepbound once weekly for 36 weeks (lead-in) ↓ 10 mg or 15 mg Zepbound once weekly for 52 weeks (randomization)	670 patients (1:1 randomization, post-lead-in)	BMI at screening=38 kg/m² BMI at randomization=30-31 kg/m² Male=29%-30% HbA1c at screening=5.5% HbA1c at randomization=5.0%-5.1%	-6% *p* <0.001 (post-lead-in, randomization phase) Placebo-adjusted: **-19%**	Randomization: 97%; 92%; 84%; 70% (all *p* <0.001)		Lead-in: Nausea 36% Diarrhea 21% Constipation 21% Vomiting 16% Randomization: Diarrhea 11% Nausea 8% Vomiting 6%	Lead-in: 2% (7%) Randomization: 3% (2%)
		10 mg or 15 mg Zepbound once weekly for 36 weeks (lead-in) ↓ placebo (randomization)			+14% (post-lead-in, randomization phase)	Randomization: 70%; 46%; 26%; 13%		Lead-in: Nausea 36% Diarrhea 21% Constipation 21% Vomiting 16% Randomization: Diarrhea 5% Nausea 3% Vomiting 1%	Lead-in: 2% (7%) Randomization: 3% (1%)

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.
The listed primary and key secondary end points of SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4 were tested under a type 1 error–control procedure.
For each trial, Zepbound was administered utilizing a 20-weeks-long dose-escalation titration period beginning at 2.5 mg once weekly and increasing by 2.5 mg every 4 weeks to attain a maintenance dose of up to 15 mg once weekly by week 20.
BMI=Body mass index. DPP-4=Dipeptidyl peptidase-4. GIP=Glucose insulinotropic peptide. GLP-1=Glucagon-like peptide-1. HbA1c=Glycated hemoglobin. RAs=Receptor agonists.
For SURMOUNT-3, the 12-week lead-in period with Intensive diet and exercise led to a reduction in body weight of 7% among all study participants.
For SURMOUNT-4, the 36-week lead-in period with Zepbound led to a reduction in body weight of 21% among all study participants.
Sources: Company reports, clinicaltrials.gov, Jastreboff et al., NEJM 2022, Garvey et al., The Lancet 2023, Wadden et al., Nat Med 2023, Aronne et al., JAMA 2023.

Exhibit 11 (continued)
Phase III SURMOUNT Trial Series Results of Zepbound in Patients With Obesity or Overweight With or Without Type 2 Diabetes

Sponsor				Eli Lilly and Company		
Mechanism of Action				Dual receptor agonist of GLP-1 and GIP		
Trial	**Disease**	**Study Arms**	**Enrollment**	**Change in Body Weight at Week 72**	**Patients Reaching ≥25% Weight Loss**	**Secondary Endpoints**
Phase III SURMOUNT-5 (NCT05822830)	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one of weight-related comorbidity* without type 2 diabetes (HbA1c < 6.5%)	Zepbound once weekly	751 patients (1:1 randomization)	**-20%**	32%	Weight loss efficacy
		2.4 mg Wegovy once weekly		**-14%**	16%	
Trial	**Disease**	**Study Arms**	**Enrollment**	**Primary Endpoint**	**Expected Completion Date**	
Phase III SURMOUNT-MMO (NCT05556512)	BMI ≥27 kg/m² Cardiovascular disease Women (55-69 years), men (50-64 years); at least 3 risk factors1 Women (≥70 years), men (≥65 years); at least 2 risk factors1 without type 2 diabetes (HbA1c < 6.5%)	Zepbound once weekly	15,374 patients (1:1 randomization)	**Time to first occurrence of composite MACE**	October 2027	
		placebo				
Phase III SURMOUNT-MAINTAIN (NCT06047548)	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one of weight-related comorbidity* without type 2 diabetes (HbA1c < 6.5%)	MTD Zepbound once weekly for 60 weeks (lead-in) ↓ MTD Zepbound once weekly for 52 weeks (randomization)	400 patients (1:1:1 randomization)	**Percent maintenance of body weight reduction achieved during the 60-Week lead-in period**	May 2026	
		MTD Zepbound once weekly for 60 weeks (lead-in) ↓ 5 mg Zepbound once weekly for 52 weeks (randomization)				
		MTD Zepbound once weekly for 60 weeks (lead-in) ↓ placebo (randomization)				

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.

[1]Cardiovascular disease risk factors include tobacco use, dyslipidemia, and hypertension.

[2]The composite MACE endpoint includes death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and heart failure events

For each trial, Zepbound was administered utilizing a 20-weeks-long dose-escalation titration period beginning at 2.5 mg once weekly and increasing by 2.5 mg every 4 weeks to attain a maintenance dose of up to 15 mg once weekly by week 20.

BMI=Body mass index. GIP=Glucose insulinotropic peptide. GLP-1=Glucagon-like peptide-1. HbA1c=Glycated hemoglobin. MACE=Major adverse cardiovascular events. MTD=Maximum tolerated dose.

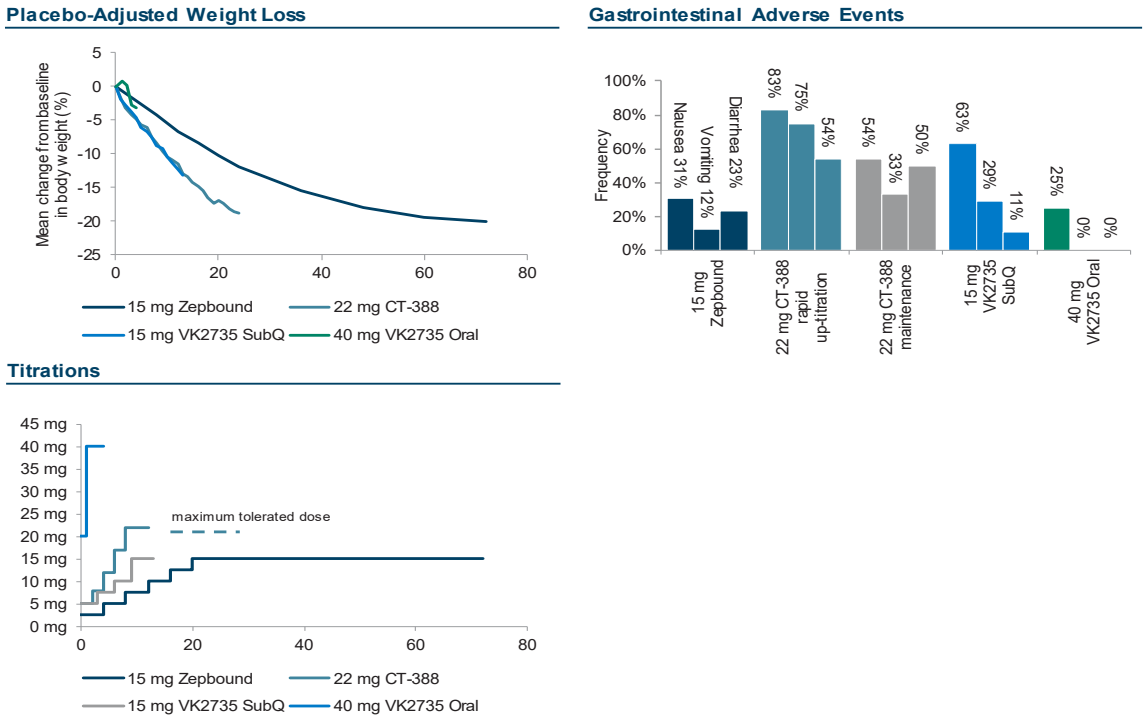
Sources: Company reports, clinicaltrials.gov.

Tirzepatide is a peptide measuring 39 amino acids long. The starting amino acid sequence was that of human GIP, and tirzepatide retains 9 homologous amino acids from GIP (positions 1, 10, 12, 15, 16, 17, 19, 23, and 28) and 10 amino acids shared by GIP and GLP-1. Four amino acids correspond to the same position in the GLP-1 molecule, and 10 amino-terminal amino acids are identical to those in the sequence of exendin-4. Numerous modifications have been made. These consist of five amino acid substitutions of alanine at the second position with α-aminoisobutyric acid, of tyrosine at position 13 with αaminoisobutyric acid, of glutamate at position 21 with alanine, of alanine at position 24 with glutamine, and of valine at position 27 with isoleucine. Lastly, to increase the half-life of the molecule, tirzepatide features a conjugation of a C20 fatty di-acid moiety to the side chain of lysine at position 20 via an Ala-Glu-Glu-Ala-γGlu spacer (Nauck & D'Alessio, *Cardiovas. Diabetol.* 2022).

Mechanistically, tirzepatide activates the GLP-1 receptor with a greater impact on cyclic AMP (cAMP) signaling than on β-arrestin recruitment. Since the β-arrestin pathway is typically associated with internalization of the GLP-1 receptor, and thereby withdrawal from the extracellular space where GLP-1 RAs can bind to GLP-1 receptor, a bias toward cAMP signaling over β-arrestin recruitment may lead to tirzepatide being a more potent activator of GLP-1 receptor than endogenous GLP-1. Tirzepatide has a half-life of roughly five days. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of GLP-1 and GIP dual RAs including Zepbound, CT-388, and subcutaneous and oral tablet formulations of VK2735 is presented in exhibit 12.

Exhibit 12

Combined Weight Loss, Adverse Events, and Titration Curves of GLP-1 and GIP Receptor Agonists



GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1.

Sources: Company documents

Phase III SURMOUNT trials of Zepbound

In the trials, once-weekly Zepbound injections demonstrated placebo-adjusted weight loss between 10% and 21% over roughly 17 to 20 months. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04184622; NCT04657003; NCT04657016; NCT04660643; NCT05822830; NCT06047548).

The initial Phase III SURMOUNT-1 trial tested Zepbound in patients with obesity. Following SURMOUNT-1, the Phase III SURMOUNT-2 trial assessed the safety and efficacy of Mounjaro in patients with obesity and type 2 diabetes. In contrast to the other SURMOUNT trials, which administered Zepbound in conjunction with diet and exercise, SURMOUNT-3 asked whether a lead-in period of intensive diet and exercise *before* starting a regimen of Zepbound would lead to additive weight loss not seen with simultaneous Zepbound, diet, and exercise. SURMOUNT-4 then sought to determine the impact on safety and efficacy related to Zepbound administration if patients discontinued Zepbound treatment for one year after a 36-week lead-in period receiving the maximum tolerated dose of Zepbound.

The fifth SURMOUNT trial assessed the relative safety and efficacy of Zepbound compared with Wegovy in patients with obesity and without type 2 diabetes. The SURMOUNT-5 trial has been completed and top-line results were announced in December 2024. Lilly has said that more data will be presented at a medical conference and published in a peer-reviewed journal this year.

SURMOUNT-MMO—MMO standing for morbidity and mortality in obesity—is testing the potential clinical benefits of Zepbound versus placebo in patients with obesity and cardiovascular disease or cardiovascular disease risk factors.

Lastly, SURMOUNT-MAINTAIN looks to see 1) what percent of participants maintain at least 80% of the weight they lost during 60 weeks of using Zepbound, one year later, and 2) what percent of participants maintain ≥15% body weight reduction if they lost ≥15% body at the end of the first 60 weeks, also measured one year later.

Efficacy. In the treatment policy estimand, including patients regardless of treatment adherence, the Phase III SURMOUNT-1 trial saw patients with overweight or obesity on Zepbound experience dose-dependent placebo-adjusted weight loss up to 18% at 72 weeks. At 3 years, patients receiving 15 mg Zepbound demonstrated sustained average weight loss of 23%. Across the dose levels, Zepbound also significantly reduced the risk of progression to type 2 diabetes in adults with prediabetes and obesity or overweight, compared with placebo (Lilly November 2024 press release; Jastreboff, et al. *NEJM* 2024).

Subsequently, the Phase III SURMOUNT-2 trial of Mounjaro demonstrated dose-dependent placebo-adjusted weight loss up to 12% in overweight or obesity and type 2 diabetes at 72 weeks. The Phase III SURMOUNT-2 results demonstrated the greater difficulty of inducing weight loss in patients with type 2 diabetes compared with those without diabetes. In the Phase III SURMOUNT-3 trial, investigators examined the effects of a 12-week lead-in period of intensive diet and exercise followed by a 72-week period on Zepbound or placebo to determine if additive weight loss could be achieved from both components in overweight or obesity. Patients receiving Zepbound demonstrated 21% and 20% placebo-adjusted weight loss at 72 weeks on the drug compared with the post-lead-in baseline and pre-lead-in baseline, respectively.

The Phase III SURMOUNT-4 trial then aimed to assess if patients receiving Zepbound for 36 weeks would maintain weight loss after 1 year on either Zepbound or placebo. Patients receiving Zepbound between weeks 36 and 88 demonstrated around 19% placebo-adjusted weight loss. In addition, patients who switched to placebo after 36 weeks maintained around 10% weight loss from baseline, even after discontinuing Zepbound for one year.

In top-line results for SURMOUNT-5, Lilly announced that Zepbound provided a 47% greater relative weight loss compared with Wegovy. Specifically, Zepbound demonstrated around 20% weight loss compared with 14% with Wegovy at 72 weeks. Furthermore, nearly 32% of people taking Zepbound achieved at least 25% body weight loss, compared with about 16% of those taking Wegovy (Lilly December 2024 press release).

Safety and tolerability. Treatment with Zepbound/Mounjaro in the SURMOUNT-1, -2, -3, -4, and -5 trials led to up to 40% nausea, 31% diarrhea, and 18% vomiting. Serious treatment-emergent adverse events were roughly balanced between the Zepbound/Mounjaro and placebo arms, occurring between 2% and 9% in the Zepbound/Mounjaro arms across trials. In addition, the discontinuation rate was higher in the Zepbound/Mounjaro arms, occurring up to the low 10s in the SURMOUNT-3 trial.

Following the top-line results of SURMOUNT-5, Lilly also removed the BMI cutoff from Zepbound's label (October 2024 version), as Novo Nordisk had done for Wegovy some months earlier. Prior to this, the label stated that the drug was intended for adults with an initial BMI of 30 kg/m^2 or greater (obesity) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea, or cardiovascular disease) (March 2024 Zepbound Label; October 2024 Zepbound Label; Jastreboff et al., *NEJM* 2022; NCT04184622; Garvey et al., *The Lancet* 2023; NCT04657003; Wadden et al., *Nat Med* 2023; NCT04657016; Aronne et al., *JAMA* 2023; NCT04660643; NCT05822830).

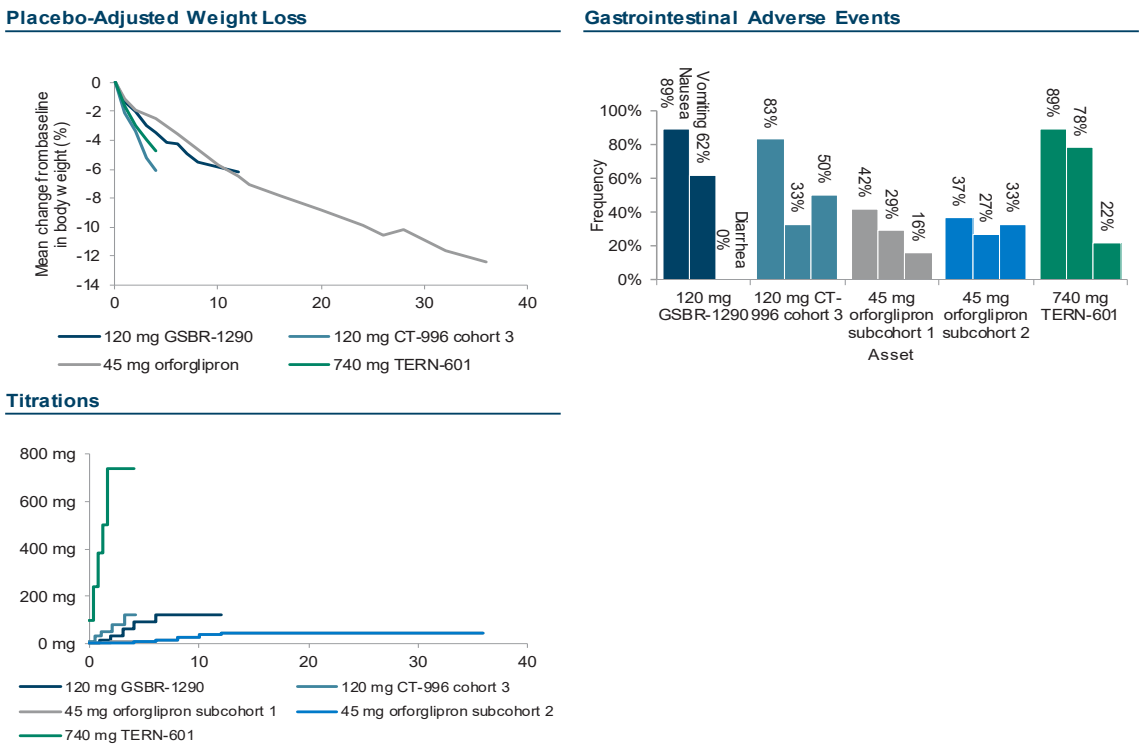
Upcoming GLP-1 and GIP Receptor Agonist Candidates

In our view, GLP-1 receptor agonists (RAs) exhibit promising weight loss; however, tolerability could be challenging considering gastrointestinal adverse events. We are also encouraged by the weight loss demonstrated by combined GLP-1 and GIP RAs; the anti-emetic effects of GIP RAs could additionally improve GLP-1 RA-associated gastrointestinal safety when given in combination (Hayes et al., *Diabetes* 2021).

Drugmakers continue to work to improve GLP-1 RAs; top of mind are increased weight loss, oral formulations, and minimization of adverse effects. Improvements are aimed at addressing current issues related to GLP-1 drugs, including relatively poor real-world persistent adherence to GLP-1 drugs over longer periods. In a retrospective study of 4,066 patients with obesity and without diabetes receiving GLP-1 who initiated therapy in 2021, persistence rates at 6 months and 1 year for all GLP-1 drugs were found to be about 46% and 32%, respectively, with the 1-year persistence rate for semaglutide at roughly 47% (Gleason et al., *J Manag Care Spec Pharm* 2024).

Other areas that improvements could address include the need to stay on therapy to maintain weight loss and the plateauing effect observed limiting the extent of potential weight loss on current-generation GLP-1 drugs. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of small-molecule GLP-1 RAs including GSBR-1290, CT-996, orforglipron, and TERN-601 is presented in exhibit 13.

Exhibit 13
Combined Weight Loss, Adverse Events, and Titration Curves of Small-Molecule GLP-1 Receptor Agonists



GLP-1=Glucagon-like peptide 1.
Sources: Company documents

Upcoming Candidates: Single Agonists

Eli Lilly's Orforglipron

Orforglipron, also known as LY3502970, in clinical development by Eli Lilly for obesity and type 2 diabetes, is a small-molecule partial agonist of GLP-1 receptor with bias for cyclic AMP signaling over β-arrestin recruitment. Rather than a peptide composed of amino acids, orforglipron is an orally bioavailable small molecule with a molecular weight of about 883 g/mol (PubChem listing). It was originally identified by Chugai Pharmaceutical Co., Ltd. and was then licensed by Eli Lilly in 2018 for global development. The significance of small-molecule GLP-1 RAs lies partly in the potential for oral dosing (which can also be achieved with peptides as seen in products like Rybelsus) and also in the greater simplicity of producing small molecules compared with peptides. Small-molecule GLP-1 RAs may therefore be less costly to produce and could in time be more accessible to patients than injectable peptide-based counterparts.

The asset is a GLP-1 RA that, similar to tirzepatide, has a greater impact on cAMP signaling than on β-arrestin. Since the β-arrestin pathway is typically associated with internalization of the GLP-1 receptor, a bias toward cAMP signaling over β-arrestin recruitment may result in orforglipron more potently activating the GLP-1 receptor than endogenous GLP-1. Orforglipron is also a partial RA, or a drug that activates its cognate GLP-1 receptor but produces an effect less than the maximal effect observed with a full agonist.

The compound forms a complex with active-state GLP-1 receptor in a binding site in the upper helical bundle in which orforglipron interacts with the extracellular domain, extracellular loop 2, and the transmembrane helices 1, 2, 3, and 7. The receptor conformation created by this complex could explain the cAMP-biased signaling and the partial agonism of the molecule (Kawai et al., *PNAS* 2020).

Orforglipron has a half-life between 25 and 68 hours, depending on the dose administered (Pratt et al., *Diabetes Obes. Metab.* 2023).

Phase II trial of orforglipron
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05051579).

Efficacy. Once-weekly orforglipron demonstrated dose-dependent placebo-adjusted weight loss up to 12% in overweight or obesity at 36 weeks.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 15% placebo-adjusted weight loss at 36 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons. For background, the efficacy estimand included patients who had adhered to treatment; a weight loss curve for the treatment policy estimand was not provided.

Safety and tolerability. Treatment with orforglipron led to up to 58% nausea, 36% diarrhea, and 32% vomiting across dosing arms; the adverse events did not exhibit dose-dependent relationships. Serious treatment-emergent adverse events also did not exhibit a dose-dependent relationship and occurred in up to 10% in the second-highest dose group, subcohort 2; the most common adverse events were retinal vein thrombosis, diverticulum intestinal, and metastatic hepatic cancer. In addition, the discontinuation rates were higher in the orforglipron arms (in the low 10s and low 20s) and were not dose-dependent, occurring at roughly 5 to 10 times the rate in the placebo arm.

Next steps. Orforglipron is being tested in four ongoing Phase III clinical trials in obesity, including ATTAIN-1 in obesity or overweight with weight-related comorbidities, ATTAIN-2 in obesity or overweight and type 2 diabetes, ATTAIN-J in Japanese adults with obesity, and ATTAIN-MAINTAIN in obesity or overweight with weight-related comorbidities. Eli Lilly expects the primary completion for these trials to occur in June 2025 (ATTAIN-J), July 2025 (ATTAIN-1), August 2025 (ATTAIN-2), and January 2026 (ATTAIN-MAINTAIN). A detailed summary of the Phase II trial results of orforglipron in overweight or obesity is presented in exhibit 14.

Exhibit 14
Eli Lilly and Company
26-Week and 36-Week Results of Orforglipron in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT05051579)

Sponsor	Eli Lilly and Company						
Mechanism of Action	GLP-1 receptor agonist						
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%						
Baseline Patient Characteristics	Age=50 years Male=38% Body weight=108 kg BMI=38 kg/m² HbA1c=5.5%	Age=57 years Male=43% Body weight=112 kg BMI=38 kg/m² HbA1c=5.7%	Age=56 years Male=38% Body weight=108 kg BMI=38 kg/m² HbA1c=5.7%	Age=55 years Male=38% Body weight=109 kg BMI=38 kg/m² HbA1c=5.6%	Age=57 years Male=39% Body weight=105 kg BMI=37 kg/m² HbA1c=5.7%	Age=51 years Male=47% Body weight=111 kg BMI=39 kg/m² HbA1c=5.6%	Age=54 years Male=42% Body weight=108 kg BMI=38 kg/m² HbA1c=5.6%
Study Arms	12 mg orforglipron once daily	24 mg orforglipron once daily	36 mg orforglipron once daily		45 mg orforglipron once daily		placebo
Enrollment	50 patients	53 patients	29 patients	29 patients	31 patients	30 patients	50 patients
Subcohorts			36 mg orforglipron subcohort 1	36 mg orforglipron subcohort 2	45 mg orforglipron subcohort 1	45 mg orforglipron subcohort 2	
Titration Schedule	3 mg for 8 weeks; 6 mg for 8 weeks; 12 mg for 20 weeks	3 mg for 2 weeks; 6 mg for 1 week; 8 mg for 1 week; 12 mg for 1 week; 24 mg for 31 weeks	2 mg for 1 week; 3 mg for 1 week; 6 mg for 1 week; 8 mg for 1 week; 12 mg for 1 week; 24 mg for 1 week; 36 mg for 30 weeks	3 mg for 3 weeks; 6 mg for 3 weeks; 12 mg for 3 weeks; 24 mg for 3 weeks; 36 mg for 24 weeks	3 mg for 2 weeks; 6 mg for 2 weeks; 8 mg for 2 weeks; 12 mg for 2 weeks; 24 mg for 2 weeks; 36 mg for 2 weeks; 45 mg for 24 weeks	2 mg for 2 weeks; 3 mg for 2 weeks; 6 mg for 2 weeks; 12 mg for 2 weeks; 24 mg for 2 weeks; 36 mg for 2 weeks; 45 mg for 24 weeks	
Change in Body Weight at Week 26	**-9%** **placebo-adjusted: -7%**	**-11%** **placebo-adjusted: -9%**	**-12%** **placebo-adjusted: -10%**		**-13%** **placebo-adjusted: -11%**		**-2%**
Change in Body Weight at Week 36	-9% placebo-adjusted: -7%	-13% placebo-adjusted: -10%	-14% placebo-adjusted: -11%		-15% placebo-adjusted: -12%		-2%
Patients Reaching ≥5%, ≥10%, and ≥15% Weight Loss at Week 26	74%; 39%; 21%	89%; 57%; 26%	90%; 71%; 34%		87%; 70%; 34%		23%; 2%; 0%
Patients Reaching ≥5%, ≥10%, and ≥15% Weight Loss at Week 36	72%; 46%; 22%	90%; 62%; 33%	92%; 75%; 43%		90%; 69%; 48%		24%; 9%; 1%
TEAE Frequency	86%	87%	83%	97%	90%	90%	76%
TEAEs Affecting ≥20% of Patients	Nausea 50% Diarrhea 24% Vomiting 26% Eructation 18% COVID-19 18% Constipation 24%	58% 36% 32% 21% 17% 32%	41% 3% 28% 17% 14% 28%	48% 14% 14% 7% 24% 24%	42% 16% 29% 6% 16% 19%	37% 33% 27% 20% 17% 13%	10% 10% 6% 0% 18% 6%
Serious TEAE Frequency	0%	4%	0%	10%	6%	0%	0%
Serious TEAEs	None reported	Gastrointestinal polyp hemorrhage 2% Acute cholecystitis 2%	Retinal vein thrombosis 2% Diverticulum intestinal 2% Metastatic hepatic cancer 2%		Vitreoretinal traction syndrome 2% Coronary artery disease 2%		None reported
TEAEs Leading to Discontinuation	14%	19%	10%	21%	16%	13%	2%

*Patients had either hypertension, dyslipidemia, and/or cardiovascular disease.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, Wharton et al., NEJM 2023, clinicaltrials.gov

Phase IIIb ATTAIN-MAINTAIN trial of orforglipron

Eli Lilly is sponsoring the study of its orally bioavailable small-molecule GLP-1 RA given once daily as a weight loss maintenance regimen over 1 year in obesity. On its third quarter 2024 earnings call, the company announced that it expects a readout this year. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06584916). A detailed summary of the Phase IIIb ATTAIN-MAINTAIN trial design of orforglipron in overweight or obesity is presented in exhibit 15.

Exhibit 15
Eli Lilly and Company
Trial Design of Orforglipron as a Maintenance Regimen in Overweight or Obesity Without Type 2 Diabetes

Phase IIIb ATTAIN-MAINTAIN Trial (NCT06584916)		
Sponsor	Eli Lilly and Company	
Mechanism of Action	GLP-1 receptor agonist	
Enrollment Criteria	Completed the Phase III SURMOUNT-5 study of Zepbound (NCT05822830) HbA1c < 6.5%	
Study Arms	orforglipron once daily for 52 weeks	placebo
Target Enrollment	300 patients	
Primary Endpoint	**Maintenance of weight loss achieved in SURMOUNT-5 at 52 Weeks**	
Secondary Endpoints	Maintenance of weight loss achieved in SURMOUNT-5 at 24 weeks Weight loss at 52 weeks	
Next Catalyst	Undisclosed	

HbA1c=Glycated hemoglobin.
Sources: clinicaltrials.gov

Roche's RG6652

RG6652, also known as CT-996, was acquired with the completed acquisition of Carmot Therapeutics in January 2024. It is an orally bioavailable small-molecule GLP-1 RA with an undisclosed structure. Roche describes it as specifically designed to be a biased agonist that activates cAMP signaling with minimal to no β-arrestin recruitment (Roche website).

Phase I trial of CT-996

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05814107).

Efficacy. In results presented at the European Association for the Study of Diabetes 2024 meeting, once-daily CT-996 demonstrated dose-dependent placebo-adjusted weight loss up to 6% in obesity at 4 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with CT-996 led to systolic blood pressure decrease, heart rate increase, elevated lipase (in one patient), and dose-independent nausea (up to 86%), dose-dependent diarrhea (up to 50%), and vomiting (up to 71%). There was one treatment-unrelated serious adverse event in cohort 1, representing around 17% of that group. In addition, there were no drug-related discontinuations.

Pharmacokinetic parameters. Generally, C_{max} and AUC exhibited a dose-dependent relationship within each multiple-ascending dose cohort. Furthermore, no significant accumulation of CT-996 was observed in plasma, up to around 1% of drug was excreted in urine over 1 day (highest in cohort 1), and no meaningful food effect was observed in the single-ascending portion of the study.

Next steps. Researchers indicated that completing part 3 of the ongoing Phase Ib study consisting of four-week cohorts in patients with obesity and type 2 diabetes is the immediate priority, followed by plans to initiate a Phase II study for CT-996 this year (Roche CT-996 results presentation). A detailed summary of the Phase I trial results of CT-996 in obesity is presented in exhibit 16.

Exhibit 16
Roche Holding AG
4-Week Trial Multiple-Ascending-Dose Results of CT-996 in Obesity Without Type 2 Diabetes

Phase I Trial (NCT05814107)

Sponsor	Roche Holding AG			
Mechanism of Action	GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 30 kg/m² Otherwise healthy			
Baseline Patient Characteristics	Age=40 years Male=33% Body weight=94 kg BMI=33 kg/m² HbA1c=5.1%	Age=35 years Male=57% Body weight=107 kg BMI=36 kg/m² HbA1c=5.2%	Age=30 years Male=33% Body weight=101 kg BMI=34 kg/m² HbA1c=4.8%	Age=43 years Male=33% Body weight=101 kg BMI=36 kg/m² HbA1c=5.1%
Study Arms	Cohort 1: 90 mg CT-996 once daily	Cohort 2: 120 mg CT-996 once daily[1]	Cohort 3: 120 mg CT-996 once daily[2]	placebo
Enrollment	6 patients	7 patients	6 patients	6 patients
Titration Schedule	10 mg for 1 week 30 mg for 1 week 60 mg for 1 week 90 mg for 1 week	10 mg for 3 days 30 mg for 4 days 60 mg for 1 week 90 mg for 1 week 120 mg for 1 week	10 mg for 3 days 30 mg for 4 days 50 mg for 1 week 80 mg for 1 week 120 mg for 1 week	
Change in Body Weight at Week 4	-2% p =NS placebo-adjusted: -1%	-6% p <0.01 placebo-adjusted: -5%	-7% p <0.001 placebo-adjusted: -6%	-1%
TEAEs	Nausea 83% Decreased appetite 17% Diarrhea 0% Constipation 33% Vomiting 17% Abdominal pain 0% GERD 33% Abdominal distension 17%	86% 14% 43% 57% 71% 57% 86% 43%	83% 83% 50% 50% 33% 17% 17% 0%	17% 17% 17% 17% 17% 17% 0% 17%
Serious Adverse Events	17%, drug-unrelated grade 2 psychotic disorder	0%	0%	0%
TEAEs Leading to Discontinuation	17%, drug-unrelated grade 2 psychotic disorder	14%, drug-unrelated right bundle branch block	0%	0%

HOMA-IR values greater than 1.9 indicate early insulin resistance. HbA1c levels between 5.7% and 6.5% are considered pre-diabetic, and levels of at least 6.5% are considered diabetic. Fasting glucose levels from 100 to 125 mg/dL are considered pre-diabetic, and levels of 126 mg/dL and greater are considered diabetic.

[1]In Cohort 2, two participants required three additional days at 90 mg before escalating to 120 mg. One patient remained at 60 mg.

[2]In Cohort 3, one participant reduced dose from 50 mg to 30 mg to 10 mg and finished the trial at 10 mg.

BMI=Body mass index. cAMP=Cyclic adenosine monophosphate. GERD=Gastroesophageal reflux disease. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. HOMA-IR=Homeostatic Model Assessment of Insulin Resistance. TEAEs=treatment-emergent adverse events.

Sources: Company reports, clinicaltrials.gov

Structure's Aleniglipron

Aleniglipron, also known as GSBR-1290, is an orally bioavailable small-molecule GLP-1 RA with a once-daily dosing schedule that completed Phase I/II clinical testing in overweight or obesity with or without type 2 diabetes (NCT05762471) and a Phase I clinical trial in Japanese and non-Japanese healthy volunteers (NCT05893043). Structurally, the molecule has heterocyclic features (GSRS listing; SureChEMBL listing). Based on the results of a Phase I capsule-to-tablet study of GSBR-1290 in otherwise healthy patients with overweight or obesity, the company aims to pursue

a tablet formulation of the drug in future trials instead of capsule formulation (NCT06139055). The GSBR designation refers to Gasherbrum Bio, Inc., which is now a wholly owned subsidiary of Structure Therapeutics.

Phase IIa trial of GSBR-1290

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05762471).

Efficacy. In results published in June 2024, once-daily capsule formulated GSBR-1290 demonstrated around 6% placebo-adjusted weight loss at 12 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 6% placebo-adjusted weight loss at 12 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with GSBR-1290 led to 89% nausea and 62% vomiting. Serious treatment-emergent adverse events were not reported in either the GSBR-1290 arm or the placebo arm. In addition, the discontinuation rate was higher in the GSBR-1290 arm, related to gastrointestinal adverse events, occurring in the midsingle digits.

Next steps. Structure announced in June 2024 its intent to submit an IND to the FDA for GSBR-1290 in chronic weight management in the third quarter and initiate a 36-week Phase IIb study in overweight or obesity in the fourth quarter (Structure June 2024 press release). A detailed summary of the Phase IIa trial results of GSBR-1290 in overweight or obesity is presented in exhibit 17.

Exhibit 17
Structure Therapeutics Inc.
Phase IIa Trial 12-Week Results of Capsule Formulation GSBR-1290 in Overweight or Obesity Without Diabetes

Sponsor and Trial ID	Structure Therapeutics Inc. (NCT05762471)	
Mechanism of Action	Small molecule GLP-1 receptor agonist	
Baseline Patient Characteristics	Age=45 years Male=46% Body weight=90 kg BMI=32 kg/m^2 HbA1c=5.5%	Age=45 years Male=59% Body weight=92 kg BMI=32 kg/m^2 HbA1c=5.5%
Study Arms	120 mg GSBR-1290 once daily for 12 weeks	Placebo
Enrollment	37 patients	27 patients
Titration Schedule (every week)	5 mg → 15 mg → 30 mg → 60 mg → 90 mg → 120 mg	
Change in Body Weight at Week 12	-6.2% *p* <0.0001	0%
Patients Reaching at Least 6%, 8%, and 10% Weight Loss at Week 12	67%; 56%; 33%	0%
Gastrointestinal TEAEs	**Nausea 89%** **Vomiting 62%** **Constipation 43%** **Decreased appetite 41%**	**11%** **4%** **15%** **11%**
Serious TEAE Frequency	0%	0%
TRAEs Leading to Discontinuation	5%	0%

GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, clinicaltrials.gov

Phase IIb ACCESS trial of GSBR-1290

The trial will test once-daily 45 mg, 90 mg, and 120 mg tablet formulation GSBR-1290 in obesity or overweight with comorbidities over 36 weeks. The first patients in the trial were dosed in November 2024, and top-line data is expected in the fourth quarter. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06693843). A detailed summary of the Phase IIb ACCESS trial design of GSBR-1290 in overweight or obesity is presented in exhibit 18 (Structure November 2024 press release).

Exhibit 18
Structure Therapeutics Inc.
Phase IIb ACCESS Trial Design of Tablet Formulation GSBR-1290 in Obesity or Overweight (With Weight-Related Comorbidities) Without Diabetes

Sponsor and Trial ID	Structure Therapeutics Inc. (NCT06693843)			
Mechanism of Action	Small molecule GLP-1 receptor agonist			
Primary Endpoint	**Weight loss at week 36**			
Secondary and Exploratory Endpoints	Safety and tolerability Pharmacokinetic parameters			
Target Enrollment	165 patients			55 patients
Study Arms	45 mg GSBR-1290 once daily	90 mg GSBR-1290 once daily	120 mg GSBR-1290 once daily	placebo
Titration Schedule (every 4 weeks)	5 mg → 15 mg → 30 mg → 45 mg	5 mg → 15 mg → 30 mg → 60 mg → 90 mg	5 mg → 15 mg → 30 mg → 60 mg → 90 mg → 120 mg	
Next Catalyst	Top-line data expected in Q4 2025			

GLP-1=Glucagon-like peptide 1.
Sources: Company reports

Phase II ACCESS II trial of GSBR-1290

The trial will test once-daily 120 mg, 180 mg, and 240 mg tablet formulation GSBR-1290 in obesity or overweight with comorbidities over 36 weeks. Top-line trial data is expected in the fourth quarter. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06703021). A detailed summary of the Phase II ACCESS II trial design of GSBR-1290 in overweight or obesity is presented in exhibit 19.

Exhibit 19
Structure Therapeutics Inc.
Phase II ACCESS II Trial Design of Tablet Formulation GSBR-1290 in Obesity or Overweight (With Weight-Related Comorbidities) Without Diabetes

Sponsor and Trial ID	Structure Therapeutics Inc. (NCT06703021)					
Mechanism of Action	Small molecule GLP-1 receptor agonist					
Primary Endpoint	**Safety and tolerability**					
Secondary and Exploratory Endpoints	Weight loss at week 36 Pharmacokinetic parameters					
Target Enrollment	82 patients					
Study Groups	Sentinel group Randomized 4:1		Main group Randomized 5:1			
Study Arms	180 mg GSBR-1290	placebo	120 mg GSBR-1290	180 mg GSBR-1290	240 mg GSBR-1290	placebo
Titration Schedule (4- or 8-week steps)	5 mg 15 mg 30 mg 60 mg 90 mg 120 mg 180 mg		5 mg 15 mg 30 mg 60 mg 90 mg 120 mg	5 mg 15 mg 30 mg 60 mg 90 mg 120 mg 180 mg	5 mg 15 mg 30 mg 60 mg 90 mg 120 mg 180 mg 240 mg	
Target Enrollment	82 patients					
Next Catalyst	Top-line data expected in Q4 2025					

GLP-1=Glucagon-like peptide 1.
Sources: Company reports

QL Biopharm's ZT002

The asset, a peptide-based GLP-1 RA, completed Phase I testing in patients with overweight (NCT06371326) and is undergoing Phase II development in obesity and Phase I development in type 2 diabetes. ZT002 possesses a flexible polypeptide c-terminal extension stemming from the GLP-1 moiety enabling greater solubility and spacing to allow two 18-carbon fatty di-acid chains attached to the molecule's GLP-1 moiety and its c-terminal polypeptide extension. The fatty di-acid chains enable increased binding to human serum albumin (K_D=0.18 µM) and thereby lengthen circulating half-life (12 days). ZT002 also has an affinity for GLP-1 receptor of 49 nM. By comparison, Wegovy has a GLP-1R K_D of 59 nM, a human serum albumin binding KD of roughly 2.1 µM, and a circulating half-life of seven days (QL Biopharm September 2024 press release).

Phase Ic trial of ZT002

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06371326).

Efficacy. In results presented at the European Association for the Study of Diabetes 2024 meeting, once-every-other-week ZT002 demonstrated dose-dependent placebo-adjusted weight loss up to 11% in overweight or obesity at 14 weeks. Patients from the 80 mg part A cohort who went on to receive 120 mg ZT002 for 12 weeks after a 4-week follow-up period demonstrated 17% weight loss at 30 weeks, with no placebo comparator arm. Researchers also reported that treatment with ZT002 improved various cardiometabolic risk factors associated with blood pressure, lipid levels, glucose metabolism, liver enzymes, and HbA1c.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 8% placebo-adjusted weight loss at 16 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with ZT002 led to up to 70% nausea (dose-independent), 80% diarrhea (dose-dependent), and 60% vomiting (dose-independent). A single serious adverse event was reported in the pooled placebo arm, representing around 13% (1/8), related to biochemical pregnancy. In addition, there were no treatment-related adverse events leading to study discontinuation.

Next steps. Next steps for the asset include interactions with the FDA to advance clinical development outside China. A detailed summary of the Phase Ic trial results of ZT002 in obesity is presented in exhibit 20 (QL Biopharm September 2024 press release).

Exhibit 20
QL Biopharm
12-Week, 14-Week, and 30-Week Results of ZT002 in Asian Patients With Obesity Without Type 2 Diabetes

	Phase Ic Trial (NCT06371326)			
Sponsor	QL Biopharm			
Mechanism of Action	GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 24 kg/m² and < 28 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%			
Baseline Patient Characteristics	Age=26 years Male=80% Body weight=97 kg BMI=31 kg/m² HbA1c=5.2%	Age=28 years Male=70% Body weight=107 kg BMI=35 kg/m² HbA1c=5.3%	Age=25 years Male=75% Body weight=103 kg BMI=34 kg/m² HbA1c=5.2%	Age=29 years Male=63% Body weight=108 kg BMI=35 kg/m² HbA1c=5.3%
Study Arms	Part A: 40 mg ZT002 once every 2 weeks	Part A: 80 mg ZT002 once every 2 weeks	Part A: pooled placebo	Part B: 120 mg ZT002 once every 4 weeks
Enrollment	10 patients	10 patients	8 patients	8 patients
Titration Schedule	10 mg for 2 weeks; 20 mg for 2 weeks; 40 mg for 8 weeks	10 mg for 2 weeks; 20 mg for 2 weeks; 40 mg for 2 weeks; 80 mg for 8 weeks; 4 weeks follow-up; 8 patients continue to Part B		Continue from Part A, 80 mg cohort; 120 mg for 12 weeks
Change in Body Weight	**At Week 12: -10%** **placebo-adjusted: -9%** **p<0.001**	**At Week 14: -13%** **placebo-adjusted: -11%** **p<0.001**	**At Week 12: -1%** **At Week 14: -2%**	**At Week 30: -17%**
TRAE Frequency	100%	100%	88%	100%
TEAEs	Nausea 70% Diarrhea 70% Vomiting 60% Constipation 20% Abdominal distension 20% Toothache 0% Abdominal pain 20%	70% 80% 50% 40% 10% 0% 10%	13% 25% 0% 0% 25% 0% 0%	63% 63% 50% 25% 13% 13% 0%
Serious Adverse Events	None reported	None reported	1 event, related to non-drug-related biochemical pregnancy	None reported
TRAEs Leading to Discontinuation	None reported			

*Patients had either pre-diabetes, hypertension, hyperlipidemia, fatty liver, obstructive sleep apnea, and/or weight-bearing joint pain.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, clinicaltrials.gov

Pfizer's Danuglipron

Danuglipron, also known as PF-06882961 (PubChem listing), is a small-molecule GLP-1R agonist in tablet form that is intended to be taken orally for treatment of obesity. The asset has undergone Phase I studies of its pharmacokinetics (NCT06153758) and how it interacts with certain other common medications, including statins and antifungal agents. Under the designation PF-06882961, it has also undergone Phase I and Phase II trials for type 2 diabetes (Pfizer July 2024 press release). To identify a small-molecule agonist of GLP-1R, the scientists who developed danuglipron conducted a high-throughput screening that identified a series of fluoropyrimidine-based GLP-1R agonists. They then optimized the lead candidates to activate GLP-1R in a unique binding mode while signaling in a fashion similar to peptide agonists (Griffith, et al. *J. Med. Chem.* 2022).

Phase IIb trial of danuglipron

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04707313).

Efficacy. Twice-daily danuglipron demonstrated up to 13% placebo-adjusted weight loss in obesity at 32 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 15% placebo-adjusted weight loss at 36 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with danuglipron led to up to 73% nausea, 25% diarrhea, and 47% vomiting. Serious treatment-emergent adverse events were not reported. In addition, treatment-related adverse events leading to study discontinuation occurred in more than half of patients receiving danuglipron, compared with a rate in the 40s for all placebo groups.

Next steps. When it announced top-line results, including the high dropout rate, in a December 2023 press release, Pfizer stated that it did not plan to advance the twice-daily formulation of danuglipron into Phase III studies. In July 2024, however, Pfizer announced that data from an ongoing pharmacokinetic study supported the forwarding of once-daily danuglipron into dose optimization studies in the second half of 2024. This study is ongoing, with results expected in March (NCT06568731). Studies of how danuglipron interacts with certain other drugs are also in progress. A detailed summary of the Phase IIb trial results of danuglipron in obesity is presented in exhibit 21 (NCT06567327; NCT06541678).

Exhibit 21
Pfizer Inc.
26-Week Results of Danuglipron in Obesity Without Type 2 Diabetes

Phase IIb Trial (NCT04707313)

Sponsor	Pfizer Inc.												
Mechanism of Action	GLP-1 receptor agonist												
Enrollment Criteria	BMI ≥ 30 kg/m² HbA1c < 6.5%												
Study Cohorts	Cohort 1					Cohort 2			Cohorts 1 and 2 placebo comparator	Cohort 3			Cohort 3 placebo comparator
Study Arms	40 mg danuglipron in four tablets twice daily for 26 weeks	80 mg danuglipron in four tablets twice daily for 26 weeks	120 mg danuglipron in four tablets twice daily for 26 weeks	160 mg danuglipron in four tablets twice daily for 26 weeks	200 mg danuglipron in four tablets twice daily for 26 weeks	120 mg danuglipron in four tablets twice daily for 26 weeks	160 mg danuglipron in four tablets twice daily for 26 weeks	200 mg danuglipron in four tablets twice daily for 26 weeks	placebo	80 mg danuglipron in two tablets twice daily for 32 weeks	140 mg danuglipron in two tablets twice daily for 32 weeks	200 mg danuglipron in two tablets twice daily for 32 weeks	placebo
Enrollment	497 patients									129 patients			
Titration Schedule	1 week titration to target dose					2 week titration to target dose				4 week titration to target dose			
Change in Body Weight at Week 26	**-5% to -9%** **placebo-adjusted: -5% to -10%**								**~+1%**				
Change in Body Weight at Week 32										**-7% to -12%** **placebo-adjusted: -8% to -13%**			**~+1%**
TEAEs	Nausea: up to 73% Vomiting: up to 47% Diarrhea: up to 25%												
TEAEs Leading to Discontinuation	>50%*								~40%**	>50%*			~40%**
Treatment-Emergent Deaths	None reported												

*This was reported for all doses of danuglipron.
**This was reported for all placebo groups.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov.

Terns's TERN-601

TERN-601 is a small-molecule GLP-1 RA with a once-daily oral dosing schedule that completed Phase I clinical development in overweight or obesity. TERN-601 was developed using Terns' internal structure-based drug discovery utilizing the company's proprietary three-dimensional Quantitative Structure Activity Relationship (QSAR) model of the receptor. According to company reports, Terns' QSAR model is able to predict novel GLP-1 RA activity more accurately than traditional physics-based modeling. The structure of TERN-601 has not been disclosed.

Phase I trial of TERN-601

For patient enrollment criteria and trial design, refer to exhibit 22.

Efficacy. Once-daily TERN-601 demonstrated dose-dependent placebo-adjusted weight loss up to 5% in overweight or obesity at 4 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Pharmacokinetic parameters. Investigators observed that doses of 240 mg in the part 1, single-ascending-dose component of the trial demonstrated an absorption profile of plasma concentrations exceeding of EC_{50} for 16 to 24 hours, representing roughly 3 to 6 times the drug's elimination half-life.

Safety and tolerability. Treatment with TERN-601 led to up to 89% nausea, 22% diarrhea, and 78% vomiting, all of which exhibited dose-dependent relationships. No serious treatment-emergent adverse events occurred across trial groups. In addition, there were no study discontinuations due to treatment-related adverse events, though one patient in the 240 mg arm (around 10%) discontinued due to treatment-unrelated menstrual bleeding.

Next steps. Terns aims to initiate a Phase II trial of TERN-601 in obesity this year. A detailed summary of the Phase I trial results of TERN-601 in overweight or obesity is presented in exhibit 22 (TERN-601 Phase I Trial Top-Line Results September 2024 corporate presentation).

Exhibit 22
Terns Pharmaceuticals, Inc.
4-Week Results of TERN-601 in Overweight or Obesity Without Type 2 Diabetes

Phase I Trial

Sponsor	Terns Pharmaceuticals, Inc.			
Mechanism of Action	GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² HbA1c < 6.5%			
Baseline Patient Characteristics	Age=45 years Male=70% Body weight=93 kg BMI=31 kg/m² HbA1c=5.5%	Age=47 years Male=89% Body weight=95 kg BMI=31 kg/m² HbA1c=5.6%	Age=47 years Male=78% Body weight=93 kg BMI=30 kg/m² HbA1c=5.5%	Age=41 years Male=78% Body weight=91 kg BMI=30 kg/m² HbA1c=5.6%
Study Arms	240 mg TERN-601 once daily	500 mg TERN-601 once daily	740 mg TERN-601 once daily	placebo
Enrollment	10 patients	9 patients	9 patients	9 patients
Titration Schedule	100 mg for 1 week; 180 mg for 1 week; 240 mg for 2 weeks	100 mg for 2 days; 240 mg for 3 days; 380 mg for 3 days; 500 mg for 20 days	100 mg for 2 days; 240 mg for 3 days; 380 mg for 3 days; 500 mg for 3 days; 740 mg for 17 days	
Change in Body Weight at Week 4	-3% placebo-adjusted: -2% *p* <0.1	-4% placebo-adjusted: -4% *p* <0.01	-6% placebo-adjusted: -5% *p* <0.0001	-1%
Patients Reaching ≥3% and ≥5% Weight Loss at Week 4	33% (*p* =NS) 11% (*p* =NS)	78% (*p* <0.1) 33% (*p* =NS)	78% (*p* <0.1) 67% (*p* <0.01)	11% 0%
TEAE Frequency	**60%**	**100%**	**100%**	**56%**
Gastrointestinal TEAEs	**Nausea 0%** **Vomiting 0%** **Constipation 20%** **Diarrhea 0%**	**78%** **44%** **0%** **22%**	**89%** **78%** **56%** **22%**	**22%** **0%** **0%** **0%**
Serious TEAE Frequency	**0%**	**0%**	**0%**	**0%**
TRAEs Leading to Discontinuation[1]	**0%**	**0%**	**0%**	**0%**

[1]One participant in the 240 mg arm discontinued the trial early due to treatment-unrelated grade 1 menstrual bleeding; the participant was replaced.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, clinicaltrials.gov

AstraZeneca and Eccogene's AZD5004

AstraZeneca licensed what it refers to as AZD5004, also known as ECC5004, an oral small-molecule GLP-1 RA, from the Chinese company Eccogene in 2023. AstraZeneca has suggested that the drug is rapidly absorbed and so may have reduced gastrointestinal adverse effects compared with other GLP-1 RAs (Reuters Nov. 2023).

Clinicaltrials.gov lists four new trials in the recruiting stage for AZD5004: a Phase I study to investigate multiple ascending doses and relative bioavailability of AZD5004 in healthy participants (NCT06555822); a Phase IIb study of the efficacy, safety, and tolerability of once-daily oral administration of AZD5004 versus placebo for 26 weeks in adults with type 2 diabetes (SOLSTICE) (NCT06579105); a Phase I study to investigate multiple ascending doses of AZD5004 in healthy

Japanese participants and participants with type 2 diabetes (NCT06703658); and a Phase II study of the effects of AZD5004 in adults who are living with obesity or overweight with at least one weight-related comorbidity (VISTA) (NCT06579092).

Eccogene previously conducted three Phase I trials under the designation ECC5004: one to determine bioavailability (NCT06268145); a second to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy participants and in patients with type 2 diabetes (NCT05654831); and a third to study drug-drug interactions with atorvastatin, rosuvastatin, digoxin, and midazolam (NCT06293742).

Phase I trial of AZD5004

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05654831).

Efficacy. In results presented at the ObesityWeek 2024 meeting, once-daily AZD5004 demonstrated dose-dependent placebo-adjusted weight loss up to 2% in patients with type 2 diabetes at 4 weeks. Participants receiving AZD5004 also demonstrated dose-dependent declines in glucose area-under-the-curve from day -1 to day 1. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with single-ascending doses of AZD5004 led to up to 84% nausea and 83% vomiting, both of which were dose-dependent. Treatment with multiple ascending doses of AZD5004 led to up to 60% nausea (dose-dependent), 33% diarrhea (dose-independent), and 20% vomiting (dose-dependent). No serious treatment-emergent adverse events were reported in either the single-ascending-dose or multiple-ascending-dose components. In addition, the discontinuation rate was not dose-dependent in the single-ascending-dose component, occurring at a midteens percentage in the 10 mg and 50 mg groups. In the multiple-ascending-dose component, the discontinuation rate was highest in the two highest dose groups, at 10% in both the 30 mg and 50 mg arms.

Next steps. AstraZeneca has said that one of the Phase II trials of the drug, which will focus on reduction in body weight in obese and overweight participants, is expected to be completed by the end of this year (Reuters November 2024 news report).

Hanmi's Efpeglenatide

Efpeglenatide, also known as HM11260C, is a peptide-based long-acting exendin-4 analog that acts as a GLP-1 RA. Originally developed for treatment of type 2 diabetes, it is also being studied for obesity, alone and in combination with efpegerglucagon, Hanmi's glucagon analog (HM15136). Efpeglenatide comprises the original exendin-4 peptide with a substitution of imidazoleacetic acid for histidine at the first position and serinamide for serine at position 39, conjugated to the fragment crystallizable (Fc) region of human IgG4 via a flexible mini-polyethylene glycol linker (GSRS listing).

Efpeglenatide has completed a Phase III trial for treatment of type 2 diabetes (Frias, et al. *Diab. Care* 2022) and a Phase II study to assess safety and efficacy in obese subjects (NCT02075281). A Phase III study of the drug in obese patients without diabetes commenced in 2024. The drug will be administered subcutaneously on a weekly basis. Results are expected in 2026 (NCT06174779).

Eli Lilly's Macupatide

GIP RAs are generally combined with a GLP-1 RA, due to their synergistic effects for weight loss. Lilly is conducting a Phase I trial of the peptide-based macupatide (LY3532226), a newer and long-lasting GIP RA, in persons with obesity (NCT06557356). Participants will have a BMI between 30

kg/m^2 and 40 kg/m$^{2.}$ The study will measure adverse events and pharmacokinetics. The drug will be administered subcutaneously. The study started in August 2024 and is expected to be completed in May.

Metsera's MET-097i

MET-097i is a fully biased GLP-1 RA with a half-life of 15-16 days, giving it the potential for once-monthly dosing. Metsera's pipeline includes lead asset MET-097i and the amylin analog MET-233i. MET-233i is in Phase I development as a monotherapy and in IND-enabling studies in combination with MET-097i. Metsera's assets in development also include the oral peptides MET-224o, a fully biased GLP-1 RA in IND-enabling studies, and MET-002o, a GLP-1 RA in Phase I development. MET-002o is a predecessor peptide to MET-224o; it is currently being assessed in a Canadian trial to determine an ideal clinical formulation for MET-224o. Aside from GLP-1 and amylin RAs, Metsera's GIP RA MET-034i and its glucagon analog MET-067i are in IND-enabling studies (Metsera pipeline). In January, Metsera filed a registration statement with a preliminary prospectus for an initial public offering of its stock.

Phase IIa trial of MET-097i

Patients receiving once-weekly MET-097i experienced up to 11% weight loss at 12 weeks. For patient enrollment criteria and trial design, refer to exhibit 23.

Efficacy. At 12 weeks, patients in the 1.2 mg MET-097i cohort without titration experienced about 11% placebo-adjusted weight loss. With titration, patients in the other 1.2 mg MET-097i arm experienced nearly 6% placebo-adjusted weight loss. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 6% placebo-adjusted weight loss at 12 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Gastrointestinal adverse events were mild to moderate and were transient. In the 1.2 mg MET-097i cohort with titration, one case of nausea was reported (5%) and two cases of vomiting were reported (10%). Also, the step-up at week 13 to a fourfold higher dose demonstrated good tolerability across cohorts, according to the press release.

Pharmacokinetic parameters. MET-097i demonstrated fourfold pharmacologic accumulation in the bloodstream over 12 weeks in the cohorts without dose titration, reflecting MET-097i's 15- to 16-day half-life.

Next steps. A Phase IIb trial testing MET-097i in obesity or overweight is fully enrolled with 239 patients, with top-line data slated for release midyear (NCT06712836). Further trials testing weekly or monthly dosing of MET-097i in obesity, overweight, and type 2 diabetes are planned for this year. In the event these trials are positive, Phase III trials are planned to follow. A detailed summary of the Phase IIa trial results of MET-097i in overweight or obesity is presented in exhibit 23.

Exhibit 23
Metsera, Inc.
12-Week Results of MET-097i in Overweight or Obesity Without Type 2 Diabetes

Phase IIa Trial						
Sponsor	Metsera, Inc.					
Mechanism of Action	GLP-1 receptor agonist					
Enrollment Criteria	Obese or overweight HbA1c < 6.5%					
Study Arms	0.6 mg MET-097i once weekly*	0.8 mg MET-097i once weekly*	1.0 mg MET-097i once weekly*	1.2 mg MET-097i once weekly*	1.2 mg MET-097i once weekly*	placebo
Enrollment	20 patients	20 patients	20 patients	20 patients	20 patients	20 patients
Titration Schedule	0.6 mg for 12 weeks; 1.2 mg or 2.4 mg once	0.8 mg for 12 weeks; 1.6 mg or 3.2 mg once	1.0 mg for 12 weeks; 2.0 mg or 4.0 mg once	1.2 mg for 12 weeks; 2.4 mg or 4.8 mg once	0.4 mg for 4 weeks; 0.8 mg for 4 weeks; 1.2 mg for 4 weeks; 2.4 mg or 4.8 mg once	
Placebo-Adjusted Change in Body Weight at Week 12				**-11%**	**-6%**	
TEAEs					Vomiting 10% Nausea 5%	
TEAEs Leading to Discontinuation	0%					

*Once-weekly MET-097i was followed by a single dose of MET-097i.
GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov

Upcoming Candidates: Dual Agonists

Viking's VK2735

VK2735 is a peptide-based dual agonist of the GIP and GLP-1 receptors that is being evaluated for both oral and subcutaneous delivery in obesity. A Phase I trial of both forms was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of VK2735 in healthy adults and otherwise healthy adults who have an increased body mass index (NCT05203237). A Phase II study, the VENTURE trial, was conducted to evaluate the safety, tolerability, weight loss efficacy, pharmacodynamic effects, and pharmacokinetics of subcutaneous VK2735 in adults who are obese or overweight with at least one weight-related co-morbid condition (NCT06068946). The structure of VK2735 has not been disclosed.

Phase I trial of subcutaneous VK2735

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05203237).

Efficacy. In 2023 results, once-weekly VK2735 demonstrated dose-dependent placebo-adjusted weight loss up to 6% in healthy volunteers and patients with obesity at 4 weeks. In addition, VK2735 demonstrated placebo-adjusted reductions (improvements) in liver fat content up to 47% in the second-highest dose group, with the caveat that the highest dose group demonstrated the least placebo-adjusted decline of around 8%. Furthermore, there appeared to be a dose response related to the reduction in apolipoprotein B (a marker for cardiovascular risk), low-density lipoprotein ("bad") cholesterol, and total cholesterol. Encouragingly, there was no change to HDL ("good") cholesterol.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with VK2735 led to up to 83% nausea (dose-dependent, highest at second-highest dose level), 29% diarrhea (dose-independent), and 33% vomiting (dose-independent). Two serious adverse events, a gallstone obstruction (with a history of gallstones) and infectious mononucleosis, were reported in the VK2735 cohorts, representing a roughly 6.5% rate across arms. In addition, there were no study discontinuations due to nausea, vomiting, or other gastrointestinal adverse events.

Pharmacokinetic parameters. The half-life for VK2735 during the study was roughly 170 to 250 hours, while the time to reach the maximum concentration of VK2735 (T_{max}) was about 75 to 90 hours. The Phase I results, along with trial design, are presented in exhibit 24.

Exhibit 24
Viking Therapeutics, Inc.
4-Week Results of VK2735 in Healthy Adults with Elevated BMI Without Type 2 Diabetes

Phase I Trial (NCT05203237)

Sponsor	Viking Therapeutics, Inc.					
Mechanism of Action	Dual GLP-1/GIP receptor agonist					
Enrollment Criteria	Healthy adults (SAD cohorts) Otherwise healthy adults with BMI ≥30 kg/m² (MAD cohorts)					
Baseline Patient Characteristics	Age=34 years Male=83% Weight=101 kg BMI=33 kg/m²	Age=39 years Male=50% Weight=115 kg BMI=39 kg/m²	Age=36 years Male=14% Weight=115 kg BMI=41 kg/m²	Age=32 years Male=67% Weight=116 kg BMI=38 kg/m²	Age=42 years Male=33% Weight=96 kg BMI=34 kg/m²	Age=29 years Male=50% Weight=121 kg BMI=39 kg/m²
Study Arms	0.5 mg VK2735 once weekly	1.5 mg VK2735 once weekly	5.0 mg VK2735 once weekly	7.5 mg VK2735 once weekly	10 mg VK2735 once weekly	placebo
Enrollment	6 individuals	6 individuals	7 individuals	6 individuals	6 individuals	10 individuals
Titration Schedule	0.5 mg for 4 weeks	1.5 mg for 4 weeks	1.5 mg for 1 week; 3.0 mg for 1 week; 5.0 mg for 2 weeks	3.0 mg for 1 week; 5.0 mg for 2 weeks; 7.5 mg for 1 week	5.0 mg for 2 weeks; 7.5 mg for 1 week; 10 mg for 1 week	
Change in Body Weight at Week 4	-3% (*p* =NS) **placebo-adjusted: -1%**	-4% (*p* =NS) **placebo-adjusted: -2%**	-4% (*p* =NS) **placebo-adjusted: -2%**	-7% (*p* =0.0003) **placebo-adjusted: -6%**	-8% (*p* =0.0002) **placebo-adjusted: -6%**	-2%
Placebo-Adjusted Liver Fat Content Reduction (Only Among NAFLD)	**+5%** **(none qualified)**	**-24%** **(-43%)**	**-23%** **(-41%)**	**-47%** **(-59%)**	**-8%** **(-20%)**	
Mean Percent Change from Baseline Liver Fat Content (Only Among NAFLD)	+4% (*p* =NS) (none qualified)	-24%, *p* =NS (-34%, *p* =0.029)	-24%, *p* =NS (-33%, *p* =0.033)	-47%, *p* =0.0023 (-50%, *p* =0.0059)	-8%, *p* =NS (-11%, *p* =NA, since n=1)	-1% (+9%)
Plasma Lipid Reduction from Baseline	Apo(B)= +3% LDL-C= +1% Total-C= -2%	Apo(B)= -2% LDL-C= -11% Total-C= -11%	Apo(B)= -13% LDL-C= -14% Total-C= -15% (*p* <0.05)	Apo(B)= -13% LDL-C= -20% Total-C= -17% (*p* <0.05 for all)	Apo(B)= -21% LDL-C= -23% Total-C= -21%	Apo(B)= +2% LDL-C= -10% Total-C= -5%
TEAEs	Decreased appetite 50% Nausea 33% Vomiting 33% Diarrhea 17% Constipation 17%	50% 67% 0% 17% 17%	57% 71% 29% 29% 29%	83% 83% 17% 0% 17%	100% 33% 17% 0% 0%	30% 50% 10% 30% 0%
Serious AEs	1 case of gallstone obstruction in the VK2735 cohorts (though the individual had a history of gallstones) 1 case of infectious mononucleosis					
Discontinuations Due to Nausea, Vomiting, or GI AEs	None reported					
Pharmacokinetic Profile	Half-life = 170 to 250 hours T_{max} ~72 hours					

AEs=Adverse events. BMI=Body Mass Index. GI=Gastrointestinal. GIP=Glucose-dependent Insulinotropic Polypeptide. GLP-1=Glucagon-like peptide-1. MAD=Multiple ascending dose. SAD=Single ascending dose. NAFLD=Nonalcoholic fatty liver disease, defined as liver fat content >5%. NS=Not significant.

Sources: Company reports, clinicaltrials.gov

Phase II VENTURE trial of subcutaneous VK2735
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06068946).

Efficacy. In top-line results published in early 2024, once-weekly VK2735 demonstrated dose-dependent placebo-adjusted weight loss up to 13% in overweight or obesity at 13 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 6% placebo-adjusted weight loss at 12 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

In updated results at the ObesityWeek conference in November 2024, the proportion of weight loss maintained at 4 weeks and 7 weeks after the final dose across dose levels was between 92% and 98% and between 75% and 91%, respectively. The investigators also presented an exploratory analysis showing that VK2735 increased the odds of patients with prediabetic status at baseline (fasting plasma glucose 100 mg/dL to 125 mg/dL or HbA1c 5.7% to 6.4%) shifting to non-diabetic status over the 13-week treatment period. The percent of prediabetic participants shifting to non-diabetic status occurred between 63% at the second-highest dose level and 94% at the highest dose level.

Safety and tolerability. Treatment with VK2735 led to up to 63% nausea (dose-dependent), 31% diarrhea (dose-independent), and 29% vomiting (dose-dependent). One case of serious treatment-emergent dehydration occurred across the VK2735 treatment arms, representing a rate of around 0.7%. In addition, the discontinuation rate exhibited a dose-dependent relationship, occurring up to the midsingle digits, and was balanced with the placebo arm.

Next steps. Viking plans to advance the subcutaneous version of VK2735 into Phase III development for obesity, based on feedback from the FDA. The Phase II results, along with trial design, are presented in exhibit 25 (Viking March 2024 press release).

Exhibit 25
Viking Therapeutics, Inc.
13-Week Results of VK2735 in Overweight or Obesity Without Type 2 Diabetes

Phase II VENTURE Trial (NCT06068946)

Sponsor	Viking Therapeutics, Inc.				
Mechanism of Action	Dual GLP-1/GIP receptor agonist				
Enrollment Criteria	BMI ≥30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity HbA1c < 6.5%				
Baseline Patient Characteristics	Age=50 years Male=23% Body weight=103 kg BMI=38 kg/m²	Age=52 years Male=34% Body weight=98 kg BMI=36 kg/m²	Age=47 years Male=34% Body weight=103 kg BMI=37 kg/m²	Age=51 years Male=23% Body weight=101 kg BMI=37 kg/m²	Age=48 years Male=18% Body weight=105 kg BMI=39 kg/m²
Study Arms	2.5 mg VK2735 once weekly	5.0 mg VK2735 once weekly	10 mg VK2735 once weekly	15 mg VK2735 once weekly	placebo
Enrollment	35 patients	35 patients	35 patients	35 patients	34 patients
Titration Schedule	2.5 mg for 13 weeks	2.5 mg for 3 weeks; 5.0 mg for 10 weeks	2.5 mg for 3 weeks; 5.0 mg for 3 weeks; 7.5 mg for 3 weeks; 10 mg for 4 weeks	5.0 mg for 3 weeks; 7.5 mg for 3 weeks; 10 mg for 3 weeks; 15 mg for 4 weeks	
Placebo-Adjusted (Unadjusted) Mean Change in Weight from Baseline at 13 Weeks	-7% (-9%)	-9% (-11%)	-11% (-13%)	-13% (-15%)	N/A (-2%)
Proportion of Patients Achieving ≥ 10% Weight Loss at 13 Weeks	39%	62%	70%	88%	4%
TEAEs	Nausea 26% Constipation 20% Vomiting 9% Decreased appetite 6% Diarrhea 31%	46% 29% 17% 14% 17%	37% 26% 17% 26% 20%	63% 29% 29% 17% 11%	20% 11% 0% 0% 9%
Serious Adverse Events	1 case of dehydration (drug-related)				None
Discontinuation Treatment (Study) Rate	6% (0%)	11% (3%)	14% (6%)	20% (6%)	14% (6%)

BMI=Body Mass Index. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide-1.
Sources: Company reports

Phase I trial of oral VK2735

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05203237).

Efficacy. In initial results released in early 2024, once-daily oral VK2735 demonstrated dose-dependent placebo-adjusted weight loss up to 3% in obesity at 4 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Further results from the Phase I participants who received the oral version of VK2735 were released at the ObesityWeek conference in November 2024. This included data from visits up to four weeks after the final dosage and new results from cohorts dosed at 60, 80, and 100 mg daily. The follow-up visits showed persistent weight loss through day 57. VK2735 demonstrated dose-dependent placebo-adjusted weight loss up to 7% in the 100 mg cohort in obesity at 4 weeks.

Safety and tolerability. Based on our analysis, while there appears to be an on-target dose-dependent increase in the frequency of mild nausea (no moderate or severe nausea events were reported in the study), other adverse events of interest were balanced across the treatment and placebo arms (e.g.,

abdominal pain: 8% versus 30%, diarrhea 3% compared with 20%). No vomiting events or severe adverse events were reported in the study. Two patients discontinued the study on the treatment arm (family emergency and abdominal pain). In updated results, adverse events were of the same nature as experienced at lower dosages, but were experienced more frequently; nevertheless, they remained of mild or moderate. The Phase I results, along with trial design, are presented in exhibit 26 (Viking press release March 2024).

Next steps. The company initiated the Phase II VENTURE-Oral study of the oral tablet formulation of VK2735 in obesity in January.

See exhibit 26 on the following page.

Phase II VENTURE-Oral trial of VK2735

The study will evaluate the safety, tolerability, pharmacokinetics, and efficacy of the asset in patients with overweight or obesity. For patient enrollment criteria and trial design, refer to exhibit 27.

See exhibit 27 on page 54.

Exhibit 26
Viking Therapeutics, Inc.
4-Week Results of Oral Tablet Formulation of VK2735 in Obesity Without Type 2 Diabetes

Phase I Trial (NCT05203237)

Sponsor	Viking Therapeutics, Inc.									
Mechanism of Action	Dual GLP-1/GIP receptor agonist									
Enrollment Criteria	BMI ≥30 kg/m² HbA1c < 6.5%									
Mean Baseline Body Weight	102 kg	95 kg	97 kg	111 kg	90 kg	108 kg	102 kg	Not reported	103 kg	98 kg
Study Arms	2.5 mg VK2735 once daily	5.0 mg VK2735 once daily	10 mg VK2735 once daily	20 mg VK2735 once daily	40 mg VK2735 once daily	60 mg VK2735 once daily	80 mg VK2735 once daily (A)	80 mg VK2735 once daily (B)	100 mg VK2735 once daily	placebo
Enrollment	8 patients	7 patients	6 patients	8 patients	8 patients	9 patients	9 patients	9 patients	9 patients	19 patients
Titration Schedule	2.5 mg for 4 weeks	2.5 mg for 1 week 5.0 mg for 3 weeks	5.0 mg for 1 week 10 mg for 3 weeks	15 mg for 1 week 20 mg for 3 weeks	20 mg for 1 week 40 mg for 3 weeks	40 mg for 1 week 60 mg for 3 weeks	60 mg for 1 week 80 mg for 3 weeks	60 mg for 1 week 80 mg for 1 week 80 mg every other day for 2 weeks	80 mg for 1 week 100 mg for 3 weeks	-
Placebo-Adjusted (Unadjusted) Mean Weight Loss at 4 Weeks	+1.0% (-0.3%) NS (8 evaluable)	+0.6% (-0.8%) NS (6 evaluable)	+0.3% (-1.1%) NS (6 evaluable)	-2.2% (-3.5%) p =0.017 (8 evaluable)	-3.7% (-5.1%) p =0.0001 (7 evaluable)	-2.7% (-4.1%) p =0.0026 (9 evaluable)	-3.9% (-5.2%) p <0.0001 (9 evaluable)	-2.6% (-4.0%) p <0.001 (9 evaluable)	-6.8% (-8.2%) p <0.0001 (7 evaluable)	N/A (-1.4%)
Proportion of Patients Achieving ≥5% Weight Loss	0% NS	0% NS	0% NS	25% NS	57% p <0.01	38% p <0.05	63% p <0.01	Not reported	100% p <0.001	0%
TEAE Frequency	75%	86%	67%	75%	88%	100%	100%	89%	100%	84%
TEAEs	Nausea 0% Constipation 0% Vomiting 0% Diarrhea 0% Abdominal pain 0% GERD 0%	14% 0% 0% 0% 14% 0%	0% 0% 0% 0% 17% 0%	25% 0% 0% 13% 0% 13%	25% 0% 0% 0% 0% 0%	22% 33% 0% 11% 11% 11%	67% 22% 11% 11% 0% 22%	44% 11% 11% 11% 0% 0%	67% 44% 11% 11% 0% 0%	11% 16% 0% 21% 11% 5%
TRAE Frequency	50%	57%	50%	50%	88%	67%	100%	78%	100%	58%
Serious Adverse Events	0%	0%	0%	0%	0%	11%	0%	0%	0%	0%
Discontinuation of Study Rate	0%	14%	0%	0%	13%	11%	11%	0%	0%	11%

BMI=Body Mass Index. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide-1. NS=not significant. TEAE=Treatment-emergent adverse event. TRAE=Treatment-related adverse event.
Sources: Company reports

Exhibit 27
Viking Therapeutics, Inc.
Phase II VENTURE-Oral Trial Design of VK2735 Oral Tablet Formulation in Overweight and Obesity without Type 2 Diabetes

Phase II VENTURE-Oral Trial

Mechanism of Action	Dual GLP-1/GIP receptor agonist						
Inclusion Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity HbA1c < 6.5%						
Study Arms	VK2735 dose 1 once daily for 13 weeks	VK2735 dose 2 once daily for 13 weeks	VK2735 dose 3 once daily for 13 weeks	VK2735 dose 4 once daily for 13 weeks	VK2735 dose 5 once daily for 13 weeks	VK2735 dose 6 once daily for 13 weeks	placebo
Target Enrollment	280 patients						
Primary Endpoint	**Weight loss at 13 Weeks**						
Secondary Endpoints	Safety and efficacy						

BMI=Body Mass Index. GIP=Glucose-dependent Insulinotropic Polypeptide. GLP-1=Glucagon-like peptide-1.
Sources: Company reports.

Roche's RG6640

RG6640, also known as CT-388, was acquired with the completed acquisition of Carmot Therapeutics in January 2024. It is a dual GLP-1 and GIP RA peptide with an undisclosed sequence that is administered subcutaneously. Roche describes it as having minimal to no β-arrestin recruitment on either receptor, which it expects will minimize receptor internalization and consequent desensitization, with the goal of prolonged pharmacological activity (Roche website). It completed a Phase I/Ib clinical trial in obese patients with or without diabetes (NCT04838405) and is undergoing Phase II clinical testing in patients with obesity or overweight with at least one weight-related comorbidity including prediabetes (NCT06525935).

Phase I/Ib trial of CT-388

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04838405).

Efficacy. In results presented at the European Association for the Study of Diabetes 2024 meeting, once-weekly CT-388 demonstrated dose-dependent placebo-adjusted weight loss of up to 19% at 24 weeks in overweight or obesity and type 2 diabetes. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 12% placebo-adjusted weight loss at 24 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with CT-388 led to transient creatine kinase elevation in two patients in the 22 mg arm and up to 83% nausea, 54% diarrhea, and 75% vomiting, all of which exhibited dose-dependent relationships and were highest in the rapid up-titration component. One case of serious treatment-unrelated spontaneous abortion was reported, representing around 8.3% of patients in the 8 mg arm. In addition, the discontinuation rate did not exhibit a dose-dependent relationship; the 8 mg arm rate occurred at nearly twice the rate of the 22 mg arm (both in the low to midsingle digits).

Next steps. Researchers aim to focus on the ongoing Phase II study of CT-388 in patients with obesity or overweight with at least one weight-related comorbidity, which was initiated in August 2024, with an estimated completion date of February 2026. Planning is underway for initiation of a Phase III study. A detailed summary of the Phase I/Ib trial results of CT-388 in obesity is presented in exhibit 28.

Exhibit 28
Roche Holding AG
12-Week and 24-Week Multiple-Ascending-Dose Results of CT-388 in Obesity Without Type 2 Diabetes

Phase I/Ib Trial (NCT04838405)

Sponsor	Roche Holding AG			
Mechanism of Action	Dual GLP-1 and GIP receptor agonist			
Enrollment Criteria	BMI ≥ 30 kg/m² Otherwise healthy			
Baseline Patient Characteristics	Age=37 years Male=17% Body weight=97 kg BMI=38 kg/m² HbA1c=5.3%	Age=32 years Male=37% Body weight=108 kg BMI=39 kg/m² HbA1c=5.4%	Age=37 years Male=70% Body weight=98 kg BMI=35 kg/m² HbA1c=5.5%	
Study Arms	8 mg CT-388 once weekly	22 mg CT-388 once weekly*	placebo once weekly for 12 weeks	placebo once weekly for 24 weeks**
Enrollment	12 patients	24 patients	3 patients	7 patients
Titration Schedule	5 mg for 3 weeks; 8 mg for 9 weeks	5 mg for 2 weeks; 8 mg for 2 weeks; 12 mg for 2 weeks; 17 mg for 2 weeks; 22 mg for 4 weeks; MTD for 12 weeks		
Change in Body Weight at Week 12	-10% p <0.001 placebo-adjusted: -9%	-12% p <0.001 placebo-adjusted: -12%	-1%	
Change in Body Weight at Week 24		-19% p <0.001 placebo-adjusted: -19%		0%
TEAE Frequency	100%	100%	100%	86%
TEAEs Day 1 to Week 12^	Decreased appetite 92% Nausea 42% Vomiting 25% Constipation 75% Dyspepsia 8% Diarrhea 50% Eructation 58% Soft feces 42% Early satiety 0% Abdominal distension 25% Abdominal pain 0%	92% 83% 75% 58% 58% 54% 54% 50% 46% 21% 21%	40% 20% 10% 0% 0% 20% 20% 10% 0% 10% 0%	
Serious Adverse Events	8%, drug-unrelated spontaneous abortion	0%	0%	0%
TEAEs Leading to Discontinuation	8%, drug-unrelated spontaneous abortion	4%, drug-unrelated pregnancy	0%	0%

*Following the 12-week initial period, a 12-week extension period administered the highest tolerated dose; of the 20 patients who completed 24 weeks of treatment, 15 patients completed on 22 mg, and 5 patients completed on 12 mg due to dosing changes.
**For the weight loss metric at 24 weeks, five placebo-arm patients corresponding to the 22 mg CT-388 or placebo cohort were assessed for weight loss.
^ From week 12 to week 24, the 22 mg cohort reported nausea (54%), diarrhea (50%), constipation (50%), eructation (38%), dyspepsia (38%), vomiting (33%), soft feces (33%), decreased appetite (4%), and abdominal pain (4%).
BMI=Body mass index. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. MTD=Maximum tolerated dose. TEAEs=treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov

Eli Lilly's LY3537031

Lilly is conducting a Phase I trial of LY3537031, a GLP-1/GIP receptor co-agonist (NCT06606106), for safety, pharmacokinetics, and pharmacodynamics. The drug will be tested on overweight and obese participants (part A) and healthy participants (parts B and C). Part C will contain only Japanese and Chinese healthy participants. Multiple ascending doses will be administered subcutaneously for a period of 20 weeks. The study started in September 2024 and its expected completion date is in July.

Novo Nordisk's NNC0519-0130

NNC-0519-0130, described as a GLP-1/GIP RA, is undergoing multiple studies for obesity, type 2 diabetes, and chronic kidney disease. Two Phase I trials have been completed: 1) a study of the safety, tolerability, pharmacokinetics, and pharmacodynamics of single subcutaneous doses of NNC0519-0130 in healthy participants and multiple subcutaneous and oral doses of NNC0519-0130 in participants with overweight or obesity and participants with type 2 diabetes (NCT05363774) and 2) an investigation of the pharmacokinetics, safety, and tolerability of multiple subcutaneous doses in Japanese and non-Japanese male participants (NCT05870670).

Five additional Phase I studies are underway. These include an investigation of pharmacokinetics of two different formulations of NNC0519-0130 in adult participants with overweight or obesity (NCT06642571); an evaluation of different dose-escalation regimens for NNC0519-0130 in participants with overweight and obesity (NCT06718998); and an investigation of the effect of impaired renal function on the pharmacokinetics of subcutaneously administered NNC0519-0130 in participants with various degrees of renal function (NCT06370819). Other Phase I trials include an investigation of the safety, tolerability, pharmacokinetics, and efficacy of subcutaneous weekly administration of the drug in participants with obesity and in participants with type 2 diabetes with either overweight or obesity (NCT06567041); and an investigation into the effect of NNC0519-0130 on blood levels of an oral birth control pill (containing the hormones ethinylestradiol and levonorgestrel) and gastric emptying in healthy postmenopausal females (NCT06513104).

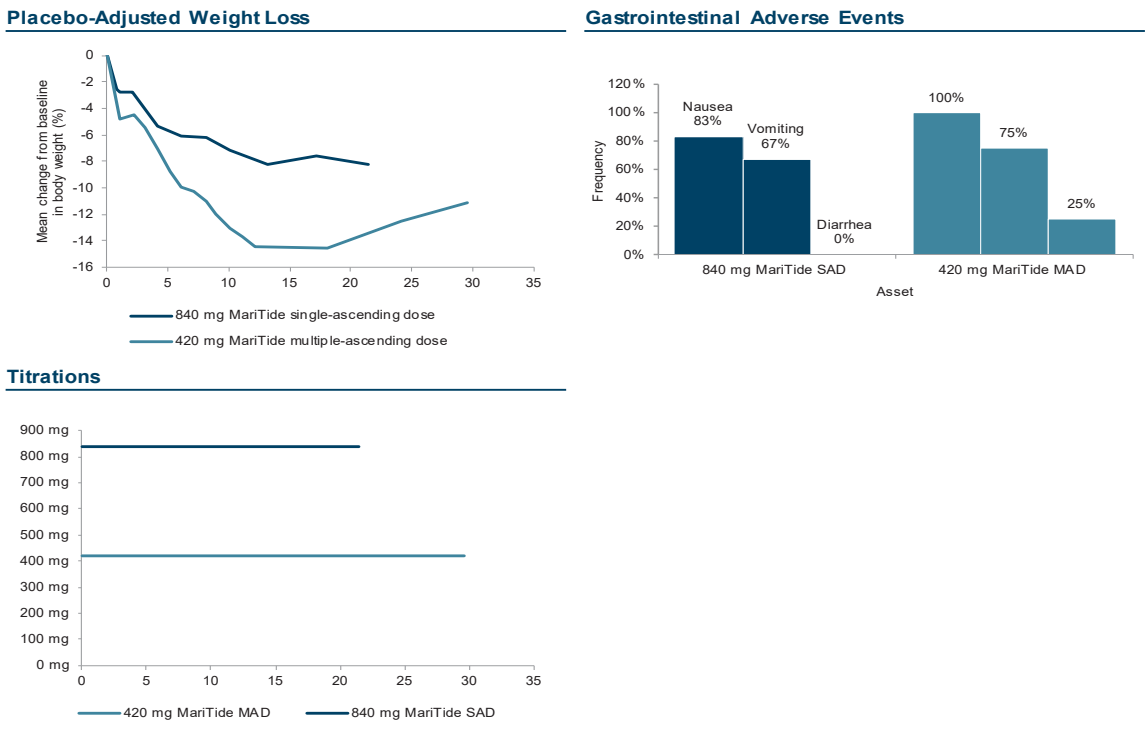
Lastly, three Phase II studies are ongoing: a study into the efficacy, safety, and pharmacokinetics of once-weekly subcutaneous NNC0519-0130 versus Wegovy 1.0 mg and placebo in people with chronic kidney disease, with or without type 2 diabetes, and with overweight or obesity, which the company refers to as a proof-of-concept and dose-finding study (NCT06717698); a dose-finding study of the safety and efficacy for lowering blood sugar of once-weekly NNC0519-0130 in participants with type 2 diabetes, which will involve a comparison to Mounjaro (NCT06326047); and a dose-finding study comparing how well different doses of the medicine help people lose excess body weight (NCT06326060). In each ongoing study, the drug is being given subcutaneously. For those studies where timing of administration is given, it is once or twice per week. Results are expected in the 2025-2026 time frame.

GLP-1 Receptor Agonist and GIP Receptor Antagonist

In our view, combining a GLP-1 RA with a GIP receptor antagonist presents a novel combination of mechanisms that could offer promising weight loss, given the up to 17% placebo-adjusted weight loss at 1 year in Phase II results of MariTide in overweight and obesity. Furthermore, MariTide's Phase II safety profile improved with dose titration, compared with the trial's non-titrating group. In addition, monthly dosing with MariTide could differentiate the asset class in its convenience. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of the GLP-1 RA and GIP receptor antagonist MariTide is presented in exhibit 29.

Exhibit 29

Combined Weight Loss, Adverse Events, and Titration Curves of GLP-1 and GIP Receptor Antagonist MariTide



GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1.

Source: Company documents

Amgen's MariTide

Maridebart cafraglutide, also known as MariTide or AMG133, is in Phase II clinical development by Amgen for obesity with or without type 2 diabetes and comprises a bivalent antibody antagonist of the GIP receptor and two GLP-1 RA peptides, with the potential for dosing once monthly and possibly at longer intervals. MariTide is a bispecific molecule consisting of a conjugate of a fully human monoclonal antibody antagonist of GIP receptor and two GLP-1 RA peptides bound by amino acid linkers. Each GLP-1 RA peptide has sequence homology to endogenous human GLP-1, with several modifications. These consist of four amino acid substitutions of alanine at the eighth position with α-aminoisobutyric acid, of valine at position 16 with tyrosine, of glycine at position 22 with glutamate, and of arginine at position 36 with glycine. In addition, the GLP-1 RA molecules possess sequence homology to endogenous human GIP. The peptide sequence including the linker is H[Aib]EGTFTSDYSSYLEEQAAKEFIAWLVKGGG(GGGGS)3K(BrAc) (Véniant et al., *Nat Metab* 2024).

It may seem counterintuitive to combine a GIP antagonist with a GLP-1 RA, given the effectiveness of tirzepatide, which uses a GIP RA. However, preclinical obesity models have shown that the combination of an anti-GIPR antibody and GLP-1R agonist results in greater weight loss that is more pronounced than either mechanism alone. Moreover, evidence suggests that this effect is seen with bispecific molecules similar to MariTide, with GIPR-Ab conjugated to GLP-1 peptide, showing a synergistic weight loss effect and improvements in metabolic parameters in diet-induced obesity (DIO) mice (Lu et al., *Cell Rep Med* 2021). The same study by Lu also showed that mechanistically, the molecule binds to GIPR and GLP-1R simultaneously, triggering receptor internalization and amplifying endosomal cAMP signaling, supporting the notion that a GIPR-Ab/GLP-1 bispecific can elicit greater weight loss than either agent alone. Though the exact mechanisms for weight loss resulting from either agonism or antagonism of GIPR are not completely clear, it has been shown

that repeat treatment with GIP ligands results in desensitization of GIPR, from both lower GIPR expression and reduced cAMP production, which may help explain these seemingly contradictory results (Killion et al., *Nat. Commun.* 2020).

Phase I trial of MariTide initial results

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04478708).

Efficacy. Presented at the World Congress Insulin Resistance, Diabetes & Cardiovascular Disease 2022 meeting, single ascending and multiple ascending doses of MariTide demonstrated generally dose-dependent placebo-adjusted weight loss of up to 10% at around 17 weeks and 11% at around 21 weeks, respectively, in obesity. In the published results, the authors noted that small sample size was a limitation of the study. No *p*-values or significance determinations were provided for human drug vs. placebo weight loss.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 10% placebo-adjusted weight loss at 20 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. In the Phase I presentation at WCIRDC in 2022, it was noted that the majority of adverse events were GI-related, including nausea and vomiting, and resolved within 48 hours, but specifics were not given on the rate of these events by dose level at the time. In the results, the rates of nausea and vomiting appeared to be dose-related, with 100% of patients treated at the 420 mg multiple ascending dose experiencing nausea and 75% experiencing vomiting.

Phase I trial of MariTide updated results

In February 2024, data were published online in *Nature Metabolism*. While the results largely confirmed what was published at the World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease (WCIRDC) in 2022, there were several new aspects, particularly with respect to nausea and vomiting by dose level and discontinuations at the highest dose in the multiple-ascending-dose cohorts. It was noted in the publication that all TEAEs were mild in the multiple-ascending-dose cohorts and resolved within 72 hours.

Safety and tolerability. In the single-ascending-dose component, treatment with MariTide led to up to 83% nausea (dose-dependent), 0% diarrhea, and 83% vomiting (dose-dependent, occurring at the highest rate in the second-highest dose group), as well as elevated amylase, lipase, and liver enzymes. In addition, no serious treatment-emergent adverse events or adverse events leading to discontinuation were reported.

In the multiple-ascending-dose component, treatment with MariTide led to up to 100% nausea (dose-dependent), 25% diarrhea (dose-dependent), and 83% vomiting (dose-dependent, occurring at the highest rate in the second-highest dose group), as well as elevated amylase and lipase. No serious treatment-emergent adverse events were reported. Furthermore, the discontinuation rate reported in the paper was 0% across arms; however, 4 patients, or roughly half of those receiving the 420 mg dose withdrew from the study before the second dose after reporting mild gastrointestinal adverse events. A detailed summary of the Phase I trial single-ascending-dose results of MariTide in obesity is presented in exhibit 30, and multiple-ascending-dose results are presented in exhibit 31 (Véniant et al., *Nat Metab* 2024).

Exhibit 30
Amgen, Inc.
120-Day and 150-Day Single-Ascending-Dose Results of MariTide in Obesity Without Type 2 Diabetes

	Phase I Trial (NCT04478708)						
Sponsor	Amgen, Inc.						
Mechanism of Action	GIP receptor antagonist and GLP-1 receptor agonist						
Enrollment Criteria	BMI ≥ 30 kg/m² and ≤ 40 kg/m² HbA1c < 6.5%						
Baseline Characteristics	Age=54 years Female=83% Body weight=95 kg BMI=34 kg/m² HbA1c=5.6%	Age=48 years Female=17% Body weight=105 kg BMI=33 kg/m² HbA1c=5.5%	Age=48 years Female=43% Body weight=96 kg BMI=34 kg/m² HbA1c=5.6%	Age=46 years Female=33% Body weight=101 kg BMI=35 kg/m² HbA1c=5.4%	Age=50 years Female=17% Body weight=107 kg BMI=34 kg/m² HbA1c=5.5%	Age=46 years Female=17% Body weight=99 kg BMI=33 kg/m² HbA1c=5.6%	Age=46 years Female=33% Body weight=97 kg BMI=33 kg/m² HbA1c=5.4%
Study Portion	Single-Ascending-Dose						
Study Arms	21 mg MariTide once	70 mg MariTide once	140 mg MariTide once	280 mg MariTide once	560 mg MariTide once	840 mg MariTide once	placebo
Enrollment	6 patients	6 patients	7 patients	6 patients	6 patients	6 patients	12 patients
Analysis Time Point	Day 120	Day 150					
Change in Body Weight	1% placebo-adjusted: ~1%	-4% placebo-adjusted: -6%	-4% placebo-adjusted: -6%	-3% placebo-adjusted: -5%	-3% placebo-adjusted: -5%	-8% placebo-adjusted: -10%	Day 120: 2% Day 150: 2%
TEAEs Affecting ≥5% of Patients	Nausea 0% Vomiting 0% Constipation 0% Diarrhea 0% Dyspepsia 0% Abdominal discomfort 0% GERD 0% Amylase elevation 0% Lipase elevation 0% Liver enzyme elevation 0%	33% 17% 0% 0% 17% 0% 0% 0% 0% 0%	57% 57% 0% 0% 57% 29% 0% 14% 14% 0%	67% 83% 17% 0% 0% 0% 17% 0% 0% 17%	83% 83% 0% 0% 0% 0% 0% 0% 0% 0%	83% 67% 50% 0% 0% 0% 0% 0% 0% 0%	25% 0% 8% 17% 8% 0% 0% 0% 0% 0%
Serious Adverse Events	0%						
Discontinuation Rate	0%						

BMI=Body mass index. GERD=Gastroesophageal reflux disease. GIPR=Glucose-dependent insulinotropic polypeptide receptor. GLP-1R=Glucagon-like peptide 1 receptor. HbA1c=Glycated hemoglobin. TEAE=Treatment-emergent adverse event.

Sources: Véniant et al., Nat Metab 2024, Company reports, clinicaltrials.gov

Exhibit 31
Amgen, Inc.
210-Day Multiple-Ascending-Dose Results of MariTide in Obesity Without Type 2 Diabetes

	Phase I Trial (NCT04478708)			
Sponsor	Amgen, Inc.			
Mechanism of Action	GIP receptor antagonist and GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 30 kg/m² and ≤ 40 kg/m² HbA1c < 6.5%			
Baseline Characteristics	Age=40 years Female=17% Body weight=102 kg BMI=34 kg/m² HbA1c=5.6%	Age=45 years Female=33% Body weight=99 kg BMI=33 kg/m² HbA1c=5.6%	Age=52 years Female=88% Body weight=91 kg BMI=33 kg/m² HbA1c=5.6%	Age=46 years Female=67% Body weight=99 kg BMI=34 kg/m² HbA1c=5.5%
Study Arms	140 mg MariTide on days 1, 29, and 57	280 mg MariTide on days 1, 29, and 57	420 mg MariTide on days 1, 29, and 57	placebo
Enrollment	6 patients	6 patients	8 patients	6 patients
Analysis Time Point	Day 210			
Change in Body Weight	-3% placebo-adjusted: -3%	-10% placebo-adjusted: -9%	-11% placebo-adjusted: -11%	~-1%
TEAEs Affecting ≥5% of Patients	Nausea 83% Vomiting 67% Diarrhea 17% Dyspepsia 17% Abdominal distension 17% Upper abdominal pain 0% Constipation 33% Amylase elevation 17% Lipase elevation 17%	67% 83% 0% 0% 0% 0% 17% 0% 0%	100% 75% 25% 13% 13% 13% 0% 0% 0%	17% 0% 0% 0% 0% 0% 0% 0% 0%
Serious Adverse Events	0%			
Discontinuation Rate	0%[1]			

BMI=Body mass index. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1R=Glucagon-like peptide 1 receptor. HbA1c=Glycated hemoglobin. TEAE=Treatment-emergent adverse event.

[1]At the highest MAD dose of 420 mg, four participants withdrew from the study before receiving the second dose after reporting mild GI-related adverse events
Sources: Véniant et al., *Nat Metab* 2024, Company reports, clinicaltrials.gov.

Phase II trial of MariTide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05669599).

Efficacy. The asset, given monthly or every other month in overweight or obesity, demonstrated up to 17% placebo-adjusted weight loss in patients without type 2 diabetes (highest in 280 mg dose group) and up to 16% in patients with type 2 diabetes (dose-dependent) at 1 year, based on the efficacy estimand. In addition, investigators noted MariTide-associated improvements in cardiometabolic parameters including systolic blood pressure, low-density lipoprotein cholesterol, triglycerides, and high-sensitivity C-reactive protein in patients without type 2 diabetes. Furthermore, similar improvements, adding improvements in HbA1c and glucose levels, were observed in patients with the type 2 diabetes receiving MariTide.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. The rates of nausea and vomiting were not provided for all arms of the trial, or any arms of the type 2 diabetes trial. In the two dose-escalation arms with an initial 70 mg starting dose, 70% of patients experienced nausea and 40% experienced vomiting, which were

predominantly mild to moderate. Although numbers were not disclosed, it appears that 50% of patients experienced mild nausea and 20% experienced moderate nausea, based on the incidence graph provided by the company. Similarly, although not disclosed, an estimated 30% experienced mild vomiting, 7% experienced moderate vomiting, and 2% to 3% experienced severe vomiting. Moreover, discontinuation rates due to GI-related events in the two dose-escalation arms were less than 8%; rates across other arms were not disclosed.

Next steps. The completion date for the first part of the study was October 2024. The second part is ongoing, with an estimated study completion date of January 2026. A detailed summary of Phase II trial results of MariTide compared with Phase III SURMOUNT-1 trial results of Zepbound in overweight or obesity without type 2 diabetes is presented in exhibit 32. Phase II trial results of MariTide compared with Phase III SURMOUNT-2 trial results of Mounjaro in overweight or obesity with type 2 diabetes are presented in exhibit 33.

Amgen has further stated that it intends to launch a broad Phase III study, which it refers to as MARITIME (Amgen November 2024 press release).

Exhibit 32
Amgen, Inc.
Results of Zepbound and Results of MariTide in Obesity and Overweight Without Type 2 Diabetes

	Phase III SURMOUNT-1 Trial (NCT04184622)				Phase II Part 1 (NCT05669599)						
Sponsor	Eli Lilly and Company				Amgen, Inc.						
Mechanism of Action	GLP-1 receptor and GIP receptor agonist				GIP antagonist and GLP-1 receptor agonist						
Enrollment Criteria	BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%				BMI ≥30 kg/m² or ≥27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%						
Study Arms	5 mg Zepbound once weekly	10 mg Zepbound once weekly	15 mg Zepbound once weekly	placebo	140 mg MariTide once monthly	280 mg MariTide once monthly	420 mg MariTide once monthly	420 mg MariTide once every other month	420 mg MariTide once every 2 weeks then once monthly	420 mg MariTide once monthly	placebo
Baseline Characteristics	Median age=47 years Female=68% Body weight=103 kg BMI=37 kg/m² Prediabetes=39%	Median age=45 years Female=67% Body weight=106 kg BMI=38 kg/m² Prediabetes=41%	Median age=45 years Female=68% Body weight=106 kg BMI=38 kg/m² Prediabetes=40%	Median age=44 years Female=68% Body weight=105 kg BMI=38 kg/m² Prediabetes=42%	Female=63% Body weight=107 kg BMI=38 kg/m²						
Enrollment	630 patients	636 patients	630 patients	643 patients	465 patients						
Titration Schedule	2.5 mg for 4 weeks; 5.0 mg for 68 weeks	2.5 mg for 4 weeks; 5.0 mg for 4 weeks; 7.5 mg for 4 weeks; 10 mg for 60 weeks	2.5 mg for 4 weeks; 5.0 mg for 4 weeks; 7.5 mg for 4 weeks; 10 mg for 4 weeks; 12.5 mg for 4 weeks; 15 mg for 52 weeks		140 mg for 52 weeks	280 mg for 52 weeks	420 mg for 52 weeks	420 mg for 52 weeks	70 mg once every 2 weeks for 4 weeks; 420 mg once monthly for 48 weeks	70 mg once; 140 mg once; 280 mg once; 420 mg for 40 weeks	
Analysis Time Point	Week 72				Week 52						
Change in Body Weight	-15% placebo-adjusted: -12%	-20% placebo-adjusted: -16%	-21% placebo-adjusted: -18%	-3%	-16% placebo-adjusted: -14%	-20% placebo-adjusted: -18%	**-19%** placebo-adjusted: -16%				-3%
Patients Achieving ≥5% Weight Loss	85%	89%	91%	35%	98%						
Rates of Nausea and Vomiting	Nausea 25% Vomiting 8%	33% 11%	31% 12%	10% 2%					70% 40%		
TEAEs Leading to Discontinuation	4%	7%	6%	3%					Due to any AE: 11% Due to GI-related AE: <8%		

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.
For the SURMOUNT-1 trial, Zepbound was administered utilizing a 20-weeks-long dose-escalation titration period beginning at 2.5 mg once weekly and increasing by 2.5 mg every 4 weeks to attain a maintenance dose of up to 15 mg once weekly by week 20.
[1]At the highest MAD dose of 420 mg, four participants withdrew from the study before receiving the second dose after reporting mild GI-related adverse events
BMI=Body mass index. HbA1c=Glycated hemoglobin.TEAE=Treatment-emergent adverse event.
Source: Company Reports, Jastreboff et al., NEJM 2022

Exhibit 33
Amgen, Inc.
Results of Mounjaro and Results of MariTide in Overweight or Obesity With Type 2 Diabetes

	Phase III SURMOUNT-2 Trial (NCT04657003)			Phase II Part 1 (NCT05669599)			
Sponsor	Eli Lilly and Company			Amgen, Inc.			
Mechanism of Action	GLP-1 receptor and GIP receptor agonist			GIP antagonist and GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 27 kg/m² HbA1c ≥ 7% and ≤ 10%			BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c ≥ 7% and ≤ 10%			
Study Arms	10 mg Mounjaro once weekly	15 mg Mounjaro once weekly	placebo	140 mg MariTide once monthly	280 mg MariTide once monthly	420 mg MariTide once monthly	placebo
Baseline Characteristics	Age=54 years Female=51% Body weight=101 kg BMI=36 kg/m² HbA1c=8.0%			Female=42% Body weight=104 kg BMI=36 kg/m² HbA1c=7.9%			
Enrollment	312 patients	311 patients	315 patients	127 patients			
Titration Schedule	2.5 mg for 4 weeks; 5.0 mg for 4 weeks; 7.5 mg for 4 weeks; 10 mg for 60 weeks	2.5 mg for 4 weeks; 5.0 mg for 4 weeks; 7.5 mg for 4 weeks; 10 mg for 4 weeks; 12.5 mg for 4 weeks; 15 mg for 52 weeks		140 mg for 52 weeks	280 mg for 52 weeks	420 mg for 52 weeks	
Analysis Time Point	Week 72			Week 52			
Change in Body Weight	-13% placebo-adjusted: -10%	-16% placebo-adjusted: -13%	-3%	-12% placebo-adjusted: -10%	-12% placebo-adjusted: -10%	-17% placebo-adjusted: -15%	-2%
Patients Achieving ≥5% Weight Loss	82%	86%	31%	99%			
Rates of Diarrhea, Nausea, Vomiting, and Constipation	Diarrhea 20% Nausea 20% Vomiting 11% Constipation 8%	22% 22% 13% 9%	9% 6% 3% 4%				
Serious Adverse Events	6%	9%	7%				
TEAEs Leading to Treatment Discontinuation	4% Nausea-related: <1% Vomiting-related: 1%	7% Nausea-related: 1% Vomiting-related: 0	4% Nausea-related: 0 Vomiting-related: 0				

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.
BMI=Body mass index. HbA1c=Glycated hemoglobin. TEAE=Treatment-emergent adverse event.
Based on efficacy estimand data.
Source: Garvey et al., Lancet 2023; Company documents

GLP-1 and GCG Receptor Agonists

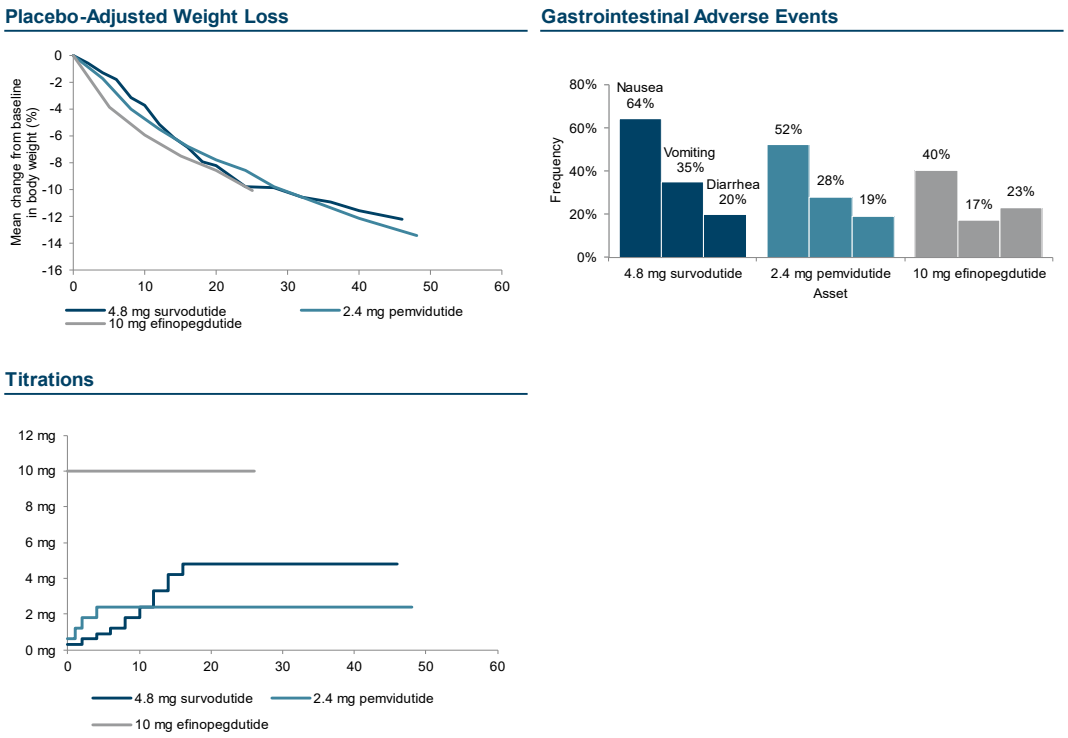
Although GLP-1 and glucagon share a precursor molecule (preproglucagon), their sequences and receptors are different. The two peptides are produced by different cell types in different organs (glucagon in the pancreas and GLP-1 in the intestine and brain), and the precursor is processed in a tissue-specific manner. Each of their receptors belong to the same family of G-protein coupled receptors, but the receptors themselves diverge in terms of the amino acid sequences of their extracellular domains that determine which ligand can bind (Runge, et al. *Brit. J. Pharmacol.* 2003).

Functionally, glucagon increases blood sugar by signaling the liver to release glucose that is stored as glycogen (chains of glucose molecules), while GLP-1 stimulates insulin release and inhibits glucagon secretion, thereby lowering blood sugar. Thus, in terms of maintaining blood sugar homeostasis, glucagon and GLP-1 work counter to each other. Accordingly, a strategy that has been investigated to treat diabetes, which causes hyperglycemia, is to promote GLP-1 signaling and antagonize glucagon signaling.

Given these countervailing effects of GLP-1 and glucagon, it may seem curious that treatment with dual GLP-1/glucagon RAs causes greater weight loss than a GLP-1 receptor single agonist. This anti-obesity effect is accomplished through mechanisms other than glucose control, namely appetite suppression, thermogenesis, and lipolysis (Muller, et al. *Nat. Rev. Drug Discovery* 2022). For example, both GLP-1 and glucagon promote fatty acid oxidation (FAO), but in different ways. GLP-1's promotion of FAO in the liver is mediated in part through transcriptional effects on crucial enzymes that control β-oxidation, whereas glucagon stimulates FAO under conditions where more free fatty acids are delivered to the liver, such as extended fasting (Sandoval & D'Alessio, *Physiol. Rev.* 2015). Thus, the effect of combining the two can be additive.

GLP-1 and glucagon RAs are encouraging in obesity, in our view, given the combined mechanisms promoting insulin secretion and potentially energy expenditure and suppressing glucagon secretion and appetite. Regarding the greatest weight loss observed for the class, pemvidutide demonstrated up to 13% placebo-adjusted weight loss at 48 weeks in Phase II results in overweight and obesity. In addition, the asset class may hold promise in treating patients living with obesity and the chronic liver disease metabolic dysfunction-associated steatohepatitis (MASH). A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of GLP-1 and glucagon RAs including survodutide, pemvidutide, and efinopegdutide is presented in exhibit 34.

Exhibit 34
Combined Weight Loss, Adverse Events, and Titration Curves of GLP-1 and GCG Receptor Agonists



GCG=Glucagon. GLP-1=Glucagon-like peptide 1.
Sources: Company documents

GCG Receptor Agonist

Hanmi's Efpegerglucagon

Efpegerglucagon, also known as HM15136, is a long-acting glucagon analog chemically conjugated with the constant region of human immunoglobulin via a non-peptidyl flexible linker. Efpegerglucagon received orphan drug designation from the FDA, the European Medicines Agency, and the Ministry of Food and Drug Safety in South Korea for the treatment of congenital hyperinsulinism and received rare pediatric disease designation from FDA. Efpegerglucagon has also been designated as an orphan drug by the EMA for the treatment of insulin autoimmune syndrome. Hanmi notes that glucagon receptor agonism is associated with increased energy expenditure and improvement of various cardiometabolic risk factors and that in nonclinical studies, improved lipid profile, kidney function, and blood pressure were observed along with weight loss (Hanmi website).

To enhance the stability and effectiveness of the drug, scientists at Hanmi attached a linker between their glucagon analog and the Fc fragment of human immunoglobulin G4. These two constituents are linked via a 10-kDa, bifunctional maleimide-polyethylene glycol-aldehyde (MALPEG-ALD) linker. The drug controls glucose homeostasis through the same mechanism as glucagon (Heo, et al. *Sci. Rep.* 2022).

The company conducted a Phase I study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of HM15136 in obese or overweight subjects with comorbidities, but results that were submitted to clinicaltrials.gov have been returned after quality control

review (NCT04167553), so the results are not public. A Phase II trial for congenital hyperinsulinism is ongoing (NCT04732416), and the company continues to describe the drug on its website as a potential obesity treatment.

Unimolecular GLP-1/GCGR Receptor Agonists

Altimmune's Pemvidutide
The asset is a dual GLP-1 and glucagon RA with a once-weekly dosing schedule that completed Phase I and Phase II clinical development. The asset was examined in a series of Phase I clinical trials in metabolic dysfunction-associated steatohepatitis (MASH), non-alcoholic fatty liver disease (NCT05006885; NCT05292911), and type 2 diabetes (NCT05134662), as well as in the Phase II MOMENTUM clinical trial in patients with overweight or obesity. Formerly known as ALT-801, it is now undergoing testing in the Phase IIb IMPACT trial in MASH (NCT05989711).

Pemvidutide is a peptide measuring 29 amino acids long with sequence homology for endogenous human GLP-1 and glucagon, with several modifications. Compared with GLP-1, pemvidutide has 11 amino acid substitutions, including the substitution of alanine at the second position with α-aminoisobutyric acid, which confers greater resistance to protease degradation (Bailey, et al. *Peptides* 2023). Other substitutions are glutamate at the third position with glutamine, valine at position 10 with tyrosine, serine at position 12 with lysine, glutamate at position 15 with aspartate, glycine at position 16 with glutamate, glutamine at position 17 with lysine, alanine at position 24 with glutamine, valine at position 27 with leucine, lysine at position 28 with glutamine, and the glycine at position 29 with threonine. Between the glutamate residue at position 16 and the lysine residue at position 20, a side chain lactam linkage is intended to stabilize the peptide's helical structure and to increase the drug's half-life (Bailey, et al. *Peptides* 2023).

In addition, the peptide is modified at the lysine at position 17 with a "EuPort domain," a moiety that, according to company documents, includes a hydrophobic alkyl chain group and a hydrophilic group and is intended to increase the half-life of pemvidutide in circulation through binding to serum albumin (Harrison, et al. *J. Hepat.* 2024). According to company documents, the amino acids at positions 3 through 13 contribute to glucagon specificity, and the amino acids at positions 22 through 29 contribute to GLP-1 specificity, by visual estimation of the figure. The C-terminal carboxylic acid (COOH) is replaced by carboxyamide ($CONH_2$) to confer resistance to degradation by carboxypeptidases (Bailey, et al. *Peptides* 2023).

Phase II MOMENTUM trial of pemvidutide
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05295875).

Efficacy. In top-line results presented in November 2023, once-weekly pemvidutide demonstrated dose-dependent placebo-adjusted weight loss up to 13% in overweight or obesity at 48 weeks. Patients also experienced dose-dependent reductions in serum lipids, including triglycerides, total cholesterol, "bad" low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and "good" high-density lipoprotein cholesterol (HDL).

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

In additional Phase II MOMENTUM body composition results presented at the American Diabetes Association's 84th Scientific Sessions in 2024, pemvidutide induced weight loss of around 16% overall; roughly 22% of the weight lost in the study was lean body mass, and the remaining 78% was fat content. According to Altimmune CEO Scott Harris, that is a superior figure compared with other assets with similar data available.

Safety and tolerability. Treatment with pemvidutide led to up to 60% nausea (dose-dependent), 19% diarrhea (dose-dependent), and 28% vomiting (dose-dependent, occurring at the highest rate at the second-highest dose), as well as cardiac adverse events. Serious treatment-related vomiting occurred in around 1% of patients at the highest dose level. In addition, the discontinuation rate due to treatment-related adverse events increased in a dose-dependent manner up to a mid-teens percentage, compared with the low single digits in the placebo arm.

Next steps. The Phase III program for pemvidutide is expected to enroll approximately 5,000 subjects across four trials. The safety and efficacy of pemvidutide doses of 1.2 mg, 1.8 mg, and 2.4 mg will be evaluated with the intention of obtaining approval for all three doses. (Altimmune press release Nov. 2024). The company plans to focus on certain co-morbidities associated with obesity, specifically those relating to lipid-associated diseases that can be ameliorated by the effects that adding a glucagon RA to a GLP-1 RA will have on lipids in the body. A detailed summary of the Phase II MOMENTUM trial results of pemvidutide in overweight or obesity is presented in exhibit 35.

Exhibit 35
Altimmune, Inc.
48-Week Results of Pemvidutide in Overweight or Obesity Without Type 2 Diabetes

Phase II MOMENTUM Trial (NCT05295875)

Sponsor	Altimmune, Inc.			
Mechanism of Action	Dual glucagon and GLP-1 receptor agonist			
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%			
Baseline Patient Characteristics	Age=50 years Male=23% Body weight=105 kg BMI=37 kg/m²	Age=50 years Male=23% Body weight=104 kg BMI=37 kg/m²	Age=49 years Male=24% Body weight=104 kg BMI=37 kg/m²	Age=50 years Male=26% Body weight=106 kg BMI=38 kg/m²
Study Arms	1.2 mg pemvidutide once weekly	1.8 mg pemvidutide once weekly	2.4 mg pemvidutide once weekly	placebo
Enrollment	98 patients	99 patients	97 patients	97 patients
Titration Schedule	1.2 mg for 48 weeks	1.8 mg for 48 weeks	0.6 mg for 1 week; 1.2 mg for 1 week; 1.8 mg for 2 weeks; 2.4 mg for 44 weeks	
Change in Body Weight at Week 48	**-10%** **placebo-adjusted: -8%** ***p* <0.001**	**-11%** **placebo-adjusted: -9%** ***p* <0.001**	**-16%** **placebo-adjusted: -13%** ***p* <0.001**	**-2%**
Patients Reaching ≥5%, ≥10%, ≥15%, and ≥20% Weight Loss at Week 48	69% *p* <0.0001 43% *p* <0.0001 21% *p* <0.005 10% *p* =NS	76% *p* <0.0001 49% *p* <0.0001 29% *p* <0.001 10% *p* =NS	84% *p* <0.0001 71% *p* <0.0001 52% *p* <0.0001 32% *p* <0.0001	18% 4% 2% 2%
Gastrointestinal Adverse Events	Nausea 26% Vomiting 6% Constipation 17% Diarrhea 8%	60% 27% 13% 10%	52% 28% 23% 19%	11% 3% 8% 5%
Cardiac AEs, Including Arrhythmias	3%	4%	3%	4%
Serious TRAEs	0 events	0 events	Vomiting: 1% (1 patient)	0 events
TRAEs Leading to Discontinuation	4%	16%	16%	2%

*Patients had either a history of cardiovascular disease, hypertension, dyslipidemia, prediabetes, and/or obstructive sleep apnea.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, clinicaltrials.gov

Zealand and Boehringer Ingelheim's Survodutide

The asset, which was licensed by Zealand to Boehringer Ingelheim, was formerly known as BI 456906. Boehringer is solely responsible for development and commercialization globally, while Zealand retains a co-promotion right in the Nordic countries. The asset, a dual GLP-1 and glucagon RA, is undergoing Phase I testing in six trials in patients with overweight or obesity with and without kidney impairment and in patients with overweight or obesity regardless of kidney impairment. It is also undergoing Phase III testing in five trials in patients with overweight or obesity; overweight or obesity with established cardiovascular disease or risk factors for cardiovascular disease; and overweight or obesity with type 2 diabetes.

Survodutide is a peptide measuring 29 amino acids long with sequence homology to endogenous human GLP-1 and glucagon, with several modifications. Compared with GLP-1, these consist of 12 amino acid substitutions of alanine at the second position with 1-aminocyclobutane-1-carboxylic acid (to increase resistance to proteolytic degradation), glutamate at the third position with glutamine, valine at position 10 with tyrosine, serine at position 12 with lysine, glutamate at position 15 with aspartate, glycine at position 16 with glutamate, glutamine at position 17 with arginine, glutamate at position 21 with aspartate, alanine at position 24 with lysine, valine at position 27 with glutamate, lysine at position 28 with serine, and glycine at position 29 with alanine. Furthermore, investigators incorporated a glycine-serine-based linker at position 24, which carries an 18-carbon fatty di-acid intended to increase terminal circulating half-life. The peptide is also amidated at the c-terminal end to further increase proteolytic stability (Klein, et al. *Diab. Res. & Clin. Pract.* 2024; Zimmerman, et al. *Mol. Metab.* 2022).

Phase II trial of survodutide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04667377).

Efficacy. Based on the planned treatment estimand (based on the maintenance dose assigned to patients at randomization), once-weekly survodutide demonstrated dose-dependent placebo-adjusted weight loss up to 12% in overweight or obesity at week 46. Patients receiving survodutide also experienced dose-dependent improvements in systolic (at the top 3 doses) and diastolic blood pressure (at the top dose level).

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with survodutide led to up to 65% nausea (roughly dose-dependent), 28% diarrhea (dose-independent), and 35% vomiting (dose-dependent). Serious treatment-related adverse events occurred at around 3% in the 3.6 mg dosing arm. In addition, the discontinuation rate exhibited a dose-dependent relationship, occurring up to the high 20s (roughly seven times the placebo rate). A detailed summary of the Phase II trial results of survodutide in overweight or obesity is presented in exhibit 36 (le Roux et al., *Lancet Diabetes Endocrinol* 2024).

Exhibit 36
Zealand Pharma A/S and Boehringer Ingelheim
46-Week Results of Survodutide in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT04667377)

Sponsors	Zealand Pharma A/S and Boehringer Ingelheim				
Mechanism of Action	Dual glucagon and GLP-1 receptor agonist				
Enrollment Criteria	BMI ≥ 27.0 kg/m² HbA1c < 6.5%				
Baseline Patient Characteristics	Age=49 years Male=34% Body weight=107 kg BMI=38 kg/m²	Age=49 years Male=31% Body weight=107 kg BMI=38 kg/m²	Age=50 years Male=33% Body weight=105 kg BMI=37 kg/m²	Age=48 years Male=30% Body weight=106 kg BMI=38 kg/m²	Age=50 years Male=31% Body weight=104 kg BMI=36 kg/m²
Study Arms	0.6 mg survodutide once weekly	2.4 mg survodutide once weekly	3.6 mg survodutide once weekly	4.8 mg survodutide once weekly	placebo
Enrollment	77 patients	78 patients	76 patients	76 patients	77 patients
Titration Schedule	0.3 mg for 2 weeks; 0.6 mg for 44 weeks	0.3 mg for 2 weeks; 0.6 mg for 2 weeks; 0.9 mg for 2 weeks; 1.2 mg for 4 weeks; 1.8 mg for 4 weeks; 2.4 mg for 32 weeks	0.3 mg for 2 weeks; 0.6 mg for 2 weeks; 0.9 mg for 2 weeks; 1.2 mg for 4 weeks; 1.8 mg for 2 weeks; 2.4 mg for 2 weeks; 3.0 mg for 2 weeks; 3.6 mg for 30 weeks	0.3 mg for 2 weeks; 0.6 mg for 2 weeks; 0.9 mg for 2 weeks; 1.2 mg for 2 weeks; 1.8 mg for 2 weeks; 2.4 mg for 2 weeks; 3.3 mg for 2 weeks; 4.2 mg for 2 weeks; 4.8 mg for 30 weeks	
Change in Body Weight at Week 46	**-6%** **placebo-adjusted: -3%; *p* =0.026**	**-13%** **placebo-adjusted: -10%; *p* <0.0001**	**-13%** **placebo-adjusted: -10%; *p* <0.0001**	**-15%** **placebo-adjusted: -12%; *p* <0.0001**	**-3%**
TRAE Frequency	61%	85%	81%	81%	38%
TEAEs Affecting ≥25% of Patients	Nausea 34% I&I 44% Vomiting 9% Constipation 12% Diarrhea 18%	65% 37% 30% 22% 28%	62% 46% 34% 25% 23%	64% 43% 35% 26% 20%	20% 43% 5% 5% 10%
Serious TRAE Frequency	0%	0%	3%	0%	0%
TEAEs Leading to Discontinuation	20%	26%	25%	29%	4%

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. I&I=Infections and infestations. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, le Roux et al., Lancet Diabetes Endocrinol 2024, clinicaltrials.gov

Phase III SYNCHRONIZE-CVOT trial of survodutide

The study will evaluate the cardiovascular safety of the asset in patients with overweight, established cardiovascular disease, and/or risk factors for cardiovascular disease, and patients with obesity, established cardiovascular disease or chronic kidney disease, and/or risk factors for cardiovascular disease. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06077864). In October 2024, the FDA granted survodutide breakthrough therapy designation for the treatment of adults with non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) and moderate or advanced fibrosis. Furthermore, Boehringer launched two Phase III studies of survodutide, LIVERAGE in adults with MASH and moderate or advanced fibrosis, and LIVERAGE-Cirrhosis in those with MASH and cirrhosis.

Merck's Efinopegdutide

Efinopegdutide, also known as MK-6204 and HM12525A, is a peptide-based GLP-1/glucagon receptor co-agonist in clinical development for fatty liver diseases and obesity. The drug is in a Phase I trial that has enrolled 48 obese but otherwise healthy people to study the drug's safety and tolerability (NCT06701305). Efinopegdutide is a synthetic peptide of oxyntomodulin (a dual agonist) conjugated via a polyethylene glycol linker to the constant region of human IgG4 (Romero-Gómez, et al. *J. Hepat.* 2023). Rights to efinopegdutide were acquired by Johnson & Johnson from Hanmi Pharmaceutical, and Johnson & Johnson conducted trials under the designation JNJ-64565111. Johnson & Johnson decided not to continue the program and the drug was temporarily discarded by big pharma in 2019. Rights to develop, manufacture, and commercialize efinopegdutide were then acquired by Merck from Hanmi in 2020.

Phase II trial of efinopegdutide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03486392).

Efficacy. Once-weekly efinopegdutide demonstrated dose-dependent placebo-adjusted weight loss up to 10%, compared with 6% for Saxenda, in severe obesity at week 26. Investigators also reported efinopegdutide dose-dependent increases (worsening) in HbA1c (up to around 0.1%), and reductions (improvements) in total cholesterol, low-density lipoprotein cholesterol, triglycerides, and (worsening) high-density lipoprotein cholesterol.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 12% placebo-adjusted weight loss at 24 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with efinopegdutide led to up to 68% nausea (in the second-highest dose group), 20% diarrhea (dose-dependent), and 55% vomiting (dose-dependent). Serious treatment-related adverse events were slightly elevated in the 10 mg efinopegdutide arm, at 3%, compared with the placebo arm. In addition, the discontinuation rate increased in a dose-dependent fashion up to the low 30s, compared with a midteens percentage for Saxenda and 0% in the placebo arm. Furthermore, the study reported one death related to myocardial infarction in the Saxenda arm (Alba et al., *Clin Obes* 2021).

Next steps. In the second half of 2024, Merck commenced a two-year Phase II study of efinopegdutide to evaluate its efficacy and safety in adults with compensated cirrhosis secondary to metabolic dysfunction-associated steatohepatitis (NCT06465186). A detailed summary of the Phase II trial results of efinopegdutide in obesity is presented in exhibit 37.

Exhibit 37
Merck & Co., Inc.
26-Week Results of Efinopegdutide Compared With Saxenda in Obesity Without Type 2 Diabetes

Phase II Trial (NCT03486392)					
Sponsor	Merck & Co., Inc.				
Mechanism of Action	Dual GLP-1 and glucagon receptor agonist				
Enrollment Criteria	BMI ≥ 35 kg/m² and ≤ 50 kg/m² HbA1c < 6.5%				
Baseline Patient Characteristics	Age=47 years Male=20% Body weight=112 kg BMI=40 kg/m² HbA1c=5.5%	Age=46 years Male=27% Body weight=112 kg BMI=40 kg/m² HbA1c=5.5%	Age=46 years Male=27% Body weight=114 kg BMI=41 kg/m² HbA1c=5.5%	Age=46 years Male=25% Body weight=115 kg BMI=41 kg/m² HbA1c=5.4%	Age=47 years Male=20% Body weight=113 kg BMI=40 kg/m² HbA1c=5.5%
Study Arms	5 mg efinopegdutide once weekly	7.4 mg efinopegdutide once weekly	10 mg efinopegdutide once weekly	3 mg Saxenda once daily	placebo
Enrollment	59 patients	118 patients	118 patients	119 patients	60 patients
Titration Schedule	5 mg for 26 weeks	7.4 mg for 26 weeks	10 mg for 26 weeks	0.6 mg for 1 week; 1.2 mg for 1 week; 1.8 mg for 1 week; 2.4 mg for 1 week; 3.0 mg for 22 weeks	
Change in Body Weight at Week 26	**-9%** **placebo-adjusted: -7%; *p*<0.001**	**-10%** **placebo-adjusted: -8%; *p*<0.001**	**-12%** **placebo-adjusted: -10%; *p*<0.001**	**-8%** **placebo-adjusted: -6%; *p*<0.001**	**-2%**
Patients Reaching ≥5% and ≥10% Weight Loss	58% (*p*<0.001) 39% (*p*<0.001)	80% (*p*<0.001) 37% (*p*<0.001)	53% (*p*<0.001) 40% (*p*<0.001)	51% (*p*<0.001) 25% (*p*<0.001)	13% 3%
TRAE Frequency	73%	86%	84%	61%	20%
Gastrointestinal TEAEs Affecting ≥10% of Patients	Nausea 51% Vomiting 20% Diarrhea 14% Constipation 12% Eructation 7% Dyspepsia 9% GERD 9%	68% 40% 20% 17% 12% 15% 11%	67% 55% 20% 18% 14% 11% 10%	40% 17% 23% 17% 4% 8% 8%	7% 0% 5% 5% 0% 3% 2%
Serious TRAE Frequency	0%	0%	3%	2%	0%
TRAEs Leading to Discontinuation	19%	24%	32%	17%	0%
Treatment-Emergent Deaths	0 events	0 events	0 events	1 event (1%) related to myocardial infarction	0 events

BMI=Body mass index. GERD=Gastroesophageal reflux disease. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. TRAEs=Treatment-related adverse events.
Sources: Company reports, Alba et al., Clin Obes 2021, clinicaltrials.gov.

Eli Lilly and Innovent's Mazdutide

The asset, also known as LY3305677, IBI362, or OXM3 (PubChem listing), is a once-weekly peptide-based GLP-1/GCG RA manufactured by China-based Innovent Biologics under a licensing agreement with Eli Lilly. Clinical trials for mazdutide have been conducted in both the United States and China. It is currently in Phase III trials for obesity. Innovent describes the drug as a mammalian oxyntomodulin analog (Innovent August 2024 press release).

Phase I trials for safety and efficacy were conducted for once-weekly doses up to 10 mg (Ji, et al. *eClinical Medicine* 2022).

Phase II trial of mazdutide
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04904913).

Efficacy. Once-weekly mazdutide demonstrated dose-dependent placebo-adjusted weight loss up to 12% in overweight or obesity at 24 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 12% placebo-adjusted weight loss at 24 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with mazdutide led to up to 41% nausea, 31% diarrhea, and 28% vomiting, all of which exhibited dose-dependent relationships. Serious treatment-emergent adverse events increased in a dose-dependent manner up to 6.6%, compared with 0% in the placebo arm. In addition, the discontinuation rate was highest in the 4.5 mg mazdutide arm, occurring in the low single digits, with no discontinuations in other arms (Ji, et al. *Nat. Comm.* 2023).

Next steps. Five Phase III studies of mazdutide in Chinese adults with overweight or obesity (GLORY-1 [NCT05607680] and GLORY-2 [NCT06164873]) or type 2 diabetes (DREAMS-1 [NCT05628311], DREAMS-2 [NCT05606913], and DREAMS-3 [NCT06184568]) are either completed or underway. On the obesity side, Innovent announced key results from the GLORY-1 trial in June 2024. A total of 610 participants were randomized to receive mazdutide 4 mg, 6 mg, or placebo in the 48-week double-blind treatment period. At week 48, average body weight percentage changes were -11% for the 4 mg arm, -14% for the 6 mg arm, and 0.3 for the placebo arm. Adverse events were characterized as mostly mild or moderate and the incidence of serious adverse events as low and comparable to placebo (Innovent June 2024 press release).

Innovent's new drug application for mazdutide for chronic weight management was accepted by the Center for Drug Evaluation (CDE) of China's National Medical Products Administration in February 2024. Its new drug application for treatment of type 2 diabetes was accepted in August 2024.

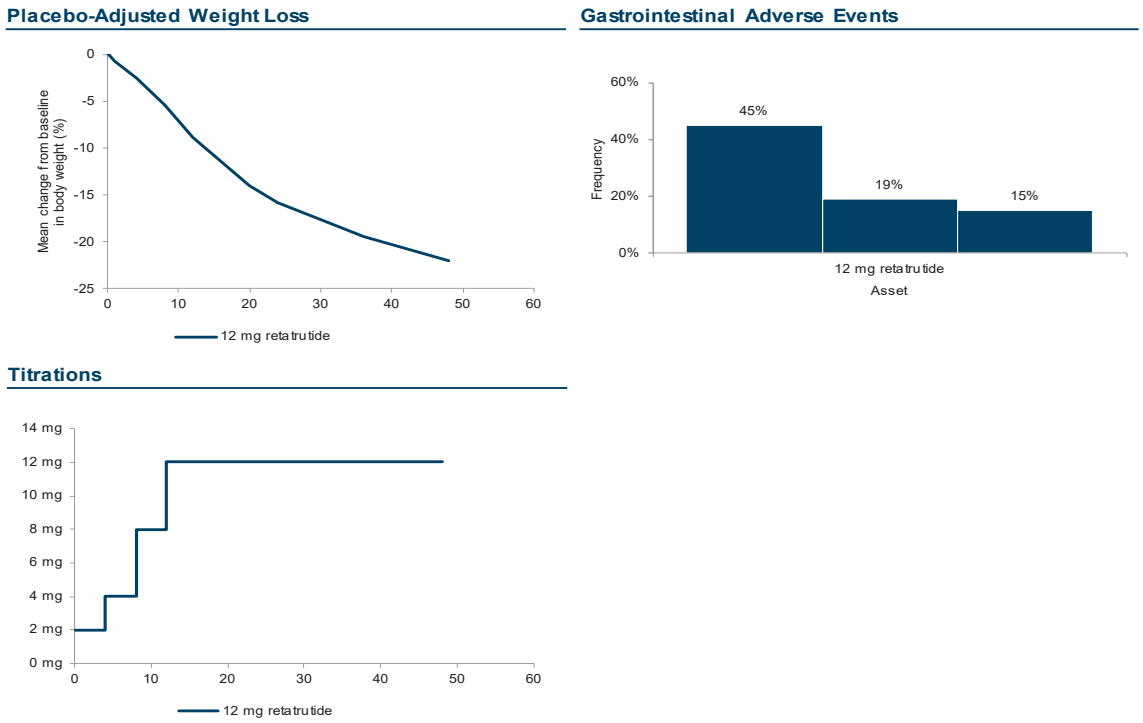
AstraZeneca's AZD9550
The company commenced Phase I testing for its dual GLP-1/GCG RA in 2023 and is now in a Phase I/II trial. The drug is being investigated for treatment of metabolic dysfunction-associated steatohepatitis, or MASH (AstraZeneca website), which is the more current term for non-alcoholic steatohepatitis, or NASH. The company has completed a Phase I study to assess the safety, tolerability, and pharmacokinetics of AZD9550 following single-ascending-dose administration to healthy participants (NCT05848440).

Phase I/II CONTEMPO trial of AZD9550
The company is conducting the study to learn how safe AZD9550 is in overweight or obesity with or without type 2 diabetes. Study completion is anticipated in April (AstraZeneca website). For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06151964).

Triple GLP-1, GIP, and GCG Receptor Agonists

We view GLP-1, GIP, and glucagon RAs as promising given the complementary mechanisms acting to promote insulin secretion and potentially energy expenditure and suppress glucagon secretion and appetite in overweight and obesity. Regarding the greatest weight loss observed for the class, retatrutide demonstrated up to 22% placebo-adjusted weight loss at 48 weeks in Phase II results in overweight and obesity. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top dose of the GLP-1, GIP, and GCG RA retatrutide is presented in exhibit 38.

Exhibit 38
Combined Weight Loss, Adverse Events, and Titration Curves of GLP-1, GIP, and GCG Receptor Agonist Retatrutide



GCG=Glucagon. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1.
Sources: Company documents

Eli Lilly's Retatrutide

The asset is in development for obesity, osteoarthritis, obstructive sleep apnea, obesity-linked adverse cardiovascular and renal outcomes, and type 2 diabetes, is a peptide-based triple agonist of the GIP, GLP-1, and glucagon receptors. Retatrutide is a 39-amino-acid peptide that was engineered from a GIP peptide backbone, with several changes. These include three amino acid substitutions at positions 2, 20, and 13. The non-canonical amino acid α-aminoisobutyric acid (Aib) at position 2 contributes protection against DPP4 cleavage; the Aib residue at position 20 provides optimized GIP activity, developability, and pharmacokinetic profile; and the α-methyl-L-leucine (αMeL) residue at position 13 aids in glucagon and GIP activity. The peptide backbone is conjugated to a 20-carbon fatty di-acid chain through a linker at the lysine residue at position 17, which enables binding to albumin to elongate pharmacokinetic half-life (Coskun et al., *Cell Metab* 2022; Zhou, et al. *Ann. Rev. Pharmacol. & Toxicol.* 2024). Retatrutide has a half-life of about six days.

Phase II trial of retatrutide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04881760).

Efficacy. In results published in 2023, once-weekly retatrutide demonstrated dose-dependent placebo-adjusted weight loss of up to 22% in obesity at 48 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with retatrutide led to up to 60% nausea, 20% diarrhea, and 26% vomiting, all of which were roughly dose-dependent, occurring most frequently at the second-highest dose level. In addition, treatment led to adverse events of special interest including antidrug antibodies and heart, liver, bile duct, kidney, and pancreas toxicities. Serious treatment-emergent adverse events were slightly elevated in the 4 mg (without titration) and 8 mg (starting at 4 mg) retatrutide arms, at 6% each, compared with the placebo arm. Furthermore, the discontinuation rate exhibited a dose-dependent relationship, occurring up to a midteens percentage, compared with no discontinuations in the placebo arm.

Next steps. Retatrutide is being examined in five ongoing Phase III clinical studies in obesity, consisting of TRIUMPH-1 in obesity or overweight, TRIUMPH-2 in type 2 diabetes and obesity or overweight, TRIUMPH-3 in obesity and cardiovascular disease, TRIUMPH-4 in obesity or overweight and osteoarthritis of the knee, and TRIUMPH-OUTCOMES in obesity. The trials are slated to complete in May 2026, May 2026, February 2026, March 2026, and February 2029, respectively. A detailed summary of the Phase II trial results of retatrutide in overweight or obesity is presented in exhibit 39 (Jastreboff et al., *NEJM* 2023; NCT05929066; NCT05929079; NCT05882045; NCT05931367; NCT06383390).

Exhibit 39
Eli Lilly and Company
24-Week and 48-Week Results of Retatrutide in Overweight or Obesity Without Type 2 Diabetes

	Phase II Trial (NCT04881760)						
Sponsor	Eli Lilly and Company						
Mechanism of Action	GIP, GLP-1, and glucagon receptor triple-agonist						
Enrollment Criteria	BMI ≥ 30 kg/m² and ≤ 50 kg/m² or ≥ 27 kg/m² and < 30 kg/m², with at least one weight-related comorbidity* HbA1c < 6.5%						
Baseline Patient Characteristics	Age=51 years Male=52% Body weight=106 kg BMI=38 kg/m² Prediabetes=39%	Age=51 years Male=52% Body weight=108 kg BMI=37 kg/m² Prediabetes=45%	Age=47 years Male=53% Body weight=107 kg BMI=37 kg/m² Prediabetes=29%	Age=46 years Male=51% Body weight=107 kg BMI=37 kg/m² Prediabetes=31%	Age=49 years Male=51% Body weight=109 kg BMI=37 kg/m² Prediabetes=43%	Age=46 years Male=52% Body weight=108 kg BMI=37 kg/m² Prediabetes=31%	Age=48 years Male=51% Body weight=109 kg BMI=37 kg/m² Prediabetes=37%
Study Arms	1 mg retatrutide once weekly	4 mg retatrutide once weekly	4 mg retatrutide once weekly	8 mg retatrutide once weekly	8 mg retatrutide once weekly	12 mg retatrutide once weekly	placebo
Enrollment	69 patients	33 patients	34 patients	35 patients	35 patients	62 patients	70 patients
Titration Schedule	1 mg for 48 weeks	2 mg for 4 weeks; 4 mg for 44 weeks	4 mg for 48 weeks	2 mg for 4 weeks; 4 mg for 4 weeks; 8 mg for 40 weeks	4 mg for 4 weeks; 8 mg for 44 weeks	2 mg for 4 weeks; 4 mg for 4 weeks; 8 mg for 4 weeks; 12 mg for 36 weeks	
Change in Body Weight at Week 24	**-7%** **placebo-adjusted: -6%**	**-12%** **placebo-adjusted: -10%**	**-14%** **placebo-adjusted: -12%**	**-17%** **placebo-adjusted: -15%**	**-18%** **placebo-adjusted: -16%**	**-18%** **placebo-adjusted: -16%**	**-2%**
Change in Body Weight at Week 48	-9% placebo-adjusted: -7%	-16% placebo-adjusted: -14%	-18% placebo-adjusted: -16%	-22% placebo-adjusted: -20%	-24% placebo-adjusted: -22%	-24% placebo-adjusted: -22%	-2%
Patients Reaching ≥5%, ≥10%, and ≥15% Weight Loss at Week 48	64%; 27%; 16%	87%; 73%; 55%	97%; 76%; 64%	100%; 90%; 73%	100%; 91%; 77%	100%; 93%; 83%	27%; 9%; 2%
TEAE Frequency	84%	73%	85%	80%	94%	92%	70%
TEAEs Affecting ≥5% of Patients	Nausea 14% Decreased appetite 13% COVID-19 19% Vomiting 3% Constipation 7% Diarrhea 9% Fatigue 4% Early satiety 4% Increased lipases 3%	18% 18% 12% 12% 15% 12% 12% 3% 9%	36% 24% 18% 12% 6% 12% 6% 3% 6%	17% 11% 17% 6% 11% 20% 3% 0% 3%	60% 31% 34% 26% 11% 20% 9% 6% 6%	45% 29% 24% 19% 16% 15% 10% 10% 8%	11% 9% 20% 1% 3% 11% 4% 6% 3%
Adverse Events of Special Interest	ADA 4% Hypersensitivity 10% Hyperesthesia/related 1% Cardiac arrhythmia 4% ISR 1% Severe GI AE 0% Hepatic disorder 7% Pancreatitis 0% MDD/SI 0% Renal event 1% MACE 3% Biliary disorder 0%	12% 3% 6% 0% 0% 0% 3% 0% 0% 3% 0% 0%	16% 6% 6% 6% 3% 3% 0% 0% 0% 0% 0% 0%	16% 9% 3% 0% 0% 3% 3% 0% 0% 0% 0% 3%	6% 20% 14% 14% 3% 3% 6% 0% 0% 3% 0% 6%	18% 13% 13% 11% 8% 6% 3% 2% 0% 0% 0% 0%	1% 3% 1% 3% 0% 0% 3% 0% 1% 1% 0% 0%
Serious TEAE Frequency	4%	0%	6%	3%	6%	3%	4%
TEAEs Leading to Discontinuation	7%	6%	9%	14%	6%	16%	0%
Deaths	0 events	0 events	1 event, related to treatment-unrelated drowning	0 events	0 events	0 events	0 events

*Patients had either hypertension, dyslipidemia, and/or cardiovascular disease.
ADA=Antidrug antibodies. BMI=Body mass index. GI=Gastrointestinal. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. ISR=Injection-site reaction. MACE=Major adverse cardiovascular event. MDD=Major depressive disorder. SI=Suicidal ideation. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, Jastreboff et al., NEJM 2023, clinicaltrials.gov

Hanmi's Efocipegtrutide

The asset, also known as HM15211, is a peptide-based triple agonist of the GIP, GLP-1, and glucagon receptors that is chemically conjugated to the constant region of human immunoglobulin via a non-peptidyl flexible linker. Hanmi has obtained orphan drug designation from the FDA and EMA for the treatment of idiopathic pulmonary fibrosis, primary biliary cholangitis, and primary sclerosing cholangitis (Hanmi website). Efocipegtrutide is a peptibody consisting of a 40-peptide glucagon analog subunit linked at its N-terminal prolyl PEG-230 cysteine to two aglycosylated IgG4 Fc fragments. Its second amino acid is substituted with the non-canonical α-aminoisobutyric acid (GSRS listing; Hanmi poster).

The candidate underwent a Phase I trial to study to evaluate its safety, tolerability, pharmacokinetics, and pharmacodynamics. Posted results showed no mortality and no serious adverse events. Reported adverse events were primarily GI disorders, which increased with dosage (NCT03374241).

This was followed by a Phase I study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of HM15211 in obese subjects with NAFLD. Primary outcomes measured were incidence of adverse events, incidence of clinical lab abnormalities, incidence and severity of clinical findings on physical examination, change from baseline in vital signs, and change from baseline in 12-lead ECG. It is not known if weight loss was a secondary outcome measured; a list of secondary outcomes was not provided. Results have been submitted to clinicaltrials.gov but not posted, as they have been twice returned after quality control review (NCT03744182).

Currently ongoing is a Phase II study to evaluate efficacy, safety, and tolerability of HM15211 treatment for 12 months in subjects with biopsy-confirmed NASH. There is no requirement that the subjects be obese. Results are anticipated late in the year (NCT04505436).

GLP-1 and GLP-2 Receptor Agonists

Like GLP-1 and glucagon, GLP-2 is derived from the preproglucagon molecule and, like GLP-1, is secreted from the intestine. Indeed, GLP-1 and GLP-2 are secreted by intestinal L cells at a 1:1 ratio in response to nutrient ingestion. A discrete population of neurons in the brainstem and hypothalamus in rats has also been shown to secrete GLP-2 (Vrang & Larsen, *Prog. Neurobio.* 2010). GLP-2's N-terminal domain is homologous to that of GLP-1, meaning that it also is subject to inactivation by DPP-4. Whereas GLP-1 reduces glucagon secretion, however, GLP-2 increases it. While the half-life of GLP-1 is about 1-2 minutes, that of GLP-2 is about 7 minutes (Marathe, et al. *Peptides* 2013).

GLP-2 binds its own G protein-coupled receptor, GLP-2 receptor, which is primarily expressed in the gut, pancreas, and brain (Sun, et al. *Cell Res.* 2020). The main functions of GLP-2 in the intestines are to increase epithelial proliferation, inhibit apoptosis, enhance barrier function, and increase digestion, absorption, and blood flow (Markovic & Brubaker *Sci. Rep.* 2019). A study of mice fed a high-fat diet showed that those that were injected intraperitoneally with a stable GLP-2 analog had less brain inflammation, oxidative stress, and neurodegeneration; although the authors stated that it is unknown whether GLP-2 can cross the blood–brain barrier, they noted that GLP-1 can permeate the barrier (Nuzzo, et al. *Neurobio. Dis.* 2019). However, in the brain, the GLP-2 receptor is expressed in the hypothalamus, hippocampus, and brainstem; both the hypothalamus and hindbrain lack full protection of a blood–brain barrier (Pálsson, et al. *Peptides* 2024).

Long-lasting analogs of GLP-2, which are administered subcutaneously, have been developed to take advantage of its abilities to regulate growth and proliferation of cells lining the gastrointestinal tract, increase intestinal portal blood flow, and decrease gastrointestinal motility (Kounatidis, et al. *Curr. Nut. Rep.* 2022). The first to be approved by the FDA was teduglutide (sold by Takeda Pharmaceuticals under the name GATTEX), which is prescribed for treatment of short bowel syndrome (SBS). Teduglutide has also been used for treatment of Crohn's disease, an inflammatory bowel disorder, due to its anti-inflammatory effects. A substitution of glycine for alanine at the N-terminal makes teduglutide more resistant to DPP-4 than endogenous GLP-2.

Two other drugs, glepaglutide (Zealand Pharma) and apraglutide (Ironwood Pharmaceuticals), have more amino acid modifications than teduglutide. Such extensive modifications may allow a long enough half-life that dosing can be reduced from daily to twice or once weekly (Kounatidis, et al. *Curr. Nut. Rep.* 2022). Moreover, while apraglutide is selective for the GLP-2 receptor, glepaglutide also has affinity for the GLP-1 receptor (Pálsson, et al. *Peptides* 2024). Zealand submitted an application for NDA, for treatment of SBS, to the FDA in December 2023. However, in December 2024 the FDA recommended an additional clinical trial to provide further evidence to confirm the efficacy and safety of glepaglutide at the to-be-marketed dose. Ironwood expects submission for a NDA, also for treatment of SBS, in the first quarter (Ironwood press release Oct. 28, 2024).

The goal of combining a GLP-1 RA with a GLP-2 agonist is to obtain both the weight loss effect of the former and the improved barrier function of the latter. Obesity is associated with a degraded intestinal barrier that allows pro-inflammatory gut content (pathogens and microbial-associated molecules) to translocate into circulation.

The combination of appetite suppression from GLP-1 RAs with improved gut barrier function from GLP-2 RAs could provide promising weight loss while helping contain inflammatory stimuli within the gut, in our view. Regarding the greatest weight loss observed for the class, dapiglutide demonstrated up to 8% placebo-adjusted weight loss at 13 weeks in Phase Ib results in overweight and obesity.

Zealand's Dapiglutide

The asset, also known as ZP7570, is a unimolecular dual GLP-1 and GLP-2 RA with a once-weekly dosing schedule undergoing development in overweight or obesity. The asset is a peptide measuring 33 amino acids long with sequence homology to endogenous human GLP-1, with key modifications. These include a substitution at the second position of α-aminoisobutyric acid and a C-18 acyl modification at position 16 with N6-(17-carboxyheptadecanoyl-γ-glu)-lysine, based on the FDA's Global Substance Registration System (GSRS) description (GSRS listing; DREAM trial protocol 2023). The modifications are designed to extend the molecule's half-life in circulation, improve potency, and improve physical and chemical stability at neutral pH.

Phase Ib trial of dapiglutide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06000891).

Efficacy. In top-line results released in September 2024, once-daily dapiglutide demonstrated 8% placebo-adjusted weight loss across dose levels in overweight or obesity at 13 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 6% placebo-adjusted weight loss at 12 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with dapiglutide led to antidrug antibodies and undisclosed rates of gastrointestinal adverse events, including nausea and vomiting. In terms of serious adverse events and TEAEs leading to trial discontinuation, researchers observed one treatment-unrelated serious adverse event in the dapiglutide arms, representing 2% of patients; two patients discontinued treatment due to adverse events related to moderate vomiting, representing around 5% of patients.

Next steps. Part 2 of this Phase Ib trial is testing doses of dapiglutide of up to 26 mg over 28 weeks, with increasing dose titration every four weeks. The company expects to present initial results from this part 2 component in the first half and present additional results from part 1 and part 2 at an upcoming scientific congress. Furthermore, Zealand plans to initiate a Phase IIb trial of

dapiglutide in overweight or obesity in the first half. A detailed summary of the Phase Ib trial results of dapiglutide in overweight or obesity is presented in exhibit 40 (Zealand Pharma September 2024 press release; NCT05788601).

Exhibit 40
Zealand Pharma A/S
13-Week Multiple-Ascending-Dose Results of Dapiglutide in Overweight or Obesity Without Type 2 Diabetes

Phase Ib Trial (NCT06000891)

Sponsor	Zealand Pharma A/S			
Mechanism of Action	Dual GLP-1 and GLP-2 receptor agonist			
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² Otherwise healthy			
Baseline Patient Characteristics	Age=46 years Male=85% BMI=30 kg/m²			
Study Arms	dapiglutide dose level 1 once daily for 13 weeks	dapiglutide dose level 2 once daily for 13 weeks	13 mg dapiglutide once daily for 13 weeks[1]	placebo
Enrollment	54 patients randomized 14:4			
Titration Schedule	every other week			
Change in Body Weight at Week 13	-6% placebo-adjusted: -8%			+2%
Serious TEAEs	**1 event, unrelated to treatment (2%)**			**0%**
Anti-Drug Antibodies	14%			0%
TEAEs Leading to Discontinuation	**2 patients, related to moderate vomiting (5%)**			**0%**

The most common adverse events were gastrointestinal, including vomiting and nausea. A low number of patients experienced mild injection site reactions.

[1]Patients randomized to the 13 mg dose cohort received the target dose for five weeks.

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. GLP-1=Glucagon-like peptide 2. TEAEs=Treatment-emergent adverse events.

Sources: Company reports, clinicaltrials.gov

ProGen's PG-102

PG-102, also known as MG12, is a bispecific GLP-1 and GLP-2 RA in which the agonist moieties are fused to a Neo Tri-ImmunoGlobulin (NTIG) Fc protein. The technology used allows the two agonists to be combined into a single molecule in a manner that is expected to increase their half-lives. The drug is being investigated for both obesity and type 2 diabetes.

Phase I trial of PG-102

The company is conducting a three-part study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the asset following subcutaneous injections in healthy adult and obese participants. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06309667).

Safety and tolerability. Treatment with PG-102 led to up to 38% nausea (dose-dependent), 13% diarrhea (dose-independent), and 13% vomiting (dose-dependent). In addition, no serious treatment-emergent adverse events or study discontinuations were reported.

Pharmacokinetic parameters. PK/PD modeling suggested weekly injections of 5 mg and 15 mg, and every-other-week or longer intervals for 30 mg and 60 mg doses. Furthermore, simulated doses of 90 mg are expected to have monthly intervals.

Next steps. These findings will be further refined and updated with the results from the ongoing multiple-ascending-dose study. ProGen is also conducting a Phase II study of PG-102 compared with placebo in obesity and type 2 diabetes. Completion of the Phase I trial is anticipated for 2026 and the Phase II trial in midyear (NCT06712615; Han, et al. *Diabetes* 2024; ProGen website).

Amylin Receptor Agonists: From Monotherapy to Duotherapy to a Single Dual Agonist Molecule

Amylin is a peptide hormone, 37 amino acids long, secreted primarily by the β cells of the pancreas, the same cells that produce insulin. Indeed, the two are secreted at a fixed molar ratio. Upon secretion after eating, amylin circulates in the blood, crosses the blood–brain barrier (BBB), and activates specific receptors in the CNS. This suppresses glucagon release from the pancreas and leads to a reduction in food intake and gastric emptying. The result is decreased blood glucose, which is associated with longer-term reductions in body weight and adiposity.

The primary locations of amylin receptors are in the nucleus accumbens, the area postrema (AP) of the brainstem, the hypothalamus, the ventral tegmental area, the lateral parabrachial nucleus, the solitary tract, and the subfornical organ. The AP, an important site of amylin receptors, is devoid of a BBB. Amylin receptors are heterodimers of the calcitonin receptor and a receptor activity modifying protein, or RAMP (Hay, et al. *Pharmacol. Rev.* 2015).

Amylin Monotherapy

Amylin itself is short-lived once secreted into circulation, having a half-life of about 13 minutes when injected as a bolus, and has a tendency to form aggregates. Synthetic analogs, to be injected subcutaneously before meals (as an adjunct to insulin), were developed for treatment of both types 1 and 2 diabetes. The available chemical structures, dosing regimens, and half-lives of peptide-based therapeutics with high sequence homology to endogenous amylin, including pramlintide (Symlin), cagrilintide, and petrelintide, are presented in exhibit 41.

Exhibit 41
Structures of Endogenous Amylin, Symlin, Cagrilintide, and Petrelintide

Amylin

Half-life: ~15 minutes

Pramlintide

Half-life: 48 minutes

Symlin:

Type 1 diabetes patients' dosing regimen: start at 15 µg before major meals, increase in 15 µg increments to maximum premeal dose of 30 µg or 60 µg as tolerated, with at least 3 days between titrations

Type 2 diabetes patients' dosing regimen: start at 60 µg before major meals, increase to 120 µg as tolerated at least 3 days later

Cagrilintide

Half-life: 159 hours to 195 hours
Dosing regimens: 0.16 mg, 0.30 mg, 0.60 mg, 1.2 mg, 2.4 mg, or 4.5 mg once-weekly injections

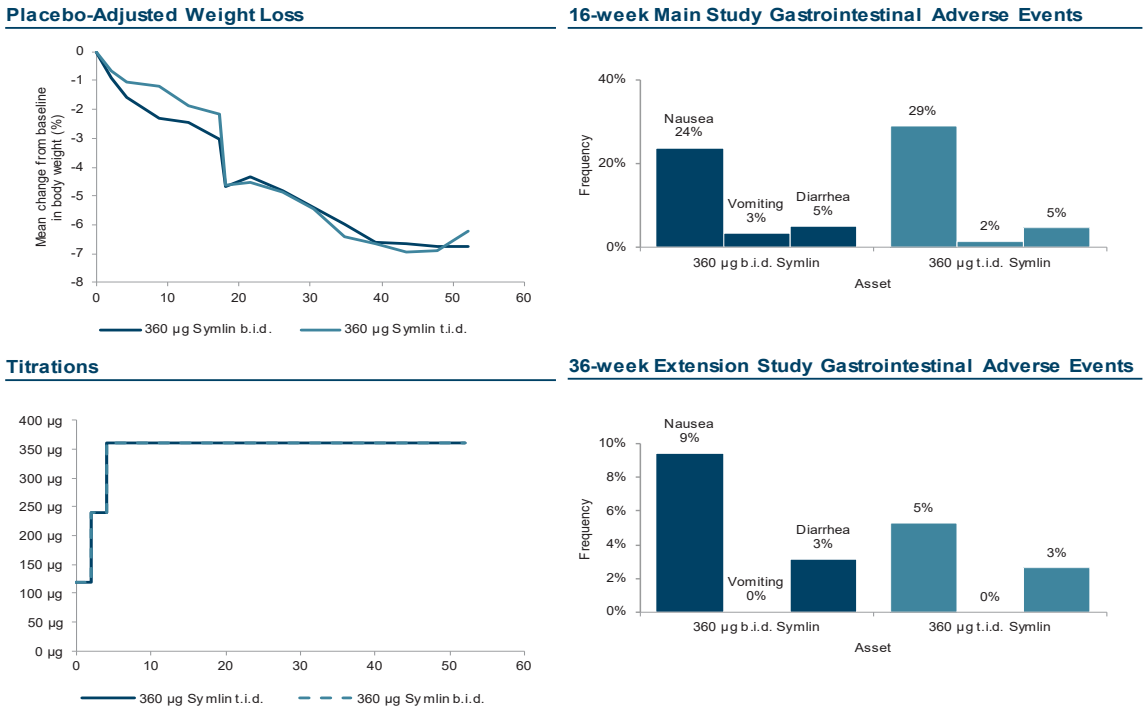
Petrelintide

Half-life: ~230 hours
Dosing regimens: 0.6 mg, 0.7 mg, 1.2 mg, 1.4 mg, and 2.4 mg once-weekly injections

Aad=2-aminoadipic acid. C20=20 carbons long. Hyp=Hydroxyproline. MeiLe=Methylisoleucine. Sar=Sarcosine.
Sources: Holst, Nat Metab 2024, Kruse et al., J Med Chem 2021, Global Substance Registration System, Company Documents

A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of Symlin is presented in exhibit 42.

Exhibit 42
Combined Weight Loss, Adverse Events, and Titration Curves of Amylin Receptor Agonist Symlin



b.i.d.=twice daily; t.i.d.=thrice daily
Sources: Company documents

AstraZeneca's Symlin

Only one amylin analogue, the peptide-based pramlintide (sold under the brand name Symlin), is approved in the U.S. Symlin was originally made by Amylin Pharmaceuticals, which was acquired by AstraZeneca in 2013. The amino acid sequence of amylin is modified in Symlin by the substitution of prolines for three of amylin's amino acids (one alanine and two serines). Symlin ameliorates amylin's tendency to aggregate and its resultant cytotoxicity. Compared with amylin, it has a somewhat longer but still relatively short half-life (20-45 minutes). In addition, based on a Viking Therapeutics poster at the 2024 American Diabetes Association meeting, Symlin has a nearly 75-fold higher agonistic activity for amylin receptor (hAMY3R) compared with calcitonin receptor (hCTR) (Yagiz et al, *Diabetes* 2024).

Symlin was approved by the FDA in 2005 for patients with type 1 or 2 diabetes in combination with mealtime insulin who have poorly controlled blood sugar despite optimal insulin therapy. However, it was never approved for obesity without type 2 diabetes.

Phase II trial of Symlin

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT00189514; NCT00112021).

Efficacy. Symlin demonstrated up to 7% placebo-adjusted weight loss (in the highest dose twice-daily cohort) in obesity at 1 year. Intriguingly, placebo-adjusted weight loss in the highest dose thrice-daily cohort was less, at 6%, based on visual estimation of the data. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with Symlin led to up to 29% nausea (dose-dependent), 6% diarrhea (dose-independent), and 7% vomiting (dose-independent). One case of severe treatment-emergent nausea, or around 2% of patients, was reported in the 360 µg three-times-daily cohort. In addition, the discontinuation rate increased in a dose-dependent manner up to a midteens percentage in the main study and to the low single digits in the extension study, compared with no discontinuations in the placebo arm. A detailed summary of the Phase II trial results of Symlin in obesity is presented in exhibit 43 (Smith et al., *Diabetes Care* 2008).

When it was observed that patients treating their diabetes with insulin experienced weight loss from the use of Symlin, scientists began studying its use as an anti-obesity medication. Subjects found that they consumed less food to feel satiated, and their preferences for high-fat and high-sugar foods were reduced (Hay, et al. *Pharmacol. Rev.* 2015). Further research seeks to produce drugs with increased stability, versatility, and weight loss effect.

Exhibit 43
AstraZeneca PLC
52-Week Results of Symlin in Obesity Without Type 2 Diabetes

Phase II Trials (NCT00189514, NCT00112021)							
Sponsor	AstraZeneca PLC						
Mechanism of Action	Amylin receptor agonist						
Enrollment Criteria	BMI ≥ 35 kg/m² and ≤ 50 kg/m² HbA1c < 6.5%						
Main Study Baseline Patient Characteristics	Age=43 years Male=27% Body weight=105 kg BMI=38 kg/m²	Age=46 years Male=29% Body weight=106 kg BMI=38 kg/m²	Age=45 years Male=28% Body weight=108 kg BMI=38 kg/m²	Age=44 years Male=25% Body weight=105 kg BMI=37 kg/m²	Age=44 years Male=29% Body weight=107 kg BMI=38 kg/m²	Age=46 years Male=27% Body weight=108 kg BMI=38 kg/m²	Age=47 years Male=27% Body weight=104 kg BMI=37 kg/m²
36-Week Extension Study Baseline Patient Characteristics	Age=45 years Male=25% Body weight=103 kg BMI=37 kg/m²	Age=48 years Male=28% Body weight=106 kg BMI=38 kg/m²	Age=44 years Male=20% Body weight=107 kg BMI=38 kg/m²	Age=46 years Male=20% Body weight=104 kg BMI=37 kg/m²	Age=44 years Male=34% Body weight=109 kg BMI=38 kg/m²	Age=47 years Male=21% Body weight=107 kg BMI=38 kg/m²	Age=49 years Male=22% Body weight=106 kg BMI=38 kg/m²
Study Arms	120 µg Symlin twice daily	120 µg Symlin thrice daily	240 µg Symlin twice daily	240 µg Symlin thrice daily	360 µg Symlin twice daily	360 µg Symlin thrice daily	placebo
Main Study Enrollment	59 patients	59 patients	54 patients	56 patients	59 patients	62 patients	59 patients
36-Week Extension Study Enrollment	28 patients	29 patients	25 patients	30 patients	32 patients	38 patients	27 patients
Titration Schedule	120 µg for 16 weeks (main study); 120 µg for 36 weeks (extension)	120 µg for 16 weeks (main study); 120 µg for 36 weeks (extension)	120 µg for 2 weeks; 240 µg for 14 weeks (main study); 240 µg for 36 weeks (extension)	120 µg for 2 weeks; 240 µg for 14 weeks (main study); 240 µg for 36 weeks (extension)	120 µg for 2 weeks; 240 µg for 2 weeks; 360 µg for 12 weeks (main study); 360 µg for 36 weeks (extension)	120 µg for 2 weeks; 240 µg for 2 weeks; 360 µg for 12 weeks (main study); 360 µg for 36 weeks (extension)	
Change in Body Weight at Week 16	**-4%** **placebo-adjusted: -1%** ***p*=NS**	**-6%[1]** **placebo-adjusted: -3%** ***p*<0.01**	**-5%[1]** **placebo-adjusted: -2%** ***p*=NS**	**-4%[1]** **placebo-adjusted: -2%** ***p*=NS**	**-6%[1]** **placebo-adjusted: -3%** ***p*<0.05**	**-5%[1]** **placebo-adjusted: -2%** ***p*<0.05**	**-3%**
Change in Body Weight at Week 52	**-3%[1]** **placebo-adjusted: -2%** ***p*=NS**	**-7%[1]** **placebo-adjusted: -6%** ***p*<0.01**	**-6%** **placebo-adjusted: -5%** ***p*=NS**	**-7%[1]** **placebo-adjusted: -6%** ***p*<0.01**	**-7%** **placebo-adjusted: -7%** ***p*<0.01**	**-7%[1]** **placebo-adjusted: -6%** ***p*<0.05**	**-1%**
Patients Reaching ≥5% and ≥10% Weight Loss at Week 52	25% (*p*=NS) 8% (*p*=NS)	44% (*p*=NS) 40% (*p*=NS)	41% (*p*=NS) 24% (*p*=NS)	57% (*p*<0.05) 22% (*p*=NS)	57% (*p*<0.05) 43% (*p*=NS)	65% (*p*<0.05) 35% (*p*=NS)	18% 12%
TEAEs in the 16-Week Main Study	Nausea 19% Headache 10% Diarrhea 3% Nasopharyngitis 0% Injection site bruising 3% Vomiting 2% Urinary tract infection 3%	17% 3% 5% 0% 3% 7% 0%	17% 4% 6% 2% 4% 0% 2%	9% 2% 2% 4% 7% 2% 5%	24% 0% 5% 9% 2% 3% 3%	29% 7% 5% 3% 2% 2% 2%	2% 0% 3% 2% 2% 0% 2%
TEAEs in the 36-Week Extension Study	Nasopharyngitis 4% Back pain 7% Nausea 0% Arthralgia 4% Diarrhea 0% Depression 0%	10% 3% 3% 3% 3% 10%	16% 8% 4% 4% 4% 4%	7% 3% 0% 7% 3% 7%	16% 3% 9% 0% 3% 0%	5% 5% 5% 3% 3% 0%	7% 0% 0% 0% 0% 0%
Severe TEAE Frequency in the 16-Week Main Study	0%	0%	0%	0%	0%	2% (1 case of severe nausea)	0%
Severe TEAE Frequency in the 36-Week Extension Study	0%	0%	0%	0%	0%	0%	0%
TEAEs Leading to Discontinuation in the 16-Week Main Study	3%	7%	7%	5%	9%	16%	0%
TEAEs Leading to Discontinuation in the 36-Week Extension Study	0%	0%	0%	0%	3%	3%	0%
Treatment-Emergent Deaths	0 events	0 events	0 events	0 events	0 events	0 events	0 events

For the 16-week study, weight loss data are presented for the 16-week evaluable population of 270 patients. For the 52 week time point, data are presented for the 52-week evaluable population of 146 patients.
[1]Based on visual estimation of the data.
BMI=Body mass index. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, Smith et al., Diabetes Care 2008, clinicaltrials.gov

Eli Lilly's Eloralintide

Eloralintide, also known as LY3841136, is a 37-amino-acid long-lasting amylin RA under development by Lilly. The drug was previously designated LY3841136 and, before that, as AMY-1176. Its sequence and modifications are described in the Global Substance Registration System. Eloralintide is undergoing Phase I and II trials in healthy, overweight, and obese participants, alone and in combination with other drugs.

Phase I trials of eloralintide

Lilly is studying eloralintide as a monotherapy or in combination with Zepbound in Japanese and non-Japanese patients with overweight and obesity. For enrollment criteria and trial designs, refer to clinicaltrials.gov (NCT06297616; NCT06345066).

Phase II trials of eloralintide

According to a Phase II chronic weight management master protocol listed on clinicaltrials.gov, patients with overweight or obesity with or without type 2 diabetes will receive eloralintide, LY3305677, eloralintide plus Zepbound, LY3549492 (undisclosed mechanism), or placebo. LY3305677 (IBI362) is a weekly-dose glucagon-like peptide-1 and glucagon receptor dual agonist. All drugs will be delivered subcutaneously, except for LY3549492, which will be dosed orally. For enrollment criteria and trial designs, refer to clinicaltrials.gov (NCT06143956; NCT06683508; NCT06230523; NCT06124807; NCT06603571; GSRS listing; Ji, et al. *EClinicalMedicine* 2021).

AstraZeneca's AZD6234

The asset is an agonist of amylin receptors with selectivity over calcitonin receptor activity. The composition of the drug has not been disclosed. Preclinical data from a study of DIO mice, presented at ObesityWeek 2024, showed that mice receiving the drug for 28 days experienced dose-dependent weight loss and food intake reduction. Weight loss at the highest dosage was roughly 10% of body weight, with no significant change in lean muscle mass. A second group of mice were treated with AZD6234 or semaglutide for two weeks and were then subjected to a washout period of another two weeks. The mice experienced dose-dependent weight loss during the first two weeks and essentially regained the lost weight during the washout period, regardless of which drug they received. However, the high-dose AZD6243 mice more than doubled the fat loss during the treatment period compared with the high-dose semaglutide mice, while preserving (compared with vehicle) lean body mass; in contrast, the high-dose semaglutide significantly reduced lean body mass compared with vehicle. The AZD6243-treated mice also experienced significant regains of body fat, and this was particularly prominent for the two highest doses. In contrast, increases in body fat for the semaglutide-treated mice were numerically greater compared with vehicle but were not significant.

Phase I trial of AZD6234

The company conducted the study to assess the safety, tolerability, and pharmacokinetics of the asset in otherwise healthy subjects who are overweight or obese. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05511025).

Efficacy. Patients in the global and Japanese cohorts receiving a single subcutaneous dose of 2.7 mg experienced around 2% and 4% weight loss, respectively, at 4 and 5 weeks.

Safety and tolerability. Treatment with AZD6234 led to up to nausea, decreased appetite, and vomiting. No serious treatment-emergent adverse events were reported. Study discontinuations were not disclosed.

Next steps. AstraZeneca is recruiting healthy participants for a second Phase I study in obese or overweight participants with at least one weight-related comorbidity for a Phase II trial (AstraZeneca Weight Management Virtual Event; AstraZeneca Poster Summary; NCT06595238; NCT06132841).

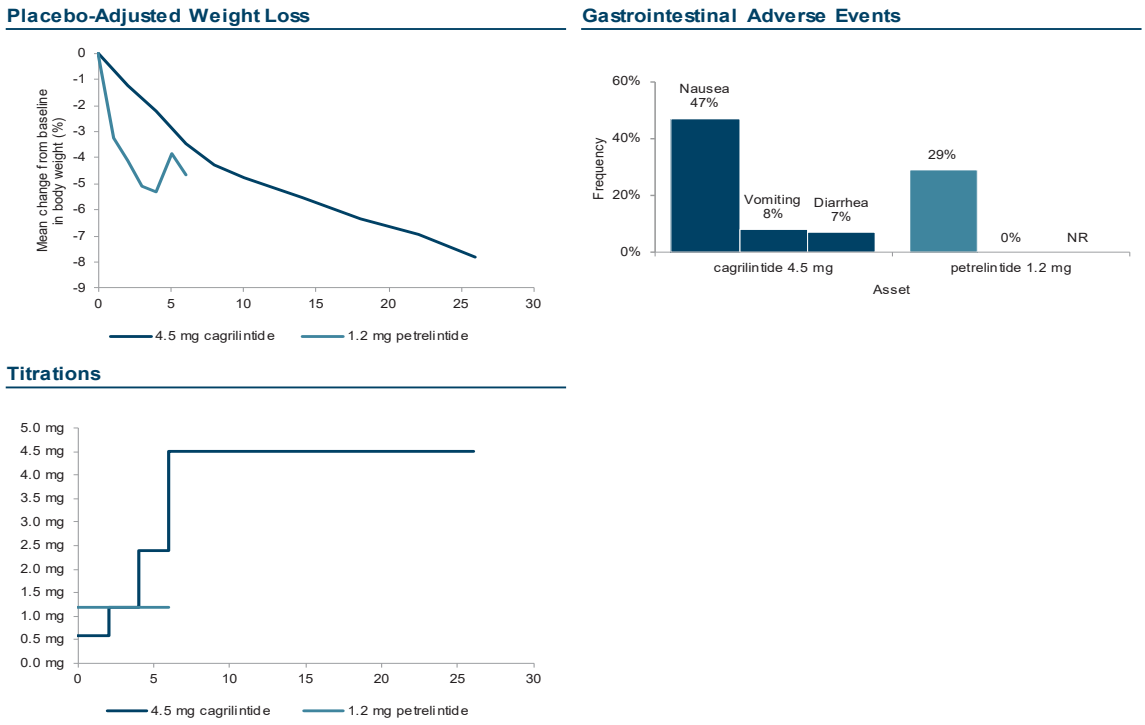
Dual Amylin and Calcitonin Receptor Agonists (DACRAs)

An amylin analog may also be modified to enable it to activate the calcitonin receptor even when that receptor is not associated with a RAMP. As mentioned above, amylin itself binds to the calcitonin receptor when that receptor heterodimerizes with a RAMP, which serves as an accessory protein to produce an amylin receptor. Such dual agonists exist naturally in other species; salmon is the most well studied. Some elements of salmon calcitonin, specifically a C-terminal proline and a salt bridge at residues 8 to 18, were incorporated into cagrilintide (Kruse et al. *J. Med. Chem* 2021), a peptide-based drug being investigated by Novo Nordisk. In contrast, a drug from Nordic Bioscience that is still in the preclinical stage starts with the salmon calcitonin backbone, an approach that it suggests will make its asset more potent and versatile (Larsen, et al. *Biomed. & Pharmacotherapy* 2022; Mohamed, et al. *Arthritis Res. & Ther.* 2024). Mammalian calcitonin promotes insulin sensitivity, whereas salmon calcitonin has been shown to inhibit gastric emptying, increase energy expenditure, and induce satiety and weight loss, although some of the studies using salmon calcitonin were performed in rodents and nonhuman primates (Mathiesen et al. *Front. Endocrin.* 2021). This class of drugs is referred to as dual amylin and calcitonin RAs, or DACRAs.

The human calcitonin receptor is known to be coupled to multiple pathways, most prominently those involved in calcium homeostasis. Human calcitonin, which is secreted from thyroid cells, is thus recognized primarily for its effects on bones. Indeed, a synthetic form of salmon calcitonin, being more potent than human calcitonin, is used in a nasal spray to treat osteoporosis in postmenopausal women. When administered to humans, salmon calcitonin has been shown to inhibit gastric emptying and gastrin release post-prandially. In mice and monkeys, and also in rat models of obesity and diabetes, salmon calcitonin reduces food intake and body weight. Because salmon calcitonin binds both the human calcitonin and human amylin receptors in vitro, however, it is unclear exactly how these results are mediated (Mathiesen et al. *Front. Endocrin.* 2021). In rodents, DACRAs have shown greater effectiveness at reducing food intake and body weight than amylin (Larsen, et al. *J. Pharmac. and Exp. Therap.* 2019), leading to development of DACRAs for humans.

In our view, DACRAs have the potential to deliver low-intensity weight loss with improved tolerability. In terms of weight loss in the Phase III REDEFINE 1 study in overweight and obesity, treatment with the DACRA cagrilintide at 2.4 mg once weekly demonstrated about 9% placebo-adjusted weight loss at 68 weeks, compared with roughly 12% for once-weekly 2.4 mg Wegovy. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of DACRAs including cagrilintide and petrelintide is presented in exhibit 44.

Exhibit 44
Combined Weight Loss, Adverse Events, and Titration Curves of Dual Amylin and Calcitonin Receptor Agonists



Sources: Company documents

Zealand's Petrelintide

The asset, also known as ZP8396, is a peptide-based amylin analog that has a balanced agonist effect on amylin and calcitonin receptors, with a once-weekly dosing schedule, which completed Phase I clinical development in overweight or obesity.

Petrelintide is a peptide measuring 36 amino acids long with sequence homology to endogenous human amylin, with several key modifications. These consist of amino acid substitutions of glycine at position 23 with sarcosine, isoleucine at position 25 with n-methylisoleucine, and proline at position 36 with hydroxyproline. In addition, there is an L-2-aminoadipic acid modification at position 15 and a lactam bridge between the aspartate residue at position 3 and the lysine residue at position 8. Furthermore, there is a 20-carbon fatty di-acid conjugated via a glutamic acid linker to the glutamate residue at position 1, intended to increase the half-life of the molecule through increased binding to circulating albumin, based on the FDA's GSRS description (GSRS listing). The amino acid modifications and the lactam bridge are designed to extend the molecule's half-life in circulation; improve potency at the amylin 1, amylin 3, and calcitonin receptors; and improve physical and chemical stability at neutral pH. Petrelintide has a half-life of about 230 hours, or nearly 10 days.

Phase I trial of petrelintide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05613387).

Efficacy. Single doses and once-weekly petrelintide demonstrated up to 4% and 5% placebo-adjusted weight loss in lean volunteers or patients with overweight at 6 weeks, respectively. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Exhibit 45
Zealand Pharma A/S
6-Week Results of Petrelintide in Lean or Overweight Participants Without Pre-Diabetes or Type 2 Diabetes

Phase I Trial (NCT05613387)

Sponsor	Zealand Pharma A/S					
Mechanism of Action	Dual amylin and calcitonin receptor agonist					
Enrollment Criteria	BMI ≥ 21 kg/m² and < 30 kg/m² HbA1c < 5.7%					
Baseline Patient Characteristics	Age=38 years Male=64% Body weight=84 kg BMI=26 kg/m²			Age=32 years Male=20% Body weight=82 kg BMI=25 kg/m²		
Study Arms	1.4 mg petrelintide single dose	2.4 mg petrelintide single dose	placebo	0.6 mg petrelintide once weekly for 6 weeks	1.2 mg petrelintide once weekly for 6 weeks	placebo
Enrollment	6 patients	6 patients	14 patients	7 patients	7 patients	6 patients
Change in Body Weight at Week 1	-4% placebo-adjusted: -4%	-4% placebo-adjusted: -4%	~-1%			
Change in Body Weight at Week 6				-5% placebo-adjusted: -5%	-5% placebo-adjusted: -5%	~-1%
TEAE Frequency (Gastrointestinal, Metabolic)	**83%, 83%**	**83%, 100%**	**0%, 0%**	**29%, 86%**	**71%, 86%**	**50%, 17%**
TEAEs	**Decreased appetite 83%** **Nausea 67%** **Vomiting 17%** **Early satiety 0%**	**100%** **83%** **67%** **33%**	**0%** **0%** **0%** **0%**	**Decreased appetite 71%** **Nausea 14%** **Food aversion 14%** **Abdominal pain 14%** **Early satiety 29%** **Vomiting 14%**	**57%** **29%** **29%** **14%** **14%** **0%**	**0%** **33%** **0%** **17%** **17%** **17%**
Severe TEAE Frequency	0%					
TEAEs Leading to Discontinuation	None reported					

"Metabolic" pertains to the "metabolism and nutrition disorders" system organ class (SOC), including the CTCAE terms acidosis, alcohol intolerance, alkalosis, anorexia, dehydration, glucose intolerance, hypercalcemia, hyperglycemia, hyperkalemia, hyperlipidemia, hypermagnesemia, hypernatremia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, iron overload, and tumor lysis syndrome.

BMI=Body mass index. CTCAE=Common Terminology Criteria for Adverse Events. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.

Sources: Company reports, clinicaltrials.gov

Safety and tolerability. Treatment with single doses of petrelintide led to up to 83% nausea and 67% vomiting, both of which exhibited dose-dependent relationships. Treatment with once-weekly petrelintide led to up to 29% nausea (dose-dependent) and 14% vomiting (dose-independent). In addition, there were no severe treatment-emergent adverse events or treatment-emergent adverse events leading to study discontinuation. A detailed summary of the Phase I trial results of petrelintide in lean volunteers or individuals with overweight is presented in exhibit 45 on the previous page (Zealand poster at ObesityWeek 2023; Zealand poster at ADA 2024).

Phase Ib trial of petrelintide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05613387).

Efficacy. In updated results, once-weekly petrelintide demonstrated dose-dependent placebo-adjusted weight loss up to 7% in overweight or obesity at 16 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 8% placebo-adjusted weight loss at 16 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with petrelintide led to up to 33% nausea (dose-dependent); in addition, 6% and 3% of patients receiving petrelintide reported diarrhea or vomiting, respectively. No serious treatment-emergent adverse events were reported. Furthermore, the discontinuation rate was higher in the petrelintide arm, due to nausea and vomiting in one patient, occurring in the low single digits. A detailed summary of the Phase Ib trial results of petrelintide in overweight or obesity is presented in exhibit 46 (Zealand poster from ADA 2024; Zealand June 2024 presentation; Zealand Pharma presentation at ObesityWeek 2024).

Exhibit 46
Zealand Pharma A/S
16-Week Multiple-Ascending-Dose Part 2 Results of Petrelintide in Overweight or Obesity Without Type 2 Diabetes

Phase Ib Trial (NCT05613387)

Sponsor	Zealand Pharma A/S			
Mechanism of Action	Dual amylin and calcitonin receptor agonist			
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² HbA1c < 6.5%			
Study Arms	2.4 mg petrelintide once weekly for 16 weeks	4.8 mg petrelintide once weekly for 16 weeks	9.0 mg petrelintide once weekly for 16 weeks	placebo
Enrollment	12 patients	12 patients	12 patients	12 patients
Titration Schedule	0.6 mg → 1.2 mg → 2.4 mg	0.6 mg → 1.2 mg → 2.4 mg → 3.6 mg → 4.8 mg	1.0 mg → 2.0 mg → 4.0 mg → 6.0 mg → 7.5 mg → 9.0 mg	
Baseline Patient Characteristics	Median age: 48 years Male: 83% Body weight: 98 kg BMI: 31 kg/m^2	Median age: 42 years Male: 75% Body weight: 89 kg BMI: 29 kg/m^2	Median age: 52 years Male: 75% Body weight: 88 kg BMI: 29 kg/m^2	Median age: 46 years Male: 83% Body weight: 93 kg BMI: 30 kg/m^2
Change in Body Weight at Week 16	-4.8% placebo-adjusted: -3.1%	-8.6% placebo-adjusted: -6.9%	-8.3% placebo-adjusted: -6.6%	-1.7%
TEAEs[1]	Nausea: 17% Diarrhea: 17% Vomiting: 0% Constipation: 0%	Nausea: 33% Constipation: 8% Vomiting: 0% Diarrhea: 0%	Nausea: 33% Constipation: 25% Vomiting: 8% Diarrhea: 0%	Nausea: 17% Constipation: 8% Vomiting: 0% Diarrhea: 0%
Serious TEAE Frequency	**0%**	**0%**	**0%**	**0%**
TEAEs Leading to Discontinuation	**0%**	**0%**	**8%**	**0%**

[1]All gastrointestinal adverse events were mild except for two moderate events (nausea and vomiting) reported by one participant who discontinued treatment after the third dose. No other patients discontinued treatment due to adverse events, and no other participants reported vomiting. The two reports of diarrhea were mild in severity. No anti-drug antibodies were observed.
BMI=Body mass index. DL=Dose level. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov.

Next steps. The company plans to report results from the Phase IIb ZUPREME-1 trial of petrelintide in obesity or overweight with at least one weight-related comorbidity without type 2 diabetes in the first half of 2026. The trial is examining five different active dose groups of petrelintide or placebo over 42 weeks (though the primary endpoint is weight loss after 28 weeks). In planned longer-term Phase II and Phase III trials, Zealand aims to reach 15%-20% weight loss with petrelintide (NCT06662539).

Novo Nordisk's Cagrilintide

The asset is a balanced DACRA with a once-weekly dosing schedule in clinical development for obesity and overweight (Kruse et al. in 2021). It is a peptide measuring 37 amino acids long with high sequence homology to endogenous amylin, with several key modifications. These consist of six amino acid substitutions of asparagine at position 14 with glutamate to prevent de-amination, valine at position 17 with arginine to increase solubility at physiological pH, alanine at position 25 with proline, serine residues at positions 28 and 29 with proline residues, and tyrosine at position 37 with proline. The arginine at position 17 also forms a helix-stabilizing salt bridge, or an interaction between two oppositely charged amino acid side chains, with the glutamate at position

14, which helps stabilize the peptide structure. The proline substitutions are designed to inhibit the development of amyloid fibrils, which for endogenous amylin can lead to the formation of aggregated amyloid deposits that could have toxic consequences. Furthermore, the tyrosine at position 37 is intended to increase the efficacy of cagrilintide. Cagrilintide, like endogenous amylin, possesses a disulfide bond between the cysteines at positions 2 and 7 and an amidated c-terminal end. Last, a 20-carbon fatty di-acid is attached via an α-glutamyl spacer to the lysine at position 1 to increase cagrilintide's half-life through increased binding to circulating serum albumin. Cagrilintide dosed between 0.16 mg and 4.5 mg once weekly has a half-life between 159 and 195 hours, or roughly one week to about eight days (Kruse, et al. *J. Med. Chem* 2021).

Phase II trial of cagrilintide

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03856047).

Efficacy. In results published in November 2021, once-weekly cagrilintide demonstrated dose-dependent placebo-adjusted weight loss up to 8%, compared with 6% in the Saxenda group, in overweight or obesity at 26 weeks, according to the treatment policy estimand (including patient data regardless of treatment adherence). Investigators also noted improvements in triglycerides and very low-density cholesterol, associated with the two highest doses of cagrilintide.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 12% placebo-adjusted weight loss at 24 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with cagrilintide led to up to 47% nausea (dose-dependent), 18% diarrhea (in the second-highest dose group), and 9% vomiting (in the second-highest dose group). Serious treatment-emergent adverse events did not exhibit a dose-dependent relationship and were highest, at 7%, in the 1.2 mg dose group (roughly twice the rate in the placebo arm). In addition, the discontinuation rate did not exhibit a dose-dependent relationship, occurring in the low to high single digits across trial arms, with Saxenda demonstrating the highest discontinuation rate (Lau, et al., *Lancet* 2021).

Next steps. Cagrilintide is being pursued as a fixed-dose combination therapy with semaglutide, in the form of CagriSema. The two drugs are expected to be delivered in a single, dual-chamber pen, with semaglutide in one chamber and cagrilintide in the other chamber. A detailed summary of the Phase II trial results of cagrilintide in overweight or obesity is presented in exhibit 47 (Reuters December 2024 article on CagriSema).

Exhibit 47
Novo Nordisk A/S
26-Week Results of Cagrilintide in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT03856047)

Sponsor	Novo Nordisk A/S						
Mechanism of Action	Dual amylin and calcitonin receptor agonist						
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%						
Baseline Patient Characteristics	Age=54 years Male=45% Body weight=110 kg BMI=38 kg/m² HbA1c=5.6%	Age=53 years Male=38% Body weight=106 kg BMI=37 kg/m² HbA1c=5.6%	Age=52 years Male=38% Body weight=104 kg BMI=37 kg/m² HbA1c=5.6%	Age=53 years Male=26% Body weight=107 kg BMI=38 kg/m² HbA1c=5.6%	Age=52 years Male=45% Body weight=111 kg BMI=38 kg/m² HbA1c=5.6%	Age=52 years Male=34% Body weight=108 kg BMI=38 kg/m² HbA1c=5.6%	Age=51 years Male=42% Body weight=106 kg BMI=37 kg/m² HbA1c=5.6%
Study Arms	0.3 mg cagrilintide once weekly	0.6 mg cagrilintide once weekly	1.2 mg cagrilintide once weekly	2.4 mg cagrilintide once weekly	4.5 mg cagrilintide once weekly	3.0 mg Saxenda once daily	placebo
Enrollment	101 patients	100 patients	102 patients	102 patients	101 patients	99 patients	101 patients
Titration Schedule	0.3 mg for 26 weeks	0.6 mg for 26 weeks	0.6 mg for 2 weeks; 1.2 mg for 24 weeks	0.6 mg for 2 weeks; 1.2 mg for 2 weeks; 2.4 mg for 22 weeks	0.6 mg for 2 weeks; 1.2 mg for 2 weeks; 2.4 mg for 2 weeks; 4.5 mg for 20 weeks	0.6 mg for 1 week; 1.2 mg for 1 week; 1.8 mg for 1 week; 2.4 mg for 1 week; 3.0 mg for 22 weeks	
Change in Body Weight at Week 26	**-6%** **placebo-adjusted: -3%** **Saxenda-adjusted: +2%**	**-7%** **placebo-adjusted: -4%** **Saxenda-adjusted: +2%**	**-8%** **placebo-adjusted: -6%** **Saxenda-adjusted: 0%**	**-10%** **placebo-adjusted: -7%** **Saxenda-adjusted: -1%**	**-11%** **placebo-adjusted: -8%** **Saxenda-adjusted: -2%**	**-8%** **placebo-adjusted: -6%**	**-3%**
Patients Reaching ≥5%, ≥10%, and ≥15% Weight Loss at Week 26	58% p <0.001 15% p =NS 3% p =NS	62% p <0.001 24% p <0.05 5% p =NS	76% p <0.001 36% p <0.001 15% p <0.01	74% p <0.001 44% p <0.001 22% p <0.001	89% p <0.001 54% p <0.001 19% p <0.01	76% p <0.001 39% p <0.001 14% p <0.05	31% 10% 3%
TEAE Frequency	71%	78%	86%	78%	88%	81%	66%
TEAEs Affecting ≥10% of Patients	Nausea 20% Constipation 11% Fatigue 8% Decreased appetite 4% Injection-site erythema 5% Vomiting 6% Diarrhea 15% Headache 10% Dyspepsia 3% Nasopharyngitis 6%	27% 9% 5% 9% 4% 6% 10% 5% 2% 9%	36% 8% 8% 8% 6% 5% 8% 11% 3% 13%	31% 17% 10% 13% 7% 9% 18% 11% 3% 4%	47% 21% 20% 17% 17% 8% 7% 7% 4% 3%	39% 26% 8% 9% 3% 20% 18% 13% 10% 10%	18% 7% 3% 4% 0% 3% 9% 12% 4% 10%
Serious TEAE Frequency	6%	2%	7%	3%	4%	4%	3%
TEAEs Leading to Discontinuation	2%	4%	6%	6%	1%	7%	3%

*Patients had either hypertension and/or dyslipidemia.
A greater amount of anti-cagrilintide antibodies were detected at higher dose levels; however, these did not appear to impact the effectiveness of cagrilintide and were not linked to serious allergic reactions.
BMI=Body mass index. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov

Structure's ACCG-2671

In December 2024, the company announced that its lead amylin development candidate would be the DACRA ACCG-2671, an oral small-molecule drug with daily dosing. The company discussed preclinical results from a study in DIO rats showing that this drug was comparable to cagrilintide in its effects on food consumption (based on a single dose) and weight loss (based on 28 days of treatment). At a dosage of 15 mg/kg, the treated rats lost roughly 15% of their body weight, although weight loss plateaued at about 21 days. The company plans to start a Phase I clinical trial by the end of the year, with results expected by the end of 2026. Phase II trials will study single and multiple ascending doses, both as monotherapy and in combination with their GLP-1 RA, GSBR-1290. The company also intends to use ACCG-2671 as the backbone for other DACRAs and selective amylin receptor agonists (SARAs) that it will develop; however, the sequence of ACCG-2671 has not been disclosed.

Viking's VK3006, VK3012, and VK3015

Preclinical data for Viking's DACRA program was presented in a poster at the 2024 annual American Diabetes Association scientific sessions. The company investigated several DACRAs, including VK3006, VK3012, and VK3015, in preclinical models and evaluated parameters pertaining to weight loss and glycemic control.

In terms of relative body weight change in diet-induced obese mice, VK3012 appeared to confer the highest maximum weight loss over a 24-day treatment period (10%), followed by VK3006 (7%) and cagrilintide (7%). In lean mice, a single injection of VK3012 also appeared to have the highest propensity to reduce appetite, food intake, and body weight, followed by VK3006 and cagrilintide.

For glycemic control, daily doses of VK3015, VK3012, VK3006, and cagrilintide performed similarly after one week of treatment (around 20% reduced blood glucose), although VK3015 and VK3012 exhibited longer durability compared with VK3006 and cagrilintide at the end of treatment (day 24). The numerically lower change for VK3006 could indicate a lower degree of persistence in the body over the period studied; this effect appears to be particularly prominent for cagrilintide. In addition, VK3012 demonstrated balanced amylin and calcitonin receptor agonism (roughly 1:1 with a slight bias toward amylin).

Eli Lilly's Colulintide

Colulintide is the recently proposed name for the DACRA that has been referred to as LY3541105 and DACRA QW II. It is a 32-amino-acid peptide (GSRS listing for colulintide; GSRS listing for LY3541105). Eli Lilly announced the discontinuation of this program during the fourth quarter 2024 earnings call.

Phase I trial of colulintide

The trial investigated the safety and efficacy of the asset, a dual amylin and calcitonin RA, in healthy volunteers and patients with overweight or obesity over 26 weeks. The study was completed in August 2024. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05380323). A detailed summary of the Phase I trial design of colulintide in overweight or obesity is presented in exhibit 48.

Exhibit 48
Eli Lilly and Company
Trial Design of Colulintide in Healthy Volunteers and Patients With Overweight or Obesity Without Type 2 Diabetes

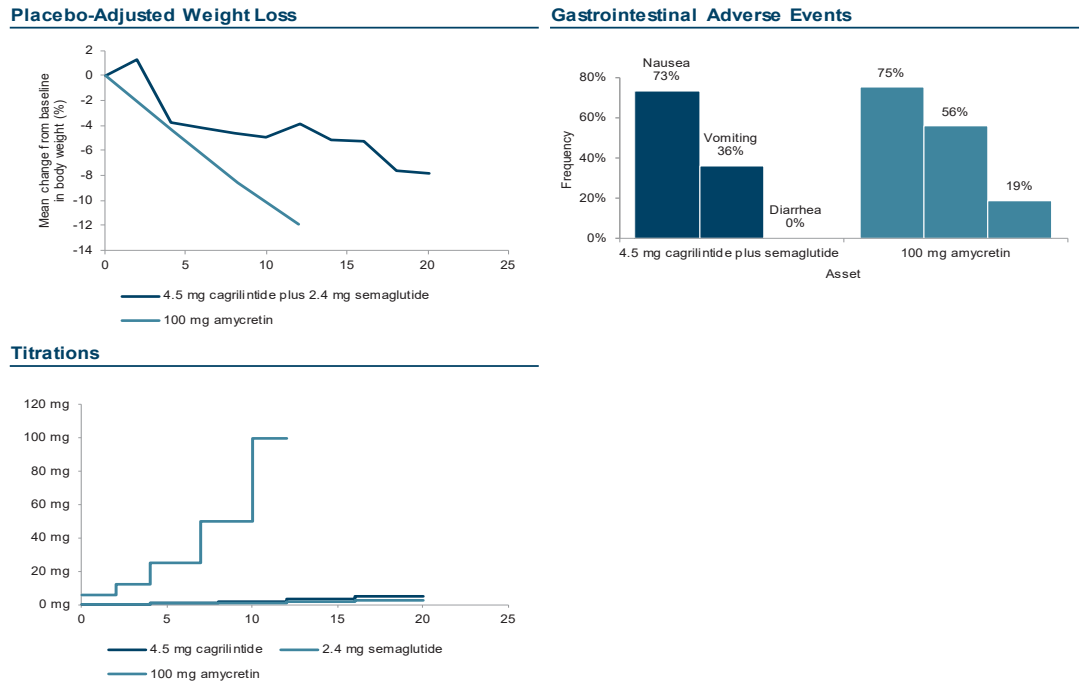
Phase I Trial (NCT05380323)						
Sponsor	Eli Lilly and Company					
Mechanism of Action	Dual amylin and calcitonin receptor agonist					
Enrollment Criteria	Part A: BMI ≥ 18.5 kg/m² and BMI ≤ 32 kg/m² Parts B and C: BMI ≥ 27 kg/m² and BMI ≤ 40 kg/m² HbA1c < 6.5%					
Study Arms	part A: colulintide SAD	part B: colulintide MAD	part C: escalating doses of colulintide	part A: placebo	part B: placebo	part C: placebo
Enrollment	205 patients					
Primary Endpoint	**Safety and tolerability**					
Secondary Endpoints	Weight loss at 26 weeks (part B only) Pharmacokinetic parameters					
Trial Status	Discontinued by Eli Lilly					

BMI=Body mass index. MAD=Multiple-ascending dose. SAD=Single-ascending dose.
Sources: Company reports and clinicaltrials.gov

Duotherapy: A Mix of a DACRA and a GLP-1 Receptor Agonist

Often, more robust weight loss occurs when a treatment modulates multiple pathways. One way to accomplish this is to mix an amylin and calcitonin RA with a GLP-1 RA. The goal is to address simultaneously both hyperglycemia and excess body weight. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top doses of GLP-1 and dual amylin and calcitonin RAs including CagriSema and amycretin is presented in exhibit 49.

Exhibit 49
Combined Weight Loss, Adverse Events, and Titration Curves of GLP-1 and Dual Amylin and Calcitonin Receptor Agonists



GLP-1=Glucagon-like peptide 1.
Sources: Phase II CagriSema results, company documents

Novo Nordisk's CagriSema

The asset is a dual subcutaneous injectable of 2.4 mg semaglutide and 2.4 mg cagrilintide, representing the combination of a GLP-1 RA and a dual amylin and calcitonin receptor agonist (DACRA) with a once-weekly dosing schedule in clinical development in overweight or obesity and/or type 2 diabetes. Combined dual amylin and calcitonin receptor and GLP-1 receptor agonism in CagriSema may lead to increased weight-loss efficacy in treated patients compared with the use of individual GLP-1 receptor or dual amylin and calcitonin RAs alone.

Phase Ib trial of CagriSema

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03600480).

Efficacy. In results published in May 2021, once-weekly cagrilintide plus semaglutide demonstrated dose-dependent placebo-adjusted weight loss up to 7% in overweight or obesity at 20 weeks. Patients in the top three cagrilintide dose cohorts also experienced placebo-adjusted improvements (reductions) in HbA1c. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 10% placebo-adjusted weight loss at 20 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with CagriSema led to up to 83% nausea (in the second-highest dose group), 17% diarrhea (dose-independent), and 75% vomiting (in the second-highest dose group). Serious treatment-emergent adverse events were elevated in the arm including 1.2 mg cagrilintide, at 8%, with no serious adverse events in other arms. In addition, the discontinuation rate occurred in the high single digits in the arms containing 0.16 mg and 1.2 mg cagrilintide, with no discontinuations in other arms. A detailed summary of the Phase Ib trial results of CagriSema in overweight or obesity is presented in exhibit 50 (Enebo et al., *The Lancet* 2021).

Exhibit 50
Novo Nordisk A/S
20-Week Results of Cagrilintide and Semaglutide (CagriSema) in Overweight or Obesity Without Type 2 Diabetes

Phase Ib Trial (NCT03600480)

Sponsor	Novo Nordisk A/S						
Mechanism of Action	semaglutide: GLP-1 receptor agonist cagrilintide: dual amylin and calcitonin receptor agonist						
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² Otherwise healthy						
Baseline Patient Characteristics	Age=43 years Male=67% Body weight=93 kg BMI=31 kg/m² HbA1c=5.4%	Age=38 years Male=58% Body weight=93 kg BMI=31 kg/m² HbA1c=5.3%	Age=40 years Male=50% Body weight=95 kg BMI=33 kg/m² HbA1c=5.4%	Age=41 years Male=50% Body weight=95 kg BMI=33 kg/m² HbA1c=5.5%	Age=43 years Male=42% Body weight=92 kg BMI=32 kg/m² HbA1c=5.2%	Age=37 years Male=73% Body weight=98 kg BMI=33 kg/m² HbA1c=5.2%	Age=41 years Male=67% Body weight=100 kg BMI=32 kg/m² HbA1c=5.4%
Study Arms	0.16 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	0.30 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	0.60 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	1.2 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	2.4 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	4.5 mg cagrilintide once weekly + 2.4 mg semaglutide once weekly	Pooled placebo + 2.4 mg semaglutide once weekly
Enrollment	12 patients	12 patients	12 patients	12 patients	12 patients	11 patients	24 patients
Titration Schedule	0.01 mg cagrilintide + 0.15 mg semaglutide for 4 weeks; 0.02 mg cagrilintide + 0.30 mg semaglutide for 4 weeks; 0.04 mg cagrilintide + 0.60 mg semaglutide for 4 weeks; 0.08 mg cagrilintide + 1.2 mg semaglutide for 4 weeks; 0.16 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	0.02 mg cagrilintide + 0.15 mg semaglutide for 4 weeks; 0.04 mg cagrilintide + 0.30 mg semaglutide for 4 weeks; 0.08 mg cagrilintide + 0.60 mg semaglutide for 4 weeks; 0.16 mg cagrilintide + 1.2 mg semaglutide for 4 weeks; 0.30 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	0.04 mg cagrilintide + 0.15 mg semaglutide for 4 weeks; 0.08 mg cagrilintide + 0.30 mg semaglutide for 4 weeks; 0.16 mg cagrilintide + 0.60 mg semaglutide for 4 weeks; 0.30 mg cagrilintide + 1.2 mg semaglutide for 4 weeks; 0.60 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	0.08 mg cagrilintide + 0.15 mg semaglutide for 4 weeks; 0.16 mg cagrilintide + 0.30 mg semaglutide for 4 weeks; 0.30 mg cagrilintide + 0.60 mg semaglutide for 4 weeks; 0.60 mg cagrilintide + 1.2 mg semaglutide for 4 weeks; 1.2 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	0.16 mg cagrilintide + 0.15 mg semaglutide for 4 weeks; 0.30 mg cagrilintide + 0.30 mg semaglutide for 4 weeks; 0.60 mg cagrilintide + 0.60 mg semaglutide for 4 weeks; 1.2 mg cagrilintide + 1.2 mg semaglutide for 4 weeks; 2.4 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	0.45 mg cagrilintide + 0.24 mg semaglutide for 4 weeks; 0.90 mg cagrilintide + 0.50 mg semaglutide for 4 weeks; 1.9 mg cagrilintide + 1.0 mg semaglutide for 4 weeks; 3.2 mg cagrilintide + 1.7 mg semaglutide for 4 weeks; 4.5 mg cagrilintide + 2.4 mg semaglutide for 4 weeks	
Change in Body Weight at Week 20	-8% placebo-adjusted: +1%	-10% placebo-adjusted: ~-1%	-11% placebo-adjusted: -1%	-16% placebo-adjusted: -6%	-17% placebo-adjusted: -7%	-15% placebo-adjusted: -7%	Pooled placebo matched to cohorts 1-5: -10% Matched placebo to cohort 6: -8%
TEAE Frequency	**92%**	**100%**	**92%**	**100%**	**100%**	**100%**	**96%**
TEAEs Affecting ≥25% of Patients	Early satiety 8% Decreased appetite 58% Nausea 50% Vomiting 0% Injection site reaction 33% Fatigue 0% Headache 8% Dyspepsia 17% Dizziness 0% Diarrhea 0% Abdominal pain 8%	25% 67% 75% 33% 33% 0% 50% 33% 25% 17% 25%	33% 58% 50% 17% 17% 25% 25% 42% 17% 17% 8%	67% 50% 50% 8% 17% 25% 17% 17% 0% 8% 8%	67% 100% 83% 75% 50% 0% 17% 33% 0% 17% 8%	91% 82% 73% 36% 27% 27% 18% 18% 0% 0% 0%	38% 58% 33% 13% 29% 4% 25% 33% 8% 38% 8%
Serious TEAE Frequency	0%	0%	0%	8%	0%	0%	0%
TEAEs Leading to Discontinuation	8%	0%	0%	8%	0%	0%	0%

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, Enebo et al., The Lancet 2021, clinicaltrials.gov

Next steps. CagriSema is being developed in the six-trial Phase III REDEFINE program, consisting of REDEFINE 1 through REDEFINE 6. REDEFINE 1 is testing once-weekly CagriSema (2.4 mg cagrilintide/2.4 mg semaglutide) compared with once-weekly 2.4 mg semaglutide or once-weekly 2.4 mg cagrilintide monotherapies or placebo in 3,400 patients with obesity or overweight with at least one weight-related comorbidity (excluding type 2 diabetes). The study includes a dose escalation period of 16 weeks, a maintenance period of 1 year, and a subsequent extension phase of around one more year (45 weeks) for the CagriSema and placebo arms.

Phase III REDEFINE 1 trial of CagriSema

Initial data from the Phase III REDEFINE 1 trial were released in December 2024.

Efficacy. After 68 weeks, the treatment policy estimand group (i.e., regardless of treatment adherence) achieved a placebo-adjusted weight loss of around 17% when taking CagriSema, compared with roughly 9% when taking 2.4 mg cagrilintide and 12% for 2.4 mg Wegovy.

Safety and tolerability. Novo did not outline detailed tolerability data in the press release, making direct comparison with Zepbound difficult. However, less than 6 of 10 patients (57%) were able to titrate up to the highest dose for CagriSema, versus 83% with cagrilintide or 70% with Wegovy, which we believe suggests a challenging tolerability profile. We argue that the tolerability component is the major driver for investors' bearish take on REDEFINE 1 since the most significant unmet medical need in the obesity space is the ability to maintain patient adherence to GLP-1–based therapies.

In our view, investors were increasingly enthusiastic about the prospect of modulating amylin as a means to provide robust weight loss with reduced GLP-1–specific lower gastrointestinal side effects. However, the tolerability headwinds demonstrated by REDEFINE 1 could challenge the feasibility of GLP-1 and amylin combinations. We surmise that going forward, a more potent dual amylin and calcitonin RA (also referred to as DACRA) without a GLP-1 component, or a GLP-1/GIP dual agonist in combination with a DACRA (with the GIP agonism component potentially counteracting lower gastrointestinal adverse events) is reasonable (Novo Nordisk press release, Dec. 2024). A detailed summary of the Phase III REDEFINE 1 trial results of CagriSema compared with the Phase III SURMOUNT-1 trial results of Zepbound in overweight or obesity is presented in exhibit 51.

Exhibit 51
72-Week Results of Zepbound and 68-Week Results of CagriSema in Patients With Obesity or Overweight Without Type 2 Diabetes

Trial	Sponsor	Mechanism of Action	Disease	Study Arms	Enrollment	Baseline Patient Characteristics	Change in Body Weight
Phase III SURMOUNT-1 (NCT04184622)	Eli Lilly and Company	Dual receptor agonist of GLP-1 and GIP	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%	15 mg Zepbound once weekly	2,539 patients (1:1:1:1 randomization)	BMI=37-38 kg/m² Body weight=103-106 kg Male=32%-33% HbA1c=5.6% Prediabetes=39%-42%	**-21% p<0.001** **Placebo-Adjusted: -18%**
				10 mg Zepbound once weekly			**-20% p<0.001** **Placebo-Adjusted: -16%**
				5 mg Zepbound once weekly			-15% *p* <0.001 Placebo-adjusted: **-12%**
				placebo			-3%
Phase III REDEFINE 1 (NCT05567796)	Novo Nordisk A/S	Wegovy: GLP-1 receptor agonist cagrilintide: dual amylin and calcitonin receptor agonist	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%	2.4 mg cagrilintide once weekly + 2.4 mg Wegovy once weekly	3,417 patients (1:1:1:1 randomization)	Body weight=107 kg	-20% Placebo-adjusted: **-17%**
				2.4 mg Wegovy once weekly			**-15%** **Placebo-Adjusted: -12%**
				2.4 mg cagrilintide once weekly			**-12%** **Placebo-Adjusted: -9%**
				placebo			-3%

*Patients had either hypertension, dyslipidemia, obstructive sleep apnea, and/or cardiovascular disease.

For SURMOUNT 1, Zepbound was administered utilizing a 20-weeks-long dose escalation titration period beginning at 2.5 mg once weekly and increasing by 2.5 mg every 4 weeks to attain a maintenance dose of up to 15 mg once weekly by week 20. The final dose levels of Zepbound were then administered once weekly for the remaining 52 weeks. Change in body weight was assessed at week 72.

For REDEFINE 1, cagrilintide was administered using a 16-week dose escalation titration consisting of 0.25 mg cagrilintide once weekly for 4 weeks, 0.5 mg cagrilintide for 4 weeks, 1.0 mg cagrilintide once weekly for 4 weeks, 1.7 mg cagrilintide once weekly for 4 weeks, and 2.4 mg cagrilintide once weekly for the remaining 52 weeks. Wegovy was administered using a 16-week dose titration consisting of 0.25 mg Wegovy once weekly for 4 weeks, 0.5 mg Wegovy once weekly for 4 weeks, 1.0 mg Wegovy once weekly for 4 weeks, 1.7 mg Wegovy once weekly for 4 weeks, and 2.4 mg Wegovy once weekly for the remaining 52 weeks. Change in body weight was assessed at week 68.

REDEFINE 1 allowed flexible dosing, in which patients could change their dosing during the trial. At 68 weeks, around 57% of patients receiving CagriSema were at the highest dose compared with around 83% for 2.4 mg cagrilintide and nearly 70% for 2.4 mg Wegovy.

BMI=Body mass index. GIP=Glucose-dependent insulinotropic peptide. GLP-1=Glucagon-like peptide-1. HbA1c=Glycated hemoglobin.

Sources: Company reports, clinicaltrials.gov

REDEFINE 2 is testing once-weekly CagriSema compared with placebo in obesity or overweight and type 2 diabetes. Initial data from the Phase III REDEFINE 2 trial are slated for release in the first quarter of 2025. Next, REDEFINE 3 is a cardiovascular outcomes trial (CVOT) testing once-weekly CagriSema compared with placebo in overweight or obesity with or without type 2 diabetes with established cardiovascular disease.

REDEFINE 4 is a head-to-head trial testing once-weekly CagriSema compared with once-weekly Zepbound with obesity without type 2 diabetes. In addition, REDEFINE 5 is a head-to-head trial testing once-weekly CagriSema compared with once-weekly Wegovy/Ozempic in patients of East Asian descent with overweight and at least two weight-related comorbidities (including type 2 diabetes) or obesity with at least one weight-related comorbidity (including type 2 diabetes).

REDEFINE 6 is testing once-weekly CagriSema compared with once-weekly Wegovy/Ozempic or placebo in patients of Chinese descent with obesity or overweight with at least one weight-related comorbidity (including type 2 diabetes).

According to clinicaltrials.gov, these trials have primary completion dates of October 2024 (REDEFINE 1), January 2025 (REDEFINE 2, REDEFINE 5, and REDEFINE 6), August 2025 (REDEFINE 4), and September 2027 (REDEFINE 3). For patient enrollment criteria and trial design, refer to clinicaltrials.gov.

A Single-Molecule Dual Agonist to the GLP-1 and Amylin Receptors

A single pill that modulates multiple weight loss pathways has the appeal of convenience and an absence of needles. To date, there is one oral medication in clinical trials, dubbed amycretin, that combines an amylin RA and a GLP-1 RA into a co-agonist. An injectable version of the asset is also being tested.

Novo Nordisk's Amycretin
The asset, a peptide-based dual GLP-1 and amylin RA, was examined in two Phase I trials in men of Japanese descent with overweight or obesity (NCT06049329) and in male and female patients regardless of descent with overweight or obesity (NCT05369390). Similar to Rybelsus, investigators used sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) technology, a small fatty-acid derivative, to achieve amycretin's oral formulation; other detailed elements of amycretin's structure have not been disclosed.

Phase I trial of oral amycretin
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05369390).

Efficacy. In first-in-human results presented at the European Association for the Study of Diabetes 2024 meeting, once-daily amycretin demonstrated dose-dependent placebo-adjusted weight loss up to 12% in overweight or obesity at 12 weeks. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 6% placebo-adjusted weight loss at 12 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with amycretin led to up to 75% nausea, 19% diarrhea, and 56% vomiting, all of which exhibited dose-dependent relationships. No serious treatment-emergent adverse events or study discontinuations were reported for parts C1 or C2. However, one serious adverse event occurred in part D of the trial related to acute cholestasis, and one serious adverse event occurred in part B of the study related to diabetic ketoacidosis. In the patient who experienced diabetic ketoacidosis, blood samples drawn beforehand indicated the presence of β cell-specific autoantibodies; that patient was subsequently diagnosed with type 1 diabetes. Investigators

also indicated that amycretin given as a single dose at levels of at least 18 mg and given for 10 consecutive days at levels of at least 12 mg was poorly tolerated by patients. A detailed summary of the Phase I trial results of amycretin in overweight or obesity is presented in exhibit 52.

Amycretin is undergoing testing in three trials in overweight or obesity (NCT06478563; NCT06064006; NCT06461039) and one trial for type 2 diabetes (NCT06542874). Another Phase I trial in patients with overweight or obesity with or without impaired kidney function is not yet recruiting (NCT06559527). It is also being tested in a Phase II trial in type 2 diabetes and in a Phase II trial in overweight or obesity.

Exhibit 52
Novo Nordisk A/S
12-Week Trial Multiple-Ascending-Dose Results of Amycretin in Overweight or Obesity Without Type 2 Diabetes

Phase I Trial (NCT05369390)

Sponsor	Novo Nordisk A/S		
Mechanism of Action	Combined GLP-1 and dual amylin and calcitonin receptor agonist		
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² HbA1c < 6.5%		
Baseline Patient Characteristics	Age=38 years Male=75% Body weight=92 kg BMI=31 kg/m²	Age=38 years Male=56% Body weight=90 kg BMI=32 kg/m²	Age=42 years Male=92% Body weight=88 kg BMI=30 kg/m²
Study Arms	Part C1: 50 mg amycretin once daily	Part C2: 100 mg amycretin once daily	placebo
Enrollment	16 patients	16 patients	12 patients*
Titration Schedule	3 mg for 2 weeks; 6 mg for 2 weeks; 12 mg for 3 weeks; 25 mg for 3 weeks; 50 mg for 2 weeks	6 mg for 2 weeks; 12 mg for 2 weeks; 25 mg for 3 weeks; 50 mg for 3 weeks; 100 mg for 2 weeks	
Change in Body Weight at Week 12	-10% placebo-adjusted: -9%	-13% placebo-adjusted: -12%	-1%
TEAE Frequency	**75%**	**94%**	**33%**
TEAEs**	**Decreased appetite 56%** **Nausea 31%** **Vomiting 38%** **Headache 25%** **Dyspepsia 25%** **Fatigue 19%** **Constipation 13%** **Diarrhea 6%** **Early satiety 31%**	**81%** **75%** **56%** **44%** **38%** **38%** **25%** **19%** **19%**	**17%** **8%** **0%** **17%** **0%** **8%** **8%** **0%** **17%**
TEAEs Leading to Discontinuation		**0%**	

*Placebo group included four patients from part D, which shares the same titration schedule as part C1 with an optimized formulation of amycretin.

**One serious adverse event occurred in part D of the trial related to acute cholestasis, and one serious adverse event occurred in part B of the study related to diabetic ketoacidosis. However, blood samples drawn beforehand from the patient who experienced diabetic ketoacidosis indicated autoantibodies for beta cells, and that patient was subsequently diagnosed with type 1 diabetes.

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin. TEAEs=treatment-emergent adverse events.

Sources: Company reports, clinicaltrials.gov

Phase Ib/IIa trial of subcutaneous amycretin

We emphasize three important caveats from Novo's data release. First, the trial observed an average weight *increase* from placebo patients, which is rare in larger obesity studies (weight *loss* is typically observed). Second, no safety data were released, which we argue could have better contextualized amycretin's clinical profile for investors. Third, Novo reported results based on those who adhered to treatment (no treatment discontinuations for the full trial; also known as efficacy estimand), which has the potential to inflate treatment effect in the real-world setting (drug labels list treatment estimand that incorporates data from all intent-to-treat patients). To establish a common ground, we used efficacy estimand for all cross-trial comparisons below. For trial design and enrollment criteria, refer to clinicaltrials.gov (NCT06064006).

Efficacy. Subcutaneous amycretin demonstrated dose-dependent placebo-adjusted weight loss up to 24% in overweight or obesity at 36 weeks. As mentioned above, the observed placebo weight gain could have inflated amycretin weight loss magnitude. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 15% placebo-adjusted weight loss at 36 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons. A detailed summary of the Phase Ib/IIa trial results of subcutaneous amycretin in overweight or obesity is presented in exhibit 53.

Exhibit 53
Novo Nordisk A/S
36-Week Results of Subcutaneous Amycretin in Overweight or Obesity Without Type 2 Diabetes

	Phase Ib/IIa Trial (NCT06064006)			
Sponsor	Novo Nordisk A/S			
Mechanism of Action	Combined GLP-1 and dual amylin and calcitonin receptor agonist			
Enrollment Criteria	BMI ≥ 27 kg/m² and < 40 kg/m² HbA1c < 6.5%			
Baseline Patient Characteristics	Body weight=93 kg			
Study Arms	1.25 mg amycretin once weekly for 20 weeks	5 mg amycretin once weekly for 28 weeks	20 mg amycretin once weekly for 36 weeks	placebo[1]
Enrollment	125 patients			
Titration Schedule	Undisclosed			
Change in Body Weight	At week 20: -10% placebo-adjusted: -12%	At week 28: -16% placebo-adjusted: -19%	At week 36: -22% placebo-adjusted: -24%	At weeks 20, 28, and 36: +2%
Common Adverse Events	Mostly mild to moderate gastrointestinal adverse events			

[1]Patients were randomized to receive either active treatment or placebo in each cohort.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin.
Sources: Company reports, clinicaltrials.gov

Cannabinoid Receptor Modulators

The cannabinoid type 1 receptor (CB1R or CB1 receptor) belongs to the family of G-protein coupled receptors (GPCRs). CB1R has both an orthosteric and allosteric binding site. Orthosteric binding is binding at the active site, in competition with the receptor's natural ligand, whereas allosteric binding occurs at a different site on the receptor, but nevertheless modulates its activity. CB1R is the most abundantly expressed GPCR in the brain. Broadly speaking, CB1R is expressed in both the central nervous system (CNS) and peripheral organs and tissues (both peripheral neurons and certain non-neuronal cells). The endogenous ligands for the receptor are endocannabinoids, which are neurotransmitters that serve as agonists to stimulate activation of CB1R upon binding. The endocannabinoids include certain lipids, such as arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl-sn-glycerol (2-AG), but the axis can also be activated by exogenous cannabinoids, such as the plant-derived tetrahydrocannabinol (THC, the psychoactive component in cannabis).

Within the CNS, CB1 receptor activity is linked to perception and regulation of pain, learning and memory, brain development, and other physiological properties. In contrast, CB1R activation in the periphery is linked to increased appetite and preservation of energy, among a number of other outcomes. Under obese or fasting conditions, the peripheral CB1R axis is activated and can lead to increased fat storage, which contributes to weight gain and is one of the key reasons why CB1R blockade is being investigated as a medicine for treating obesity.

Perhaps not surprisingly, inhibition of CB1R in the brain has been linked to psychiatric adverse events, an unfortunate feature of first-generation CB1R inverse agonists (drugs that reduce activity at a receptor below basal levels, the opposite of an agonist) that prevented further advancement of these candidates. An example of this was rimonabant, which was originally approved in a range of ex-U.S. countries but was withdrawn worldwide in 2008 due to these adverse events. These first-generation inverse agonists were small molecules, likely enabling them to cross the BBB and access CB1 receptors in the CNS. Therefore, the potential of CB1R inhibition for treating obesity is tied to targeting peripheral expression of the CB1 receptor while avoiding CNS-expressed CB1R.

In the periphery, CB1 receptors are expressed in many organ systems in the body, including the gastrointestinal system, adipose tissue, liver, pancreas, lungs, kidney, and skeletal muscle. The downstream effects of CB1R activation vary, depending on the type and location of the cells expressing the receptor. They range from delaying gastric emptying (thus impacting digestion), to increasing fatty acid synthesis in the liver, to both altering insulin secretion and contributing to insulin resistance in pancreatic cells, and to promoting systemic inflammation.

CB1R expression can also be upregulated under certain conditions, which makes more receptor molecules available for binding, or, conversely, downregulated. Again, the effects that have been observed are tissue-dependent. Within adipose tissue, upregulation leads to increases in de novo fatty acid synthesis and accumulation of triglycerides, along with decreases in lipolysis. De novo fatty acid synthesis is also increased by CB1R upregulation in the liver and pancreas, where fibrosis is also increased and insulin signaling is decreased. Metabolic disorders, such as obesity and diabetes, can result from these metabolic changes. For example, in the kidneys, upregulation elevates inflammation and fibrosis, which can contribute to chronic kidney disease. In mice, CB1R knockdown in the intestine leads to a reduction in caloric intake, and knockdown in fat tissue, the liver, or skeletal muscle prevents diet-induced obesity. When CB1R expression is knocked down in the adipose tissue of mice, it is very difficult for mice to gain body fat, even when fed a high-fat diet (in contrast, the high-fat diet induces considerable gains in body fat in CB1 wild-type mice). Therefore, blocking CB1R activation could have significant implications in reducing the likelihood of not only obesity but also other metabolic disorders.

The impact of the CB1R axis on hunger control is linked to changes in several key hormones that have receptors in the brain and play a role in regulating appetite. These hormones include leptin (secreted by fat cells), cholecystokinin (CCK), and ghrelin (the latter two secreted by enteroendocrine cells). Broadly speaking, secretion of leptin and/or CCK contributes to hunger reduction, while ghrelin secretion has the opposite effect of stimulating hunger. Focusing on leptin specifically, one of the key features of obesity is leptin resistance, which, based on studies in the diet-induced mouse model, can be reversed by CB1R antagonism. It is hypothesized that restoration of the leptin axis is an important component of establishing long-term weight control, and in fact inhibition of peripherally expressed CB1R is known to completely reverse leptin resistance. In animals fed a low-fat/standard diet (i.e., animals who likely retain leptin sensitivity), treating with leptin leads to reductions in weight and food intake. However, in animals consuming a high-fat diet, leptin treatment has no impact, suggesting that they have acquired resistance to leptin's effect. Administration of an antagonist for peripheral CB1R to these animals, however, restores leptin's ability to induce weight loss. CB1R antagonism also stimulates secretion of CCK while reducing secretion of ghrelin, with the net impact of reducing hunger cues.

Inhibiting the CB1R axis can also play a role in promoting the breakdown of fat, increasing expenditure of energy, and restoring the balance of cytokines secreted by fat tissue. These cytokines are known as adipokines; they can have both beneficial and detrimental effects and are often out of balance in obese patients. In addition, inhibition of CB1R in the liver is linked to restored insulin sensitivity, which is important for patients who are pre-diabetic, and also reduces liver fat and steatosis and the degree of leptin resistance. In the muscle, blocking CB1R can also lead to improved endurance and the ability to run for longer periods of time, based on animal models, and is again associated with high energy expenditure and the ability to eat more while maintaining a normal weight.

An interesting feature of CB1R inhibition, according to preclinical studies in mice, is that even though caloric intake is reduced, energy expenditure actually increases, in contrast to pure caloric restriction, where energy expenditure tends to decrease. In preclinical mouse model studies, even when mice are fed the same diet, those with CB1R knockout in adipose tissue gain less weight compared with animals with wild-type CB1R. Therefore, the weight loss observed from CB1R inhibition is attributed to not only caloric reduction, but also increased energy expenditure, which could distinguish this modality from appetite suppression medicines, such as incretin mimetics. This also supports a combination approach with incretin mimetics, such as GLP-1 RAs, as the additional impact of energy expenditure is likely to be additive with the GLP-1 mechanism.

Compared with other targets investigated for obesity, CB1R exhibits a potentially competitive profile as a target given its broad impact across a range of key characteristics. We highlight that CB1R is one of the only targets that preserves lean muscle mass. While anti-obesity drugs that target myostatin also provide this feature, they do not provide features such as decreased appetite that are likely key to stimulating weight loss. Therefore, while CB1R inhibition can be combined with and would likely complement other targets, there is also potential for CB1R inverse agonists to serve as monotherapies and still be highly effective.

While development of first-generation CB1R inverse agonists in obesity was halted due to psychiatric adverse events, second-generation CB1R inverse agonists that target CB1 receptors only in the periphery may exhibit reduced or a lack of neuropsychiatric adverse events while offering weight loss with muscle preservation and favorable tolerability compared with Wegovy. Regarding the greatest weight loss observed for the class, monlunabant demonstrated up to 6% placebo-adjusted weight loss at 16 weeks in Phase IIa results in obesity and metabolic syndrome.

First-Generation CB1R Inverse Agonists: Sanofi's Rimonabant, Merck's Taranabant, Pfizer's Otenabant, Sanofi's Surinabant, and Bristol Myers's Ibipinabant

The small-molecule CBIR inverse agonist rimonabant was developed by Sanofi. It was first approved (under the name Acomplia) in Europe in 2006 and later approved in a number of other countries. However, in the United States its NDA, using the brand name Zimulti, was rejected by the FDA in 2007. Based on the Phase III RIO-North America trial, the therapy led to placebo-adjusted weight loss of about 1% and 5% at 1 year for the 5 mg and 20 mg doses, respectively. In addition, there were no observed changes in lean muscle mass, indicating that weight loss was primarily due to fat loss. After the FDA rejected the application, the agent was removed worldwide from the market in 2008. In the same time frame, Merck stopped Phase III development of taranabant and Pfizer stopped Phase III development of otenabant, while Phase II development of Sanofi's surinabant and Bristol Myers Squibb's ibipinabant was also halted. In these cases, cessation of development (or removal from the market, in the case of rimonabant) was related to serious psychiatric adverse events, including anxiety, depression, and suicidal ideation, likely resulting from the ability of the drugs to penetrate the brain.

Phase III RIO-North America trial of rimonabant
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT00029861).

Efficacy. Once-daily rimonabant demonstrated dose-dependent placebo-adjusted weight loss up to 5% in overweight or obesity at 1 year; at 2 years, patients who continued on the top dose regained around 2% placebo-adjusted body weight. Patients receiving rimonabant also demonstrated dose-dependent improvements in high-density lipoprotein (increases) and total cholesterol (decreases).

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated 18% and 20% placebo-adjusted weight loss at 48 and 72 weeks, respectively, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Represented as a proportion of any-grade treatment-emergent adverse events, treatment with rimonabant in the first year led to up to 11% nausea (dose-dependent) and 7% diarrhea (in second-highest dose group). Serious treatment-emergent adverse events were roughly balanced between arms, occurring at up to 5% in the 20 mg group. In addition, the discontinuation rate exhibited a dose-dependent relationship, occurring up to a midteens percentage, which was roughly two times the placebo rate. Among discontinuations in the first year, psychiatric adverse events, consisting of either depressed mood, anxiety, irritability, or insomnia, led to rimonabant dose-dependent discontinuation rates around two to three times the placebo arm rate, all in the low to midsingle digits.

In the patient groups that received the same treatment over 2 years, frequencies of serious treatment-emergent adverse events and adverse events leading to discontinuation were roughly balanced with the placebo arm (all in the midsingle digits). Investigators observed depressed mood in around 1% of patients across trial arms and dose-dependent anxiety in up to 1% of patients, with no reports of anxiety in the placebo arm. Furthermore, the study reported two deaths, related to gunshot or cardiac arrest in a patient with past long QT syndrome. A detailed summary of the Phase III RIO-North America trial results of rimonabant in overweight or obesity is presented in exhibit 54 (Pi-Sunyer et al., *JAMA* 2006).

Exhibit 54
Sanofi-Aventis
104-Week Results of Rimonabant in Overweight or Obesity Without Type 2 Diabetes

Phase III RIO-North America Trial (NCT00029861)

Sponsor	Sanofi-Aventis		
Mechanism of Action	CB1 receptor inverse agonist		
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%		
Baseline Patient Characteristics	Age=44 years Male=20% Body weight=106 kg BMI=38 kg/m²	Age=46 years Male=19% Body weight=103 kg BMI=37 kg/m²	Age=45 years Male=19% Body weight=105 kg BMI=38 kg/m²
Study Arms	5 mg rimonabant once daily for 104 weeks[1]	20 mg rimonabant once daily for 104 weeks[1]	placebo
Enrollment	1,214 patients	1,219 patients	607 patients
Change in Body Weight at Week 52	**-3%** **placebo-adjusted: -1%** ***p*<0.001**	**-6%** **placebo-adjusted: -5%** ***p*<0.001**	**-2%**
Placebo-Adjusted Change in Body Weight at Week 104	**-1%** ***p*=0.02**	**-3%** ***p*<0.001**	
Patients Reaching ≥5% and ≥10% Weight Loss at Week 52	26% (*p*=0.004) 11% (*p*=NS)	49% (*p*<0.001) 25% (*p*<0.001)	20% 9%
Patients Reaching ≥5% and ≥10% Weight Loss at Week 104		40% (*p*<0.001) 17% (*p*<0.001)	19% 8%
TEAE Frequency	83%	86%	82%
TEAEs Affecting ≥10% of Patients at Week 522	URTI 16% Nasopharyngitis 16% Nausea 7% Sinusitis 9%	19% 17% 11% 9%	15% 14% 6% 12%
Psychiatric TEAEs at Week 52[2]	Anxiety 3% Insomnia 3% Depressed mood 4%	6% 6% 5%	2% 4% 3%
Nervous System TEAEs at Week 52[2]	Headache 9% Dizziness 5%	8% 6%	10% 4%
Serious TEAE Frequency at Week 52[2]	4%	5%	4%
TEAEs Leading to Discontinuation[2]	9%	13%	7%

*Patients had either hypertension and/or dyslipidemia.

[1]Rimonabant-treated patients were re-randomized at year 1 to receive placebo or continued to receive the same dose. Placebo-group patients continued to receive placebo. Patients who received the same treatment both years include: placebo (298 patients), 5 mg (300 patients), and 20 mg (333 patients).

[2]Out of 1,013 patients (5 mg), 1,042 patients (20 mg), and 498 patients (placebo) evaluable.

BMI=Body mass index. CB1=Cannabinoid-1 receptor. HbA1c=Glycated hemoglobin. RIO=Rimonabant in obesity. TEAEs=Treatment-emergent adverse events. URTI=Upper respiratory tract infection.

Sources: Company reports, Pi-Sunyer et al., JAMA 2006, clinicaltrials.gov.

As mentioned, rimonabant had originally been approved by the EMA in 2006 following the positive Phase III RIO-Europe studies that began in 2001 (NCT00386061). However, after reviewing post-marketing safety data for rimonabant, the EMA's Committee for Medicinal Products for Human Use determined that serious psychiatric disorders may have been more common in the observed greater population than the rates observed in the RIO trials. In a similar vein, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) wrote that taking rimonabant roughly doubled the risk of psychiatric disorders compared with receiving placebo. In June 2007, the regulatory application for rimonabant was rejected by the FDA; the agency cited the drug's potential links to suicidal ideation as its justification. Further reviews by the EMA led the agency to withdraw its marketing authorization for rimonabant in January 2009. No other CB1 antagonists have received marketing approval since (Sayburn *BMJ* 2008; Van Gaal et al., *Diabetes Care* 2008; Sam et al., *J Obes* 2011; Crater et al., *Diabetes Obes Metab* 2023; Cohen et al., *Obesity [Silver Spring]* 2024).

Next-Generation CB1R Inverse Agonists

Second-generation CB1R modulators, which began development shortly after the withdrawal of rimonabant, are designed to be peripherally restricted and avoid, or at least reduce, access to the CNS by minimizing penetration of the blood–brain barrier (BBB). In theory, this should avoid the detrimental safety issues associated with first-generation inverse agonists. However, CB1 receptors are also present in at least one area of the brain that is not protected by the BBB, namely the area postrema (AP) (Haspula & Clark, *Int'l J. Mol. Sci.* 2020).

The second-generation class of CB1R-related small-molecule drugs that were designed to avoid penetration of the BBB and work only in the periphery were often structured with the addition of a polar group *(*Cinar, et al. *Pharmacology & Therapeutics* 2020). Whereas rimonabant was a three-arm molecule, many of the second-generation drugs had a fourth arm branching out from the center, which also allowed for the possibility of additional interactions with amino acids in the binding pocket (Shivshankar, et al. *IJMS* 2024).

Novo Nordisk's Monlunabant

An example of such a four-arm modulator is monlunabant, an inverse agonist. The drug has been under development by Novo Nordisk since its 2023 acquisition of Inversago Pharma (where the compound was referred to as INV-202).

As noted, first-generation CB1R inverse agonists that were also CNS-penetrant induced weight reduction, reduced insulin resistance, and improved lipid profiles; however, they were also linked to worsening anxiety and depression, which led to discontinuation of their development. By restricting exposure to peripheral tissues, INV-202/monlunabant has been dosed as high as 200 times the predicted therapeutic dose in nonhuman primates without psychotropic adverse effects.

Phase Ib trial of INV-202

Results of the trial were presented in poster format at the 83rd American Diabetes Association scientific sessions held in 2023 and were published in 2024. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05282446).

Efficacy. Once-daily INV-202 demonstrated placebo-adjusted weight loss of around 4% in metabolic syndrome at roughly 4 weeks. Patients receiving INV-202 also demonstrated statistically significant improvements (reductions) in HbA1c levels and low-density lipoprotein cholesterol. In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with INV-202 led to 35% nausea, 25% diarrhea, 25% vomiting, 40% nervous system disorders (including 5% fainting). Four subjects, or 20% of patients, receiving INV-202 and one receiving placebo reported CNS adverse events of interest, including either irritability, insomnia, and/or feeling depressed in the INV-202 group and nervousness in the placebo group. These events will be important to understand and monitor as INV-202 moves into larger trials. No suicidality signal was recorded in the trial. In addition, no serious treatment-emergent adverse events or adverse events leading to discontinuation were reported (Crater et al., *Diabetes Obes. Metab.* 2024).

Phase IIa trial of monlunabant

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05891834).

Efficacy. In results announced in September 2024, once weekly monlunabant demonstrated roughly 6% placebo-adjusted weight loss in obesity and metabolic disorder at 16 weeks. The press release communicating the top-line results indicated that some additional weight loss was achieved at monlunabant dose levels greater than 10 mg, though specific details were not disclosed. Weight loss figures were based on the hypothetical estimand, as if all patients had adhered to treatment.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 8% placebo-adjusted weight loss at 16 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. The most frequently experienced TEAEs were gastrointestinal, most of which were mild to moderate and occurred in a dose-dependent fashion. Investigators also reported mild to moderate neuropsychiatric adverse events including anxiety, irritability, and sleep disturbances. Observed neuropsychiatric adverse events occurred more frequently in a dose-dependent manner in the monlunabant arms compared with placebo. Researchers did not report any serious neuropsychiatric adverse events.

Next steps. A Phase II study designed to assess the efficacy, safety, tolerability, and pharmacokinetic parameters of INV-202/monlunabant in diabetic kidney disease due to either type 1 diabetes mellitus or type 2 diabetes mellitus was conducted from 2022 to 2024 (NCT05514548). Results have not been announced.

Novo Nordisk recently conducted a Phase I research study investigating safety and concentration in the blood over 21 days after one dose of monlunabant in healthy weight Japanese and Caucasian men. However, results have not yet been posted (NCT06542536).

In addition, based on the results of the Phase IIa trial described above, the company aims to initiate a larger Phase IIb trial in obesity this year. The trial will test the safety profile and dosing of monlunabant over a longer time course in a global patient population. A detailed summary of the Phase IIa trial results of monlunabant in obesity and metabolic syndrome is presented in exhibit 55 (Novo Nordisk September 2024 press release).

Exhibit 55
Novo Nordisk A/S
16-Week Results of Monlunabant in Obesity and Metabolic Syndrome Without Type 2 Diabetes

Phase IIa Trial (NCT05891834)

Sponsor	Novo Nordisk A/S			
Mechanism of Action	CB1 receptor inverse agonist			
Enrollment Criteria	BMI ≥ 30 kg/m² with at least three weight-related characteristics* HbA1c < 6.5%			
Baseline Patient Characteristics	Body weight=110 kg			
Study Arms	10 mg monlunabant once daily for 16 weeks	20 mg monlunabant once daily for 16 weeks	50 mg monlunabant once daily for 16 weeks	placebo
Enrollment	243 patients			
Change in Body Weight at Week 16[1]	**-6%** **placebo-adjusted: -6%**			**-1%**
Gastrointestinal TEAEs	The most frequent adverse events Most were mild to moderate and were dose dependent.			
Neuropsychiatric TEAEs	Mild to moderate anxiety, irritability, and sleep disturbances occurred more frequently in a dose-dependent manner in the monlunabant arms compared with placebo.			
Serious TEAEs	No serious neuropsychiatric adverse events were observed.			

*Patients had at least three of the following: 1) increased waist circumference (males≥40 inches; females≥35 inches), 2) fasting glucose≥100 mg/dL or an HbA1c > 5.7%, 3) triglycerides ≥ 150 mg/dL, 4) HDL < 40 mg/dL for males or < 50 mg/dL for females, and/or 5) hypertension.

[1]Patients receiving 10 mg lost 7.1 kg, and patients receiving placebo lost 0.7 kg. Based on the hypothetical estimand corresponding to if all people adhered to treatment. "Limited" additional weight loss was observed at higher doses of monlunabant.

BMI=Body mass index. CB1=Cannabinoid-1 receptor. HbA1c=Glycated hemoglobin. HDL=High-density lipoprotein cholesterol. TEAEs=Treatment-emer

Sources: Company reports, clinicaltrials.gov

Corbus's CRB-913

The company is advancing the asset, a peripherally restricted CB1R inverse agonist, in preclinical studies. CRB-913 has demonstrated potential for inducing weight loss both as a monotherapy and in combination with incretin analogs (Zepbound, Wegovy, or Saxenda). In the diet-induced obesity mouse model, monotherapy treatment led to a 22% decrease in body weight by day 18, while the combination with Zepbound, Wegovy, or Saxenda led to reductions of 33%, 29%, or 17%, respectively, over the same period. Importantly, there were minimal changes in lean body mass, and based on preclinical data, the concentration of the agent in the brain is 12-fold lower than Novo's monlunabant and 21-fold lower than rimonabant (Morningstar, et al. *Obesity* 2023). The first patient in single-ascending- and multiple-ascending-dose studies is expected to be dosed in the first quarter (Corbus November 2024 press release).

Skye's Nimacimab

The company announced its clinical development program for the CB1R inverse agonist monoclonal antibody, also known as RYI-018 or JNJ-2463, in December 2023. Nimacimab is being developed as a weight loss medicine for patients who are obese or overweight with co-morbidities. The asset is an engineered IgG4 antibody that targets CB1 receptors located in the periphery. Exchange of the fragment antigen-binding (Fab) regions is prevented through a mutation in the hinge region of the antibody. The drug is administered by subcutaneous injection. Skye obtained nimacimab in August 2023 through the acquisition of Bird Rock Bio, which discovered nimacimab and was investigating the asset in clinical trials for NAFLD and diabetic kidney disease. When Skye first acquired

nimacimab, the company was planning for clinical development in glaucoma and chronic kidney disease. By the end of 2023, however, Skye redirected its focus to the obesity market and received the IND for a Phase II obesity trial in early 2024.

Based on evidence to date, nimacimab is selective for periphery receptors and largely avoids receptors expressed in the CNS and brain, thereby mitigating the potential for psychiatric adverse events. This is likely due to the antibody format that prevents passing the BBB, in contrast to small-molecule formats like rimonabant. In several preclinical biodistribution studies in nonhuman primates, nimacimab did not accumulate in the brain, even after three weekly doses. Specifically, the ratio in the cerebrospinal fluid versus serum was below the limit of quantification after the first dose (day 1), and less than 0.02% after both the second dose (day 8) and the third dose (day 15) when administered at 3 mg/kg.

In addition, nimacimab preferentially binds to CB1R over other GPCRs and exhibits a differentiated mechanism of action compared with small-molecule inverse agonists, such as rimonabant. These inverse agonists act as competitive inhibitors by binding to the CB1 receptor's orthosteric site, which is where endocannabinoids also bind to stimulate CB1R signaling. Competitive mechanisms are concentration dependent, and this can mean that large quantities of an orthosteric drug are required to yield effective results, which could have negative safety consequences (Nussinov & Tsai, *Curr. Pharm. Des.* 2012). In contrast, nimacimab is a negative allosteric modulator and thus binds at the allosteric site of CB1 receptors. This inhibits CB1R signaling even when endocannabinoids bind to the orthosteric site. We therefore believe that nimacimab is a more potent inverse agonist of the CB1R axis. From a pharmacokinetic standpoint, the half-life of nimacimab is 18 to 21 days, which could enable dosing at biweekly or even monthly intervals. This could be viewed as an important advantage over the weekly dosing required for Zepbound (5-day half-life) and Wegovy (7-day half-life).

Based on preclinical toxicology data, no adverse effects were observed for nimacimab up to a dose level of 75 mg/kg administered intravenously once a week for four weeks. The same safe dose level was identified in 3- and 26-week studies where nimacimab was administered subcutaneously twice a week. Overall, these studies highlight the wide safety window of nimacimab, at least in the preclinical setting. Of particular importance, in the clinical setting, Phase I data demonstrated no neuropsychological side effects (more detail is provided below).

Beyond the potential for reduced neuropsychiatric events, the Phase I trial for nimacimab demonstrated improved gastrointestinal tolerability over GLP-1–based therapies, thus demonstrating an overall favorable safety profile. In addition, weight loss treatment with nimacimab may lead to improved body composition (i.e., retention of lean muscle mass) compared with medicines targeting GLP-1. The improved tolerability of nimacimab could also lead to patients maintaining treatment for longer periods of time, thus contributing to sustained weight loss. This would be differentiating from the GLP-1 class, where weight typically rebounds in individuals who halt treatment due to tolerability issues.

Regarding the benchmark for success, Skye believes that weight loss in the range of 5% to 8% would be clinically, and potentially commercially, meaningful when coupled with other positive benefits, such as body composition and tolerability. Ideally, Skye hopes to see a mean weight loss greater than 10% with improvements in triglycerides, the ratio of fat to lean body mass, and sensitivity to insulin and leptin. In addition, nimacimab will ideally demonstrate a tolerable gastrointestinal adverse event profile with no neuropsychiatric adverse events and the ability to accommodate a once-monthly dosing regimen. From a development standpoint, the ongoing Phase IIa trial is serving as a proof-of-concept study, while a future Phase IIb dose-optimization trial (to potentially start in 2026) will explore monthly versus weekly dosing and a registration-enabling Phase III trial will evaluate the optimized dose against placebo.

As part of nimacimab's development, Skye is also hoping to improve upon the technology used for administration. Currently, the therapy is dispensed via a prefilled syringe with a safe injection unit. However, the Phase IIb trial is designed to employ a prefilled syringe with an auto injector, which will also serve as the first commercial format. Eventually, the company hopes to further advance the apparatus by incorporating smart technology to simplify the patient experience and improve adherence to the dosing regimen.

While Skye is initially exploring nimacimab as a therapy for weight loss, the company plans to explore additional metabolic disorders as expansion opportunities for nimacimab and create a comprehensive metabolic franchise. Potential additional indications will be explored alongside development within obesity.

Nimacimab is protected by a broad patent estate that consists of both granted patents and applications in both the United States and foreign territories. Excluding the potential of Hatch-Waxman extension, the patents will expire between 2035 and 2036.

Phase I trial of nimacimab

The asset was evaluated in a study conducted by Bird Rock Bio in patients with non-alcoholic fatty liver disease (NAFLD). For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03261739).

Efficacy. There were no significant weight changes over the course of the study for patients taking nimacimab (in contrast, for placebo patients, there was a roughly 3% increase in weight at day 67). Skye believes this result may have been impacted by the heterogeneity in the studied patients and that four weeks was likely not long enough to see considerable change in weight given the heavily diabetic nature of the population.

However, significant changes in biomarkers were observed. Specifically, low-density lipoprotein cholesterol was reduced by about 7% in patients treated with the 2.5 mg/kg dose of nimacimab but increased by about 8% in patients treated with placebo. Significant changes in hyaluronic acid were also observed and encouraging trends for makers of inflammation and fibrosis reduction were noted.

Safety and tolerability. Treatment with nimacimab led to up to 10% nausea (dose-independent), 62% diarrhea (in the second-highest dose group), 10% vomiting (in the second-highest dose group), and no reports of neuropsychiatric adverse events. Of particular importance, there were no cases of suicidal ideation or behavior in the 29-day follow-up period. The frequency of serious treatment-emergent adverse events was not disclosed; in addition, there were no treatment-related discontinuations. Refer to exhibit 56 for an overview of the Phase I trial design and the comprehensive safety results.

Exhibit 56
Skye Bioscience, Inc.
4-Week Results of Nimacimab in Diabetic or Pre-Diabetic Non-Alcoholic Fatty Liver Disease With Pre-Diabetes or Type 2 Diabetes

Phase I Trial of Nimacimab (NCT03261739)

Sponsor	Skye Bioscience, Inc.			
Mechanism of Action	Inhibitor of cannabinoid receptor 1			
Enrollment Criteria	BMI ≥ 25 kg/m² and ≤ 40 kg/m² Liver fat by MRI ≥10% HbA1c ≥ 5.7%			
Study Arms	0.6 mg/kg nimacimab once weekly for 4 weeks	1.2 mg/kg nimacimab once weekly for 4 weeks	2.5 mg/kg nimacimab once weekly for 4 weeks	placebo
Enrollment	21 patients	21 patients	21 patients	20 patients
Baseline Characteristics	Female=48% Age=53 years Type 2 diabetes=76% Body weight=94 kg BMI=34 kg/m²	Female=52% Age=54 years Type 2 diabetes=91% Body weight=90 kg BMI=33 kg/m²	Female=43% Age=53 years Type 2 diabetes=86% Body weight=93 kg BMI=33 kg/m²	Female=55% Age=51 years Type 2 diabetes/=80% Body weight=94 kg BMI=34 kg/m²
TEAEs	Diarrhea 33% URTI 5% Nausea 10% Dizziness 10% Vomiting 5% Dry mouth 0% Headache 24% Abdominal pain 0% Neck pain 10% ECG QT prolongation 10%	62% 10% 0% 14% 10% 5% 14% 14% 0% 0%	29% 14% 10% 5% 5% 5% 0% 0% 0% 0%	40% 10% 10% 5% 10% 0% 15% 0% 0% 0%
Columbia-Suicide Severity Rating Scale	Suicidal ideation (baseline)=0% Suicidal ideation (day 29)=0% Suicidal behavior (baseline)=0% Suicidal behavior (day 29)=0%	Suicidal ideation (baseline)=0% Suicidal ideation (day 29)=0% Suicidal behavior (baseline)=0% Suicidal behavior (day 29)=0%	Suicidal ideation (baseline)=0% Suicidal ideation (day 29)=0% Suicidal behavior (baseline)=0% Suicidal behavior (day 29)=0%	Suicidal ideation (baseline)=0% Suicidal ideation (day 29)=0% Suicidal behavior (baseline)=0% Suicidal behavior (day 29)=0%

BMI=Body mass index. ECG=Electrocardiogram. HbA1c=Glycated hemoglobin. MRI=Magnetic resonance imaging. TEAE=Treatment-emergent adverse event. URTI=Upper respiratory tract infection.
Sources: Company reports and clinicaltrials.gov

Phase II CBeyond trial of nimacimab

The ongoing study, initiated in August 2024, is designed to demonstrate the asset's impact on weight loss (while sparing lean muscle mass) and potential for combination with GLP-1 RAs. Interim data for the trial is expected to be released in the second quarter, while top-line results are slated for the fourth quarter of 2025 (Skye ObesityWeek 2024 presentation). For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06577090). A detailed summary of the Phase II CBeyond trial design of nimacimab in overweight or obesity is presented in exhibit 57.

Exhibit 57
Skye Bioscience, Inc.
Trial Design of Nimacimab With or Without Wegovy in Overweight or Obesity Without Type 2 Diabetes

Phase II CBeyond Trial of Nimacimab (NCT06577090)

Sponsor	Skye Bioscience, Inc.			
Mechanisms of Action	Nimacimab: Inhibitor of cannabinoid receptor 1 Wegovy: GLP-1 receptor agonist			
Inclusion Criteria	BMI ≥ 30 kg/m² and ≤ 45 kg/m² or ≥ 27 kg/m² and ≤ 30 kg/m² with at least 1 weight-related co-morbidity[1] HbA1c < 6.5%			
Study Arms	200 mg nimacimab once weekly for 26 weeks	200 mg nimacimab + 1.4 mg or 2.4 mg Wegovy once weekly for 26 weeks	1.7 mg or 2.4 mg Wegovy once weekly for 26 weeks	placebo
Target Enrollment	40 patients	20 patients	20 patients	40 patients
Primary Endpoint	Mean weight loss at 26 weeks for nimacimab monotherapy compared to placebo			
Secondary Endpoints	Safety and tolerability, neuropsychiatric and cognitive evaluation, change in body composition, and change in metabolic parameters			
Exploratory Endpoints	Weight loss, body composition, and improvement in sleep			
Next Catalyst	Interim readout: Q2			

[1]Dyslipidemia, cardiovascular disease, obstructive sleep apnea, or controlled arterial hypertension.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin.
Sources: Company reports and clinicaltrials.gov

Muscle-Sparing Assets: Apelin, Activin, and Androgen Receptor Modulators

In weight loss, the preferred goal is to lose fat rather than muscle. Skeletal muscle is important not just for strength and mobility, but also because it mediates insulin action and glucose homeostasis and contributes to energy expenditure. Some obesity drugs, particularly the GLP-1 RAs, can cause substantial muscle loss. Based on existing studies, the decrease in fat-free mass with GLP-1 RAs ranges from 25% to 39% over 36-72 weeks. Moreover, if a patient discontinues use of a GLP-1 RA and regains weight, regained mass is usually fat rather than muscle. To a degree, this loss of muscle can be compensated for through exercise and nutrition (Prado, et al. *Lancet Diabetes & Endocrinol.* 2024).

There are two pharmacological approaches to address this problem. One is to use alternatives to GLP-1 RAs whose use does not result in muscle loss, such as CB1R antagonists or inverse agonists, as discussed above. The second is to supplement GLP-1 with another drug that helps preserve muscle and may also increase weight loss, such as bimagrumab, as described below. An additional medication may entail its own risks (Prado, et al. *Lancet Diabetes & Endocrinol.* 2024). For example, muscle spasms and falls have been reported with bimagrumab.

Muscle-sparing assets in weight loss offer an encouraging set of novel mechanisms that could promote differentiated weight loss made up mostly of fat, in our view. These assets, including apelin, activin, and androgen receptor modulators, may not suffer from the muscle loss associated with GLP-1 RAs. Furthermore, patients stopping treatment with muscle-sparing assets may not regain fat mass to the same degree compared with stopping GLP-1 RAs. Regarding the greatest weight loss observed for the class, bimagrumab demonstrated up to 6% and 22% placebo-adjusted weight and fat mass loss at 48 weeks, respectively, in Phase II results in overweight and obesity with type 2 diabetes.

Apelin

The human apelin gene codes for a 77-amino-acid prepropeptide that is cleaved into peptides of differing lengths and properties. The name apelin is derived from "APJ endogenous ligand." APJ was discovered before the ligand and was named based on its roughly 50% homology to the angiotensin receptor. Each of the forms of apelin binds the APJ receptor, which is a G-protein coupled receptor, but with variations in potency and outcome. A second ligand of APJ, named elabela, has also been identified. Both apelin and its receptor are expressed in many tissues and organs, including brain, heart, liver, kidney, gastrointestinal tract, endothelium, skeletal muscle, and adipose tissue (Li, et al. *Front. Endocrin.* 2022). In addition, APJ can form heterodimers with other GPCRs, and these heterodimers can bind some forms of apelin (Chen, et al. *Life Sci.* 2023).

Apelin has been variously referred to as an adipokine (secreted by adipose tissue), a myokine (secreted by muscle tissue), and an exerkine (secreted consequent to exercise by any cell type). These three types of molecules each act, in their own ways, as signals that affect the behavior of the secreting cell (autocrine effects) or other cells that are nearby (paracrine effects) or farther away (endocrine effects) within the body. Apelin secretion appears to increase under certain conditions, such as obesity and type 2 diabetes. However, apelin secretion also increases as a result of resistance and aerobic exercise. (Wen, et al. *Front. Endocrin.* 2023).

Of the multiple forms of apelin, apelin-13 so far appears to be the most bioactive. Findings suggest that apelin-13 can reduce obesity by inhibiting adipocyte differentiation in human cell culture, promoting fat breakdown in mice, and reducing lipid storage in mouse cell culture. It also has been shown to have an anti-inflammatory effect in humans and rodents (Wen, et al. *Front. Endocrin.* 2023). In some cases, apelin-13 can ameliorate skeletal muscle atrophy in mice (Enoki, et al. *J. Cachexia, Sarcopenia & Muscle* 2023). Notably, apelin peptides, including apelin-13, have a relatively short half-life (about 5 minutes) once secreted.

Apelin Receptor Agonists

A number of synthetic, orally bioavailable molecules have been investigated as ligands for APJ, both agonists and antagonists (Huang, et al. *J. Cell. Phys.* 2018; Gargalovic, et al. *Circulation: Heart Failure* 2021). The initial interest in apelin RAs arose not in the context of obesity or skeletal muscle, but because the apelin-elabela-APJ axis is a regulator of cardiovascular physiology (Narayan, et al. *Bioorg. Med. Chem.* 2022). Antagonists were studied because certain cardiac pathologies were thought to be attributable to apelinergic signaling; subsequently it was suggested that high levels of apelin in such diseases might, to the contrary, have a protective effect (Wysocka, et al. *Front. Physiol.* 2018). Apelin agonists are being studied for the treatment of hypertension, atherosclerosis, heart failure, and kidney disease (Chapman, et al. *Cardiovas. Res.* 2023). None of these drugs has yet been approved by the FDA.

BioAge's Azelaprag

The company is developing an orally delivered small-molecule apelin RA, azelaprag, which it characterizes as an "exercise mimetic." The drug has undergone Phase I testing for pharmacokinetics, pharmacodynamics, and safety (Azelaprag PubChem listing). Azelaprag was previously known as AMG 986 when it was under development by Amgen, and as BGE-105. BioAge commenced trials of azelaprag for obesity and for muscle atrophy (BioAge form 424B4 dated 09-26-2024).

In December 2024, BioAge announced the discontinuation of the Phase II STRIDES clinical trial after observations of liver transaminitis without clinically significant symptoms in some subjects on azelaprag. No transaminase elevations were observed in the Zepbound-only treatment group. The company has said that it is assessing the next steps for the azelaprag program (BioAge press release Dec. 2024).

Phase II STRIDES trial of azelaprag

Before its discontinuation, the study aimed to assess the efficacy and safety of once- or twice-daily capsule formulation oral azelaprag plus once-weekly Zepbound over 24 weeks, in participants with obesity aged 55 or older. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06515418).

At the ObesityWeek 2024 conference, BioAge presented preclinical data on whether combining azelaprag with the CB1R antagonist rimonabant improved weight loss compared with rimonabant alone. Diet-induced obese mice treated with azelaprag and rimonabant demonstrated significantly increased weight loss compared with rimonabant monotherapy (around 27% vs. 17% in 14 days; $p<0.0001$). The combination also increased lean muscle mass compared with monotherapy (roughly 70% vs. 64% in 14 days, $p<0.0001$) and decreased fat mass percentage (around 24% vs. 32% in 14 days, $p<0.0001$), bringing body composition within the range of lean controls (nearly 71% lean and 25% fat).

Although rimonabant was never available in the United States and was withdrawn from the European market, the work provides an interesting proof of concept for azelaprag as an adjunct therapy to CB1R antagonists and inverse agonists, if the issue that arose in the STRIDES Phase II trial does not also arise in this context.

An SEC filing by BioAge states that it also intends to initiate a Phase II clinical trial to assess azelaprag in combination with Wegovy in the first half (BioAge form 424B4 dated 09-26-2024). However, given the discontinuation of the Phase II STRIDES trial and the azelaprag program more broadly, we believe this trial is unlikely to commence.

Structure's ANPA-0073

The company is developing its orally delivered small-molecule apelin RA, ANPA-0073, for muscle-sparing weight loss. This drug has undergone Phase I trials in Australia for safety, tolerability, pharmacokinetics, and pharmacodynamics of single- and multiple-ascending doses (ACTRN12621000644864) and to study drug-drug interactions with sildenafil (Viagra) (ACTRN12622000657729), both in healthy volunteers. In the trials, the asset is indicated for pulmonary arterial hypertension.

Results from the PK/PD study were presented at the 2023 International Conference of the American Thoracic Society.

Safety and tolerability. Treatment with ANPA-0073 led to up to 17% nausea, 33% diarrhea, and 17% vomiting (all of which were observed at the highest-dose). In addition, treatment led to elevated blood creatine phosphokinase and heart rate. Furthermore, no serious treatment-emergent adverse events or adverse events leading to discontinuation were observed. However, one patient receiving placebo experienced moderate headache and was withdrawn from the study.

Next steps. The company has said that it is evaluating ANPA-0073 for potential selective or muscle-sparing weight loss. It is also being evaluated for idiopathic pulmonary fibrosis. The company has further said that it is conducting long-term chronic Good Laboratory Practices toxicology studies, expected to be completed this year.

Activin Type II Receptor and Ligands

Skeletal muscle cells express the activin type II A and B receptors (ActRIIA/B). When their ligands, such as myostatin (GDF-8) or activin A, bind ActRIIA/B, these receptors can then heterodimerize with the activin type I receptor. This action triggers intracellular signaling cascades that negatively affect muscle mass. A striking illustration of interference with this phenomenon may be seen in Belgian Blue cattle, which have a mutation in the myostatin gene that that eliminates virtually all the active region of the molecule. This releases the restraint on muscle growth and results in a "double-muscled" phenotype (McFerron & Lee, *PNAS* 1997). It is interesting to note that obesity is associated with increased levels of myostatin (Consitt & Clark, *J. Frailty Aging* 2017).

Antagonists of activin type II receptors aim to block the inhibition of muscle growth by preventing binding of the receptors' ligands. Signaling through the activin heterodimer inhibits activation of the PI3K/Akt/mTOR pathway, which is triggered by binding of IGF1 to its receptor and which increases muscle protein synthesis. Signaling through the activin heterodimer activates the Smad2/Smad3 pathway, which leads to muscle degradation. Akt inhibition also leads to muscle breakdown via activation of the FOX0 transcription factor (Kanbay, et al. *Aging Clin. & Exper. Res.* 2024).

Adipose tissue also expresses ActRIIA/B, and antagonism of these receptors is expected to reduce adipose tissue. In one illustrative study, subcutaneous injection of a decoy activin receptor IIB to deplete ligands for the receptor in mice fed a high-fat diet reduced the amount of fat gained compared with mice on the same diet that received injections of vehicle. The authors found that mice that were administered the decoy receptor had greater expression of genes that promote thermogenesis, allowing them to burn rather than store fat. The ligands that were depleted by the decoy receptor included GDF-8/myostatin and activins A and B (Koncarevic, et al. *Endocrinology* 2012).

Activin Type II Receptor Antagonists and Ligand Neutralizers

Eli Lilly's Bimagrumab

The asset is a dual-specific anti-ActRIIA/B antibody that blocks binding by myostatin and activin A (Morvan, et al. PNAS 2017). It was originally developed by Novartis as a treatment for a rare muscle-wasting disease. When clinical trial results were disappointing, the drug was licensed to Versanis Bio, which began to assess it as an obesity treatment, either alone or in combination with Wegovy. Versanis was then acquired by Lilly in 2023. Lilly is conducting multiple Phase II studies with overweight and obese participants. Bimagrumab is administered intravenously.

Phase II trial of bimagrumab

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03005288).

Efficacy. Once-every-four weeks bimagrumab demonstrated statistically significant placebo-adjusted changes in body weight, fat mass, and lean mass of around -6%, -22%, and +5%, respectively, in overweight or obesity with type 2 diabetes at 48 weeks. Patients receiving bimagrumab also demonstrated a significant improvement (reduction) in HbA1c. In addition, in the bimagrumab arm, patients demonstrated declines in subcutaneous and abdominal visceral fat of around 1.7 L and 1.5 L, respectively, compared with respective declines of nearly 0.5 L and less than 0.1 L in the placebo arm.

In an abstract presented at the 83rd annual scientific sessions of the American Diabetes Association in 2023, investigators revealed that at week 48, patients receiving bimagrumab demonstrated a placebo-adjusted increase in appendicular lean mass at week 48 of around 4% (p=0.009). Furthermore, the observed fat mass loss at week 48 was maintained 12 weeks after the last bimagrumab dose (Attie, et al. *Diabetes* 2023).

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 18% placebo-adjusted weight loss at 48 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with bimagrumab led to 11% nausea and 41% diarrhea, as well as elevated muscle spasms and lipases compared with placebo. Serious treatment-emergent adverse events were balanced between arms, at 8%. In addition, the discontinuation rate was higher in the bimagrumab arm, occurring at a midteens percentage, compared with no discontinuations in the placebo arm (Heymsfield et al., *JAMA* 2021). A detailed summary of the Phase II trial results of bimagrumab in overweight or obesity is presented in exhibit 58.

Exhibit 58
Eli Lilly and Company
24- and 48-Week Results of Bimagrumab in Overweight/Obesity With Type 2 Diabetes

Phase II Trial (NCT03005288)		
Sponsor	Eli Lilly and Company	
Mechanism of Action	Activin type II receptor antagonist	
Enrollment Criteria	BMI ≥ 28 kg/m² and ≤ 40 kg/m² HbA1c ≥ 6.5% and < 10%	
Baseline Patient Characteristics	Age=61 years Male=38% Body weight=90 kg Fat mass=36 kg BMI=33 kg/m² HbA1c=8.0%	Age=60 years Male=68% Body weight=97 kg Fat mass=35 kg BMI=33 kg/m² HbA1c=7.7%
Study Arms	10 mg/kg bimagrumab once every 4 weeks for 48 weeks	placebo
Enrollment	37 patients	38 patients
Change in Fat Mass at Week 48	**-22%** **placebo-adjusted: -22%** ***p* <0.001**	**~-1%**
Patients Reaching ≥5%, ≥10%, and ≥15% Fat Mass Loss at Week 48	96% (*p* <0.001) 92% (*p* <0.001) 77% (*p* <0.001)	21% 10% 10%
Change in Body Weight at Week 48	-7% placebo-adjusted: -6% *p* <0.001	~-1%
Patients Reaching ≥5% Weight Loss at Week 48	65% (*p* <0.001)	10%
Change in Lean Mass at Week 48	+4% placebo-adjusted: +5% *p* <0.001	-1%
Change in HbA1c at Week 48	-0.8% placebo-adjusted: -0.8% *p* =0.005	~+0.1%
TEAE Frequency	84%	82%
TEAEs Affecting ≥10% of Patients	Diarrhea 41% Muscle spasms 41% URTI 16% Lipase level increased 11% Headache 0% Nausea 11%	11% 3% 13% 5% 13% 0%
Serious TEAE Frequency	8%	8%
TEAEs Leading to Discontinuation	14%	0%
Treatment-Emergent Deaths	None reported	

BMI=Body mass index. HbA1c=Glycated hemoglobin. TEAEs=Treatment-emergent adverse events. URTI=Upper respiratory tract infection.
Sources: Company reports, Heymsfield et al., JAMA 2021, clinicaltrials.gov

Phase II trial of bimagrumab plus Wegovy

The trial is investigating the safety and efficacy of the combination in overweight and obesity over 48 weeks, with an estimated completion in June according to company documents. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05616013). A detailed summary of the Phase II trial design of bimagrumab plus Wegovy in overweight or obesity is presented in exhibit 59.

Exhibit 59
Eli Lilly and Company
Trial Design of Bimagrumab and Wegovy in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT05616013)

Sponsor	Eli Lilly and Company								
Mechanisms of Action	bimagrumab: activin type II receptor antagonist Wegovy: GLP-1 receptor agonist								
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%								
Study Arms	10 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, and 40; 30 mg/kg bimagrumab at weeks 52 and 64	10 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, 40, 52, and 64 + 1.0 mg Wegovy once weekly	10 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, 40, 52, and 64 + 2.4 mg Wegovy once weekly	30 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, 40, 52, and 64	30 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, 40, 52, and 64 + 1.0 mg Wegovy once weekly	30 mg/kg bimagrumab at baseline and at weeks 4, 16, 28, 40, 52, and 64 + 2.4 mg Wegovy once weekly	placebo at baseline and at weeks 4, 16, 28, and 40; 30 mg/kg bimagrumab at weeks 52 and 64	placebo + 1.0 mg Wegovy once weekly	placebo + 2.4 mg Wegovy once weekly
Enrollment	507 patients								
Wegovy Titration Schedule		0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 56 weeks	0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 4 weeks; 1.7 mg for 4 weeks; 2.4 mg for 48 weeks		0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 56 weeks	0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 4 weeks; 1.7 mg for 4 weeks; 2.4 mg for 48 weeks		0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 56 weeks	0.25 mg for 4 weeks; 0.5 mg for 4 weeks; 1.0 mg for 4 weeks; 1.7 mg for 4 weeks; 2.4 mg for 48 weeks
Primary Endpoint	**Weight loss at 48 Weeks**								
Secondary Endpoints	Safety and tolerability Changes in body composition and HbA1c								
Next Catalyst	Estimated completion: June								

*Patients will have either hypertension, insulin resistance, sleep apnea, or dyslipidemia.
BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin.
Sources: Company reports and clinicaltrials.gov

Phase II trial of bimagrumab plus Zepbound

The study is testing the safety and efficacy of the combination in overweight and obesity over 24 weeks. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06643728). A detailed summary of the Phase II trial design of bimagrumab plus Zepbound in overweight or obesity is presented in exhibit 60.

Exhibit 60
Eli Lilly and Company
Trial Design of Bimagrumab and Zepbound in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT06643728)							
Sponsor	Eli Lilly and Company						
Mechanisms of Action	bimagrumab: Activin type II receptor antagonist Zepbound: dual GLP-1 and GIP receptor agonist						
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related comorbidity* HbA1c < 6.5%						
Study Arms	Zepbound dose 1	Zepbound dose 2	bimagrumab dose 1 + Zepbound dose 1	bimagrumab dose 1 + Zepbound dose 2	bimagrumab dose 2	bimagrumab dose 2 + Zepbound dose 2	placebo
Target Enrollment	140 patients						
Primary Endpoint	**Weight loss at 24 Weeks**						
Secondary Endpoints	Safety and tolerability Change in body composition						
Next Catalyst	Estimated completion: November 2026						

*Patients will have either hypertension, cardiovascular disease, obstructive sleep apnea, and/or dyslipidemia.

BMI=Body mass index. GIP=Glucose-dependent insulinotropic polypeptide. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin.

Sources: Company reports and clinicaltrials.gov

Investigator-sponsored Phase II trial of bimagrumab vs. Wegovy

The study is testing the effect of treatment on body composition, insulin sensitivity, and bone density in adults with obesity at 52 weeks. The study aims to conclude in 2028; it is not yet recruiting patients. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05933499). A detailed summary of the Phase II trial design of bimagrumab with or without Wegovy in overweight or obesity is presented in exhibit 61.

Exhibit 61
Eli Lilly and Company
Trial Design of Bimagrumab vs. Wegovy in Overweight or Obesity Without Type 2 Diabetes

Phase II Trial (NCT05933499)			
Sponsor	Massachusetts General Hospital		
Mechanisms of Action	bimagrumab: Activin type II receptor antagonist Wegovy: GLP-1 receptor agonist		
Enrollment Criteria	BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related condition HbA1c < 6.5%		
Study Arms	bimagrumab at weeks 0, 4, 16, 28, and 40	placebo for bimagrumab + 2.4 mg Wegovy once weekly	placebo
Target Enrollment	65 patients		
Primary Endpoints	**Changes in body composition, bone mineral density, and visceral adipose tissue**		
Next Catalyst	Estimated completion: August 2028		

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. HbA1c=Glycated hemoglobin.
Sources: clinicaltrials.gov

Regeneron's Garetosmab and Trevogrumab
Garetosmab, also known as REGN2477, is an antibody targeting activin A, and trevogrumab, also dubbed REGN1033 and SAR391786, is an anti-myostatin antibody. Garetosmab was originally developed and trialed for treatment of an ultrarare bone disease that causes skeletal deformities, loss of mobility, and, ultimately, death. Trevogrumab previously underwent a Phase II trial for sarcopenia.

Phase II COURAGE trial of trevogrumab, garetosmab, and Wegovy
The trial is studying the safety and efficacy of the assets in obesity after an initial stage testing safety and tolerability in healthy persons. Trevogrumab will be administered with or without garetosmab, in addition to Wegovy. The study is expected to conclude in 2026. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06299098).

Biohaven's Taldefgrobep Alfa
Taldefgrobep alfa, also known as BHV-2000 or BMS-986089, is a human recombinant protein designed to specifically bind myostatin (GDF-8), licensed from Bristol Myers Squibb. By binding to myostatin, the drug blocks the formation of the myostatin-activin receptor complex. The myostatin-taldefgrobep complex thus acts as an ActRIIA/B antagonist. Taldefgrobep alfa is classified as an adnectin, which is an engineered scaffold that is based on the 10th fibronectin type III domain (Madireddi, et al. *Neuromusc. Disord.* 2016).

Taldefgrobep alfa was originally developed for treatment of Duchenne muscular dystrophy (Muntoni, et al. *Neurol. Ther.* 2024). Biohaven has investigated it for a rare disease, spinal muscular atrophy (SMA). In a Phase III clinical trial for SMA, patients receiving it experienced decreased fat mass and increased lean mass and bone density (NCT05337553). The company said that given these changes in body composition, it planned to advance taldefgrobep alfa into a placebo-controlled Phase II obesity study in fourth quarter 2024, with the drug administered using a self-administered autoinjector.

Scholar Rock's Apitegromab
The asset, also known as SRK-015, is a monoclonal antibody that binds to the precursor forms of myostatin, known as promyostatin and latent myostatin, inhibiting the formation of mature, active myostatin. It has undergone testing for SMA, an autosomal recessive neuromuscular disorder of motor neurons (Crawford, et al. *Neurol.* 2024). It is in a Phase IIb study to determine its efficacy and safety for the treatment of adults who are overweight or obese (EMBRAZE) when it is being administered with Wegovy or Zepbound. Results from the trial are expected late this year. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06445075).

Androgen Receptor Modulation

Androgen signaling via the androgen receptor (AR) is important in the development and maintenance of muscle. In muscle, androgens have an anabolic effect, increasing both mass and strength. In the absence of an androgen ligand, the AR resides in the cytoplasm of the cell, bound by chaperone proteins. Upon ligand binding, the AR changes conformation, the chaperones dissociate, and the AR translocates to the nucleus, where it engages in transcriptional activity.

The AR is also present in some breast cancers, where it is a regulator of tumor growth. Whether it serves as a positive or negative regulator in any specific circumstance depends on its interactions with other signaling pathways, including that of the estrogen receptor (ER). In ER+ cancers, for example, high AR expression has been linked to a better prognosis.

Veru's Enobosarm
The asset, also known as Ostarine, is an oral, non-steroidal selective androgen receptor modulator (SARM) being investigated as an adjunct to GLP-1 RAs for obesity. Enobosarm, (2S)-3-(4-cyanophenoxy)-N-[4-cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methylpropanamide (PubChem listing), like other SARMs, binds the AR much as an androgen does to initiate muscle mass increase. However, SARMs aim to produce fewer of the androgenic side effects of anabolic steroids (Turza, et al. *J. Mol. Struct.* 2020).

Enobosarm was the subject of several trials for breast cancer (NCT02368691; NCT03264651; NCT04869943; Palmieri, et al. *Lancet Oncology* 2024).

Phase IIb QUALITY trial of enobosarm
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06282458).

Efficacy. Once-daily enobosarm plus once-weekly Wegovy demonstrated placebo-plus-Wegovy-adjusted changes in fat mass and lean mass of around -2% (p=NS) and +3% (p=0.002), respectively, in patients with overweight or obesity at 16 weeks. In addition, patients in both groups demonstrated similar weight loss of around 4 kg to 5 kg; however, around 32% of weight loss in the placebo plus Wegovy arm was due to lean mass loss, compared with around 9% in the enobosarm plus Wegovy groups. Functionally, a greater proportion of patients in the placebo plus Wegovy arm demonstrated at least a 10% decline in stair climb power (roughly 43%) compared with around 19% in the enobosarm plus Wegovy groups.

Safety. Based on aggregate, blinded data, there are no significant differences associated with enobosarm treatment compared with previous studies.

Next Steps. The Phase 2b extension clinical trial, in which patients will discontinue a GLP-1 RA but continue receiving placebo or enobosarm for 12 more weeks is ongoing; results are expected in April. Furthermore, the company has announced plans to request an end-of-Phase II meeting with the FDA.

The company aims to advance the asset, likely to be administered once daily over one year, into a Phase III clinical trial in patients with overweight or obesity eligible to receive Wegovy or Zepbound. The proposed primary endpoint will be the effect on stair climb power, by the percent of patients that lose at least 10% power from baseline (Veru January 2025 press release). The trial design and results are presented in exhibit 62.

Exhibit 62
Veru Inc.
16-Week Results of Enobosarm Plus Wegovy in Overweight or Obesity With or Without Type 2 Diabetes

Phase IIb QUALITY Trial (NCT06282458)

Sponsor	Veru Inc.		
Mechanism of Action	Enobosarm: Selective androgen receptor modulator Wegovy: GLP-1 receptor agonist		
Enrollment Criteria	≥60 years of age BMI ≥ 30 kg/m² or ≥ 27 kg/m² with at least one weight-related condition, including type 2 diabetes		
Study Arms	3 mg enobosarm once daily + Wegovy once weekly for 16 weeks	6 mg enobosarm once daily + Wegovy once weekly for 16 weeks	placebo + Wegovy once weekly for 16 weeks
Enrollment	100 patients		48 patients
Wegovy Titration Schedule	0.25 mg for 4 weeks; 0.50 mg for 4 weeks; 1.00 mg for 4 weeks; 1.70 mg for 4 weeks		
Change in Lean Mass at Week 16	**-1%; *p* =0.002** **placebo-adjusted: +3%**		**-4%**
Change in Fat Mass at Week 16	-11%; *p* =NS placebo-adjusted: -2%		-9%
Change in Body Weight at Week 16	-4 kg		-5 kg
Proportion of Weight Loss Due to Lean Mass Loss at Week 16	9%		32%
Proportion of Patients Who Lost ≥10% Stair Climb Power at Week 16	19% (19/98); *p* =0.0049		43% (20/47)
Next Catalyst	Phase IIb extension trial results in April		

BMI=Body mass index. GLP-1=Glucagon-like peptide 1. NS=Not significant.
Sources: Company reports, ClinicalTrials.gov

"Next-Wave" Assets: Mitochondrial Protonophores, PYY Receptor Agonists, and a Leptin Receptor Agonist

Mitochondrial Protonophores

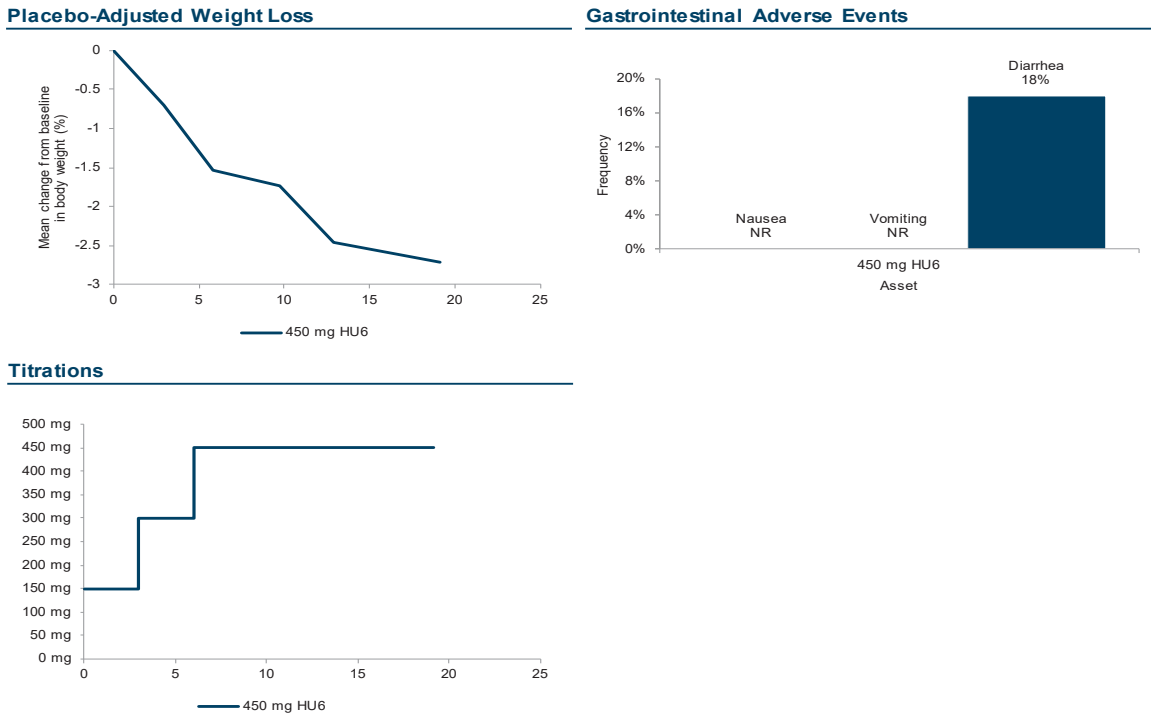
Mitochondria can produce ATP, the energy currency of the body, by transporting electrons from the food we consume through complexes in the mitochondrial membrane and using energy from those electrons to push protons from the mitochondrial matrix to the other side of the mitochondrial membrane, creating a proton gradient. Those protons then flow back into the matrix through a complex of proteins that is partly embedded in the mitochondrial membrane and that partly protrudes into the matrix, ATP synthase. The protons thereby power the production by ATP synthase of ATP from ADP and inorganic phosphate that are present in the matrix.

This process of producing ATP thus depends on the integrity of the mitochondrial membrane and its ability to create a proton gradient. If protons could flow freely through the membrane, then insufficient protons would pass through the ATP synthase complex, and the energy needs of the organism would not be satisfied. Nearly 100 years ago, the molecule 2,4-dinitrophenol (DNP), a mitochondrial protonophore, was used as a weight loss drug. DNP was able to transport protons across the mitochondrial membrane back into the matrix by binding the protons and diffusing through the lipid bilayer of the inner mitochondrial membrane. DNP thereby uncoupled electron transport and generation of the mitochondrial membrane gradient from ATP production. Instead, the energy was dissipated as heat. Unfortunately, ingestion of DNP was sometimes fatal, because individuals taking it at higher doses could not produce enough ATP to survive. Use of DNP as a diet drug was banned by the FDA in 1938 (Shrestha, et al. *Mol. Metab.* 2021).

It has been suggested that in addition to its ability to carry protons through the inner mitochondrial membrane, DNP has other mechanisms of action. Specifically, it is thought that DNP can accelerate the uncoupling activity of endogenous protonophores located in the mitochondrial membrane. There are two known families of proteins with members that serve as natural mitochondrial uncouplers by facilitating proton leak: the uncoupling proteins (UCPs) and the adenine nucleotide translocases (ANTs) (Demine, et al. *Cells* 2019). UCPs are proton transporters, whereas ANTs exchange cytosolic ADP for matrix ATP. UCPs have various normal physiological functions, including thermogenesis. ANTs serve mainly to export newly synthesized ATP molecules out of the mitochondria, but also play a role in apoptosis, a form of programmed cell death. Each can be activated by ligands typically present in the body. For example, both UCPs and ANTs can be induced by oxidized lipids (Shrestha, et al. *Mol. Metab.* 2021). Experiments with isolated mitochondria and planar bilayer membranes provide some evidence that DNP acts on members of the UCP and ANT families to enhance its protonophoric action (Žuna, et al. *Biomolecules* 2021).

We are encouraged by novel, "next-wave" mechanisms such as mitochondrial protonophores, leptin agonists, and PYY analogs that could promote weight loss with favorable weight loss and tolerability compared with current obesity therapeutics. Next-wave assets offer an orthogonal approach, such as increasing energy expenditure from protonophore modulation, to allow potential combination with assets with other mechanisms of action. Regarding the greatest weight loss observed for the group, the mitochondrial protonophore HU6 demonstrated up to 3% placebo-adjusted weight loss at 19 weeks in Phase IIa results in obesity-related heart failure with preserved ejection fraction. A plot depicting the placebo-adjusted weight loss, adverse events, and titration schedules associated with the top dose of the controlled metabolic accelerator HU6 is presented in exhibit 63.

Exhibit 63
Combined Weight Loss, Adverse Events, and Titration Curves of Controlled Metabolic Accelerator HU6



Sources: Company documents

Mitochondrial Protonophores: The 21st Century Version

Rivus's HU6

The asset, with IUPAC name (1R,2S)-2-[[(6-bromo-1H-indazol-4-yl)amino]methyl]cyclohex-3-en-1-ol (PubChem entry) is a small-molecule ANT activator that the company has dubbed a "controlled metabolic accelerator." Indications for the drug are obesity-related heart failure with preserved ejection fraction (HFpEF), metabolic dysfunction-associated steatohepatitis (MASH), type 2 diabetes, and obesity (company website). HU-6 is a prodrug that is metabolized in the liver to produce DNP, with the goal of reducing hepatic lipid content by inducing a higher level of β-oxidation of fat (Noureddin, et al. *Lancet Gastroent. & Hepat.* 2023).

Phase IIa HuMAIN trial of HU6

For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05284617).

Efficacy. Once-daily HU6 demonstrated placebo-adjusted changes in body weight, fat mass, and lean mass of -3%, -7%, and +1%, respectively, in obesity-related heart failure with preserved ejection fraction (HFpEF) at 19 weeks. Fat mass loss was primarily driven by visceral fat mass loss; changes in subcutaneous fat, epicardial fat, intramuscular fat, intermuscular fat, and thigh muscle volume by MRI were not statistically different between trial arms. As lean muscle did not significantly decline on HU6, this suggests that HU6 could aid in weight loss that focuses on fat loss while preserving lean muscle mass. In addition, patients receiving HU6 demonstrated improvements in systolic blood pressure.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 10% placebo-adjusted weight loss at 20 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with HU6 led to 18% diarrhea and 9% constipation. Serious treatment-emergent adverse events in the HU6 arm, at 12%, occurred at roughly four times the placebo rate. Furthermore, the discontinuation rate was higher in the HU6 arm, occurring in the midsingle digits, compared with no discontinuations in the placebo arm. Moreover, the study reported one death, representing 3% of patients, in the HU6 arm (Rivus Pharma Phase IIa HuMAIN-HFpEF trial presentation). A detailed summary of the Phase IIa HuMAIN trial results of HU6 in obesity-related HFpEF is presented in exhibit 64.

Exhibit 64
Rivus Pharmaceuticals, Inc.
19-Week Results of HU6 in Obesity-related HFpEF

Phase IIa HuMAIN Trial (NCT05284617)

Sponsor	Rivus Pharmaceuticals, Inc.	
Mechanism of Action	Controlled metabolic accelerator / mitochondrial uncoupler	
Enrollment Criteria	BMI ≥ 30 kg/m²; LVEF≥50%; NYHA functional class II-III; KCCQ-OSS≤80 Chronic HFpEF	
Baseline Patient Characteristics	Age=64 years Male=48% Body weight=110 kg BMI=39 kg/m² Atrial fibrillation=21% Diabetes=43% 6-minute walk distance=346 m KCCQ-OSS=63 points	Age=65 years Male=36% Body weight=111 kg BMI=40 kg/m² Atrial fibrillation=21% Diabetes=24% 6-minute walk distance=341 m KCCQ-OSS=60 points
Study Arms	450 mg HU6 once daily	placebo
Enrollment	33 patients	33 patients
Titration Schedule	150 mg for 3 weeks; 300 mg for 3 weeks; 450 mg for 3 months (92 days)	
Change in Body Weight at Week 19	**placebo-adjusted: -3%** ***p*=0.003**	
Change in Lean Mass at Week 19	placebo-adjusted: +1% *p*=NS	
Change in Fat Mass at Week 19	placebo-adjusted: -7% *p*=0.0001	
Change in Visceral Fat at Week 19	By InBody Scale: placebo-adjusted: -7% *p*=0.001 By MRI[1]: placebo-adjusted: -10% *p*=0.003	
TEAE Frequency	76%	63%
TEAEs Affecting ≥5% of Patients	Diarrhea: 18% vs. 6% COVID-19: 15% vs. 3% Dyspnea: 12% vs. 0% Constipation: 9% vs. 0% Joint swelling: 9% vs. 0% Fatigue: 6% vs. 3% Headache: 6% vs. 9% Pain in extremity: 6% vs. 3% Back pain: 3% vs. 6% Cellulitis: 3% vs. 6% Flushing: 3% vs. 6% Influenza: 3% vs. 6% Arthralgia: 0% vs. 9%	
Serious TEAE Frequency	12%	3%
TEAEs Leading to Discontinuation	6%	0%
Treatment-Emergent Deaths	1 event (3%)	0 events

[1]Assessed in 44 patients across both trial arms.
BMI=Body mass index. HFpEF=Heart failure with preserved ejection fraction. KCCQ-OSS=Kansas City cardiomyopathy questionnaire overall summary score. LVEF=Left ventricular ejection fraction. MRI=Magnetic resonance imaging. NYHA=New York Heart Association. TEAEs=Treatment-emergent adverse events.
Sources: Company reports, clinicaltrials.gov

Phase IIa trial of HU6

Results from the study to evaluate the safety and efficacy of once-daily HU6 in non-alcoholic fatty liver disease and high BMI have been reported. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04874233).

Efficacy. Once-daily HU6 demonstrated placebo-adjusted changes in liver fat content and weight loss up to -41% and -2 kg (both at the second-highest dose level), respectively, in non-alcoholic fatty liver disease (NAFLD) and high BMI at around 9 weeks (61 days). In addition, significant weight loss was maintained at the follow-up visit 10-14 days after the last dose. Furthermore, all HU6 groups lost a small amount of skeletal muscle mass over the trial period (less than 0.2 kg).

Investigators also observed significant placebo-adjusted improvements (reductions) in liver fibrosis as measured by FibroScan controlled attenuation parameter (CAP) score, glycated albumin, a marker poor glycemic control, and C-reactive protein, an inflammatory marker, in the HU6 arms.

Safety and tolerability. Treatment with HU6 led to 32% flushing, 25% diarrhea, and 12% palpitations across treatment arms. Moreover, there were no serious treatment-emergent adverse events; the discontinuation rate did not exhibit a dose-dependent relationship, occurring at up to 10% in the low-dose group, which was balanced with the placebo arm.

When the results were published, it was suggested by some commenters that the flushing experienced by some participants might be a sign of undetected increases in core body temperature, which could be a matter of concern (Taylor, et al. *Lancet Gastroent. & Hepat.* 2024). The authors of the study responded that a decrease in reactive oxygen species could explain the vasodilatory effect, but that further studies were underway that should address the issue (Rivus October 2023 press release; Noureddin, et al. *Lancet Gastroent. & Hepat.* 2024).

Other trials and next steps. A Phase IIa study of HU6 on energy metabolism, muscle and liver substrate metabolism, and mitochondrial function in subjects who are overweight or obese with type 2 diabetes was withdrawn when the FDA redirected the protocol to another division; it is expected to be refiled at a later date (NCT06104358).

Additional studies that do not explicitly address obesity are ongoing. A Phase II study of three dose levels of HU6 (150 mg, 300 mg, and 450 mg) in approximately 204 subjects with non-alcoholic steatohepatitis is active (NCT05979779). A Phase I trial of HU6 to compare the bioavailability of a once-daily 450 mg tablet dose and a 150 mg capsule dose three times daily is also ongoing (NCT06486558),

Rivus is not a publicly traded company. It has conducted private placements pursuant to the SEC's Regulation D and is said to be contemplating an IPO.

OrsoBio's TLC-6740, TLC-1180, and TLC-1235

The company is developing the three mitochondrial protonophores for obesity that it acquired from Gilead Sciences in 2020. TLC-6740 is an oral, liver-targeted mitochondrial protonophore; TLC-1180 and TLC-1235 are described by the company as having unique attributes compared to TLC-6740, including greater systemic distribution (OrsoBio press release). Although the company provides only limited information about the structure of these drugs and the mechanisms by which they work, the drugs appear to be pharmacologically manipulated versions of DNP (OrsoBio poster; Perry, et al. *Science* 2015; Goedeke & Schulman *Mol. Metab.* 2021).

At ObesityWeek 2024, OrsoBio presented preclinical results of TLC-1180 plus semaglutide in mice with diet-induced obesity (DIO)

TLC-1180 plus semaglutide demonstrated statistically significant vehicle-adjusted changes in body weight and fat mass of around 26% and 40% in DIO mice at roughly four weeks, exceeding values for either agent as a monotherapy. TLC-1180 also reduced lean mass by around 7% (*p*=NS), representing roughly half the lean mass loss associated with semaglutide-containing arms. In addition, TLC-1180 demonstrated an ability to sustain and deepen vehicle-adjusted weight and fat mass loss at around 6 weeks (39 days), including animals who discontinued semaglutide at roughly 4 weeks. Furthermore, while semaglutide significantly reduced vehicle-adjusted food intake, TLC-1180 monotherapy did not.

In a separate ObesityWeek 2024 poster, high-dose TLC-1180 induced statistically significant, dose-dependent weight loss up to 5% and dose-dependent increases in energy expenditure up to 120% of baseline in DIO mice at 1 week.

While the dosing schedule for TLC-1180 was not disclosed in the poster, TLC-1180 has been described in recent news as "suitable for weekly oral or subcutaneous administration."

OrsoBio is privately owned, and Eli Lilly is an investor in the company. Announcing a series B funding round in September 2024, the company stated that it intended to advance TLC-6740 into later-stage clinical trials and TLC-1180 and TLC-1235 into IND-enabling studies.

Phase I/Ib study of TLC-6740

The initial part of the study is testing the safety and pharmacokinetic parameters of the asset in healthy subjects; the second portion will test those endpoints (plus an investigation on food effect) in obesity with or without type 2 diabetes. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT05822544).

PYY

Peptide tyrosine tyrosine, generally referred to as peptide YY or PYY, was discovered in 1980 when it was isolated from the small intestine of pigs. The name is derived from the fact that the 36-amino-acid peptide has a tyrosine residue at each terminal, and the single letter designation for tyrosine is Y. It exists in two forms, PYY_{1-36} and PYY_{3-36}, the latter being the result of cleavage of the first two amino acids by DPP4. The longer form binds and activates all five Y receptors, whereas the truncated form has high affinity for only the Y2 receptor. PYY_{3-36} is believed to more actively control food intake (Cooper, *Nutr. Res. Rev.* 2014). The Y receptors bind both PYY and neuropeptide Y (NPY) and are sometimes referred to as NPY receptors. NPY is a 36-amino-acid peptide that also plays a role in regulating food intake, and it has 70% homology with PYY (Brothers & Wahlestedt, EMBO *Mol. Med.* 2010).

PYY, like GLP-1, is secreted by enteroendocrine L-cells in response to food intake. The Y receptors, which are G-protein-coupled receptors, are found in both the gut and brain. The receptors in the arcuate nucleus of the hypothalamus are understood to mediate PYY's effect on hunger. PYY passes freely through the blood–brain barrier (Cooper, *Nutr. Res. Rev.* 2014).

By the early 2000s, the satiety effect of PYY had been recognized. A 2003 paper in The New England Journal of Medicine described the effects of PYY_{3-36} delivered intravenously over a 90-minute period to both obese and lean fasting human subjects who received either the peptide or saline and were offered an ad libitum buffet lunch 30 minutes later. Caloric intake during the lunch was decreased by 30% in obese subjects and 31% in lean subjects who were given PYY, compared to the control subjects. Based on food diaries, the investigators also found a significant food intake inhibition that lasted for 12 hours after the infusion. The subjects did not report nausea, feelings of

reduced food palatability, or other adverse effects. Notably, fasting PYY levels correlated negatively with body weight, although it was not known whether obesity was the cause of low PYY or the reverse (Batterham, et al. *NEJM* 2003).

Research since 2003 has continued to provide evidence that PYY plays a role in weight loss. For example, investigators undertook a recent analysis of the results from a trial of the type 2 diabetes drug dapagliflozin (sold by AstraZeneca under the brand name Farxiga) for patients with HFpEF to determine why patients given the drug had greater weight loss than those given placebo. The investigators found that of the 3,072 proteins in the plasma of subjects that were measured, only PYY, which increased, was significantly changed in patients receiving the drug compared with those given a placebo (Reddy, et al. E*ur. Heart J.* 2024).

PYY Analogs

Despite more than two decades of knowledge about the satiety effect of PYY3-36, its adoption as an obesity therapy has faced hurdles. Like many endogenous peptides, it has a short half-life (about 10 minutes) and side effects at higher dosages (Chen, et al. *Bioorg. Chem*. 2023). There are also issues surrounding the delivery method; it is not absorbed well when ingested orally and subcutaneous injections are not as effective as desired, perhaps because they do not allow the peptide to bind its receptor in the gastrointestinal tract (Cooper, *Nutr. Res. Rev.* 2014).

These obstacles have led to the development of analogs, as with other natural molecules found to have a therapeutic effect on obesity. Researchers have employed a variety of approaches, including modifications to the amino acid sequence, PEGylation, lipidation, fusion with other peptides or proteins, and using only a portion of the peptide. A few have undergone clinical trials (Chen, et al. *Bioorg. Chem*. 2023; Melson, et al. *Int'l J. Obesity* 2024). No PYY analog has yet been submitted for FDA approval.

Eli Lilly's Nisotirostide
The company has conducted three Phase I trials for nisotirostide, or LY3457263 (PubChem listing), a PYY analog and RA. The drug has been administered by itself in healthy participants (NCT04641312), alone and with Trulicity in type 2 diabetes (NCT05377333), and with Zepbound in obesity (NCT05582096). No results have been posted.

Novo Nordisk's NNC0165-1875
The company conducted Phase I and Phase II trials for NNC0165-1875, another PYY analog, in combination with Wegovy (NCT03707990; NCT04969939). However, it has been reported that efforts to develop this drug have been dropped (Rubinić, et al. *Pharmacol. Res. Perspect.* 2024).

Metsera's Y14
The asset, a PYY analog developed at Imperial College London, does not have the first residue of PYY1-36 and makes substitutions for six other residues, resulting in a 35-residue peptide. An extended-release formulation in zinc chloride diluent has a half-life in rats of around 17 hours.

Phase I trial of Y14
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03673111).

Efficacy. Multiple doses of Y14 demonstrated dose-dependent placebo-adjusted weight loss up to 4 kg (around 4%) in obesity or overweight with or without type 2 diabetes or prediabetes at around 4 weeks (31 days). This was also associated with a placebo-adjusted reduction in food intake of 55% as of day 30, which was comparable to food intake reduction at day 2.

In comparison, in the efficacy estimand of the Phase III SURMOUNT-1 trial of Zepbound, patients with overweight or obesity demonstrated up to 4% placebo-adjusted weight loss at 6 weeks, acknowledging all limitations and caveats associated with cross-trial comparisons.

Safety and tolerability. Treatment with Y14 led to primarily gastrointestinal adverse events including nausea, vomiting, and constipation, as well as antidrug antibodies and low blood sugar. No serious adverse events were reported, and one patient in the treatment period 2 of cohort A1, representing 33% of the group, discontinued the trial due to gastrointestinal and injection site adverse events (Tan, et al. *Diab. Obes. Metab.* 2021).

It is interesting to note that although the trial results were initially submitted to clinicaltrials.gov in 2021, they have been resubmitted three times after being returned for quality control review. The most recent return was in November 2024, and the results have not yet been resubmitted in response (NCT03673111).

Y14 was spun out into a U.K. company, Zihipp Ltd, which was acquired in 2023 by New York-based Metsera, which is focused on medicines for obesity and metabolic disorders. In January, Metsera filed a registration statement with a preliminary prospectus for an initial public offering of its stock. According to this document, the company is working on multiple PYY analogs.

Boehringer Ingelheim's BI 1820237

Phase I trial of BI 1820237

The company recently published the results of the study of its Y2 RA, alone and in combination with Novo's early-generation GLP-1 RA Saxenda, in otherwise healthy men with overweight or obesity. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT04903509).

Efficacy. Significant reductions from baseline were observed for energy intake from the buffet lunch for the part 1 participants that received the two highest doses (1.8 mg or 2.4 mg). No significant weight loss was observed.

Safety and tolerability. The most common adverse effects were nausea and vomiting, which were severe in five persons in the first two parts and three persons in the third part. Only one adverse event, a contusion, was serious, and it was deemed unrelated to the drug. (Beetz, et al. *Diab. Obes. Metab.* 2024).

Next steps. In October 2024, Gubra announced that Boehringer had halted development of the asset (Gubra October 2024 press release).

CinFina's CIN-110

In March 2024, the company announced that the FDA had cleared its investigational new drug application for CIN-110, a PYY1-36 analog, which it describes as a large molecule, having an extended half-life, that is selective for the Y2 receptor. The company intends CIN-110 to be both a monotherapy and co-administration agent, dosed subcutaneously. According to the company, the drug is also designed to reduce the nausea and vomiting that can accompany administration of PYY1-36. CinFina in-licensed rights to develop CIN-110 from Janssen in 2021. A previously published article by several Janssen scientists described a cyclized PYY3-36 analog conjugated to an anti-human IgG Fc monoclonal antibody (Rangwala, et al. *Cell Metab.* 2019), although it is not known if this is the basis for CIN-110.

Phase I trial of CIN-110

For patient enrollment criteria and trial design, refer to the poster. CinFina Pharma is a portfolio company of the Cincinnati, Ohio-based CinRx Pharma, which is privately held.

Efficacy. Single doses of CIN-110 demonstrated placebo-adjusted weight loss up to around 1% (at the second-highest dose level) in obesity at around 1 week (day 8). In addition, CIN-110 demonstrated dose-dependent placebo-adjusted reductions in caloric intake up to 28% at 1 week, by visual estimation of the data.

Pharmacokinetic parameters. Regarding pharmacokinetic parameters, maximal concentration and area-under-the-curve (to 336 hours) values in plasma increased in a dose-dependent manner, and half-life was greatest at around 4 days at the second-lowest dose level.

Safety and tolerability. Of 24 patients, 3 mild events of nausea occurred, which did not increase in prevalence with increasing dose.

Early-stage Academic Research on Chimeric Peptides
Creative work being done in academic laboratories may suggest that similar efforts are being carried out in the biotech industry but are not published. For example, a 2023 paper studied a chimeric peptide monomer that includes partial amino acid sequences of a GLP-1 RA, exendin-4, and PYY. The investigators found that the drug acts as a triple RA, binding and activating the GLP-1 receptor as well as the Y1 and Y2 receptors in cell culture, and reducing food intake and body weight in rats (Chichura, et al. *Sci. Rep.* 2023). The authors intend to patent the drug and conduct trials in primates (Syracuse University announcement).

Leptin

Leptin is a 167-amino-acid product of the leptin gene, discovered in 1994 when it was found that a mouse model of obesity had a homozygous mutation of the gene, resulting in overeating. Leptin is secreted primarily by white adipose tissue (WAT). In obesity, therefore, the amount of leptin in circulation increases because the amount of WAT increases (Kelesidis, et al. *Ann. Intern. Med. 2010*).

Leptin receptors are expressed in the brain and in peripheral tissues. Leptin is actively transported through the blood–brain barrier (BBB). It also acts on areas of the hypothalamus that are not protected by the BBB. Downstream pathways of the leptin receptor include the JAK-STAT signaling pathway, the PI3K/Akt pathway, and the MAPK pathway, all of which are involved in regulating energy balance by influencing appetite and metabolism when activated by leptin binding to its receptor (Perakakis, et al. *JACC* 2021).

Leptin Receptor Agonism

Because providing the missing leptin to the mutant mice caused them to lose weight, it was initially thought that administering leptin to humans could reduce obesity. However, scientists soon found that obesity is often accompanied by a resistance to the effects of leptin, possibly as a result of an excess of the hormone. Thus, leptin RAs have been developed primarily for treatment of leptin deficiency but may also be a useful adjunct to obesity treatments that reduce an individual's WAT and/or otherwise ameliorate leptin resistance.

Regeneron's Mibavademab
Mibavademab, also known as REGN4461, is a monoclonal antibody that acts as leptin receptor (LEPR) agonist. It activates the LEPR in the presence or absence of leptin. Mibavademab is of the protein subtype IgG4 and contains two modifications: substitution of pidolic acid at the N-terminal and removal of lysine at the C-terminal of the two heavy chain subunits (GSRS listing). The drug was developed as a treatment for lipodystrophy that results from genetic leptin deficiency or that is acquired (often due to autoimmune disorders, infections, or certain medications).

Phase I trial of mibavademab
For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT03530514).

Efficacy. Multiple doses of mibavademab demonstrated up to 3 kg (around 4%) placebo-adjusted weight loss (highest in the patient subgroup consisting of men with low leptin levels and overweight or obesity) at around 11 weeks (78 days). All groups excepting the patient group of women with higher baseline leptin levels, experienced placebo-adjusted weight loss. (Gewitz, et al., *Clin. Transl. Sci.* 2024).

Safety. Adverse events associated with mibavademab were reported as mild to moderate in severity.

Phase II trial of mibavademab plus Zepbound
Eli Lilly is conducting the study, testing the efficacy of mibavademab as a monotherapy or with Zepbound in obesity. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06373146).

Unspecified Assets

Certain drugs from major companies have advanced to clinical trials for obesity, but their mechanisms of action have not been publicly described.

Eli Lilly's LY3549492

Phase I trials of LY3549492
The asset has undergone two Phase I trials: a study in healthy participants that completed in January 2022 and a study of carbon-14-labeled drug in healthy participants that completed in February 2024. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06194500; NCT04758234).

Phase II trials of LY3549492
Two Phase II studies for obesity are ongoing: a study to investigate weight management with LY3549492 compared with placebo in obesity or overweight and a master protocol study (LY900038) of multiple intervention-specific appendices (ISAs) in obesity or overweight. In the latter trial, LY3549492 will be compared with Zepbound, LY3305677 (mazdutide), and LY3841136 (eloralintide). In both Phase II trials, the drug is being administered orally. Completion of each is anticipated for 2026. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06683508; NCT06143956).

Amgen's AMG 513

Phase I trial of AMG 513
The single- and multiple-ascending-dose study is testing the asset's safety and tolerability in obesity; results are anticipated in August. For patient enrollment criteria and trial design, refer to clinicaltrials.gov (NCT06585462).

In February, the FDA placed a clinical hold on the study; discussions are progressing to reopen the study (Amgen February 2025 press release).

Conclusion

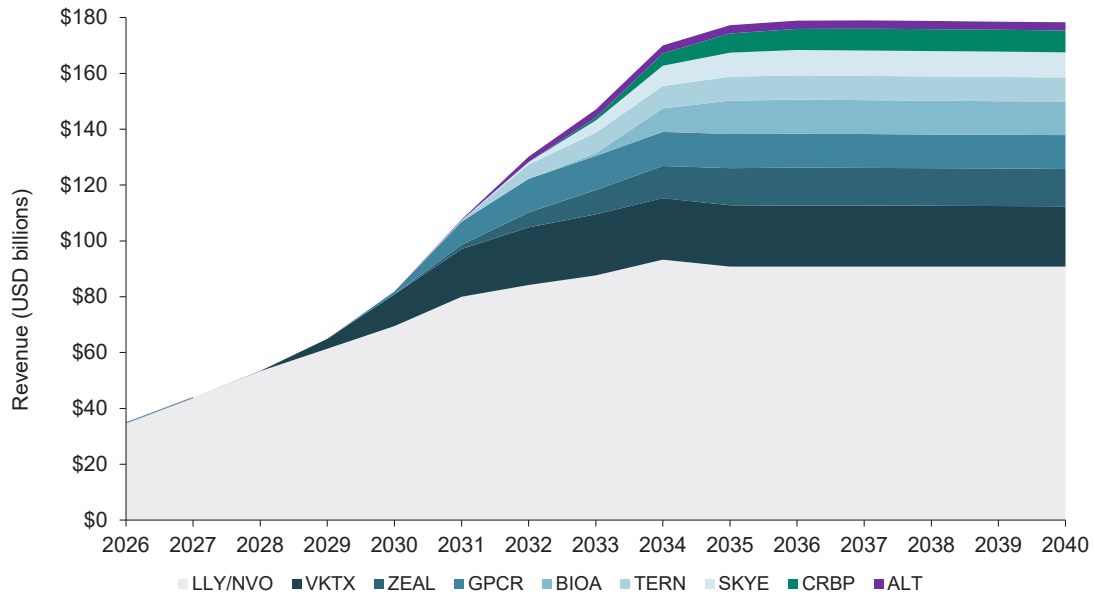
Fueled by the commercial success of Wegovy and Zepbound, the obesity space has benefited from significant investments in the past several years. The inflow of capital has resulted in a torrid pace of innovation, which then poses a challenge for investors to contextualize and analyze the competitive landscape. To that end, our report aims to serve as a one-stop shop that captures relevant clinical data, categorized by the therapeutic modality and mechanism of action. Furthermore, we devised a formula that encapsulates both the efficacy and tolerability of investigational anti-obesity medications, which can be used to quantify clinical attributes within the same class. While therapeutic agents that specifically preserve lean body mass have garnered considerable investor attention, we await further regulatory clarity from the FDA and will likely provide additional commentary in a future edition.

Appendix

We collected consensus estimates for future revenues from Eli Lilly's and Novo Nordisk's late-stage obesity franchises (to 2035, then assumed no growth thereafter). To illustrate revenue contributions from obesity therapies beyond the current duopoly, we overlaid products developed by companies that we cover (exhibit 65 below). We emphasize that these revenue projections are not probability-adjusted, and given the late-stage nature of Eli Lilly's and Novo Nordisk's investigational assets, we expect the probability of success to be greater for the two market leaders than the eight contenders.

Exhibit 65

Projected Revenues of Weight Management Drugs From Covered Companies Operating in the Obesity Space



Note: Consensus revenues for LLY/NVO only project to 2035. We have assumed flat growth from 2035 onward.
Sources: Bloomberg, company reports, and William Blair Equity Research

The prices of the common stock of other public companies mentioned in this report follow:

Altimmune, Inc. (Market Perform)	$5.91
Amgen Inc. (Outperform; covered by Matt Phipps, Ph.D.)	$315.63
AstraZeneca PLC	$78.40
BioAge Labs, Inc. (Market Perform)	$4.18
Biohaven Ltd. (Outperform)	$36.43
Corbus Pharmaceuticals Holdings, Inc. (Outperform)	$7.50
Eli Lilly and Company	$901.80
Merck & Co., Inc.	$91.43
Metsera, Inc.	$27.33
Novo Nordisk A/S	$90.95
Pfizer, Inc.	$26.74
Regeneron Pharmaceuticals, Inc.	$723.47
Roche Holding Ltd	$41.81
Scholar Rock Holding Corp.	$36.35
Skye Bioscience, Inc. (Outperform)	$2.89
Structure Therapeutics, Inc. (Outperform)	$21.09
Terns Pharmaceuticals, Inc. (Market Perform)	$3.71
Veru, Inc.	$0.52
Viking Therapeutics, Inc. (Outperform)	$28.32
Zealand Pharma A/S (Market Perform)	DKK 719.00

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DOW JONES: 43433.10
S&P 500: 5956.06
NASDAQ: 19075.30

Additional information is available upon request.

Current Rating Distribution (as of February 27, 2025):

Coverage Universe	Percent	Inv. Banking Relationships *	Percent
Outperform (Buy)	70	Outperform (Buy)	9
Market Perform (Hold)	29	Market Perform (Hold)	1
Underperform (Sell)	1	Underperform (Sell)	0

*Percentage of companies in each rating category that are investment banking clients, defined as companies for which William Blair has received compensation for investment banking services within the past 12 months.

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