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BIOINSIGHTS℠

Mirror, Mirror on the Wall; Who Has the Best Obesity Drug of All?

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Piper Sandler Investment Research

At Piper Sandler, our biopharma investment research team delivers to clients market-driven and actionable insights across the biotech and pharmaceutical sectors. We build strong partnerships with clients, and they trust our unique perspective to guide their investment strategies.

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Source: Piper Sandler Research.

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1. Executive Summary

Executive Summary: Mirror, Mirror on the Wall; Who Has the Best Obesity Drug of All?

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All eyes are on obesity; the space is very hot. With $19.62B raised from 3Q23 to September 4, 2024 (across 45 completed deals), it is clear that obesity continues to be a hot, investable area. Big Pharma's strong interest in obesity is underscored by LLY having 10+ and NVO having 8+ obesity agents in development, and other large players are committed to making further investments in their own cardiometabolic pipelines. Aggregate global obesity sales by 2030 for each currently-approved agent is projected to exceed $120B (with $121B for Wegovy and $126B for Zepbound), highlighting the massive opportunity for these and other novel agents to capture this "mega-blockbuster" market. ***See pages 10-19.***

Catalyst-rich 2H24 with 16 key GLP-1 data readouts. Notably, there are 13 injectable and 3 oral GLP-1 catalysts between now and YE24, marking a catalyst-rich fall with continued validation of this MoA in the obesity space. Please ***email us for our Vol. 13 obesity tracker*** with 300+ obesity catalysts across 125+ agents and 92 clinical datasets from 13 oral agents and 17 injectables. ***See pages 55-56.***

Shifting the needle: next-generation anti-obesity agents are addressing key unmet needs in the space. In this deep-dive (***see here for our 2023 obesity report***) we examine how developers are addressing major challenges and limitations in the anti-obesity therapeutics space. For example, current supply chain constraints, due to massive demand for GLP-1s and manufacturing complexity, can be solved with the oral small molecules that are easier and cheaper than current SC agents to produce and store. Poor treatment adherence and high rates of discontinuation with GLP-1s — due to a variety of factors, including poor GI tolerability — can be mitigated with more convenient oral options that reduce treatment burden and improve real-world utility. This is crucial as anti-obesity agents require chronic treatment to provide consistent, durable benefits. Next, there are concerns regarding lean muscle loss, highlighting the importance of weight loss *quality* (especially for frail populations). Protection of lean mass has become a key focus for novel agents to provide muscle-sparing when used alone and/or in combination with incretins to facilitate high-quality (i.e., fat-selective) weight loss. Lastly, when thinking about obesity treatment, it is important to consider the benefits to co-morbidities, as this will ultimately help to segment the market according to different subpopulations of obese patients. As anti-obesity drugs continue to establish clinically-meaningful improvements across weight-related co-morbidities (CVD, CKD, and many others), this will further expand reimbursement and overall payer sentiment for obesity therapeutics. ***See pages 61-66.***

What are some novel MoAs in development for obesity? Looking at the competitive landscape, next-generation anti-obesity drugs with novel MoAs are emerging to overcome challenges and limitations of existing incretin-based therapeutics. We examine some of these new approaches in our report, including amylin analogs, apelin receptor agonists, CB1 receptor modulators, leptin-melanocortin modulators, mitochondrial uncoupling agents, NLRP3 inflammasome inhibitors, and targeting of the INHBE pathway. These and other novel therapies are being advanced into the clinic and represent not only potential monotherapies for obesity and its comorbidities, but also promising combination therapies given complementary MoAs. ***See pages 68-80.***

Within this report, we provide detailed profiles for 18 public and 13 private companies that are active within the anti-obesity therapeutics space.

Source: Piper Sandler Research.

Obesity Therapeutics Companies Profiled in This Report

Obesity therapeutics companies profiled in this report. The 30 public and private companies shown below are profiled within **Section 3** of this report. Company logos are hyperlinked to the relevant profiles.

Source: Company Materials. Piper Sandler Research.

2. Deep Dive into Obesity Therapeutics

2.1. Investments in the Obesity Landscape Continue to Grow

Obesity is a Very Hot Space; We Think There is a Lot More Still to Come

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A closer look at recent capital raising, M&A, and strategic alliance deals in the anti-obesity therapeutics space. Our analysis of capital raisings (equity offerings and venture financings), mergers and acquisitions, and strategic alliances (partnerships and licensing deals) for companies developing agents to treat obesity identified **45 completed deals totaling $19.62B in disclosed deal value** from Q3 2023 to September 4, 2024 (**Exhibits 1 & 2**), per GlobalData's Deals Database. Among disclosed deals, equity offerings and venture financings totaled $4.11B with an average deal size of $158.0M, mergers, acquisitions, and asset transactions totaled $5.06B with an average deal size of $1.27B, and licensing agreements and partnerships totaled $10.45B with an average deal size of $1.49B.

Some notable deals in the obesity therapeutics space between 3Q23 and September 2024 include: (1) **Roche's (OTC: RHHBY)** $3.1B acquisition of Carmot Therapeutics in January 2024; (2) **Eli Lilly's (LLY, not covered)** acquisition of Versanis for up to $1.93B in August 2023; (3) **AstraZeneca's (AZN, not covered)** $2.01B licensing agreement with **Eccogene** in November 2023; (4) **Zealand Pharma's (ZEAL, not covered)** $1.0B raise in a private placement of shares in June 2024; (5) **Viking Therapeutics'** (**VKTX, not covered**) $632.5M raise in a public offering of stock in March 2024; (6) **Structure Therapeutics' (GPCR, Rahimi, OW)** raise of $547.41M in a public equity offering in June 2024; (7) **Novo Nordisk's (NVO, not covered)** $255.97M licensing agreement with **Omega Therapeutics (OMGA, Tenthoff, OW)** in January 2024; (8) **Crinetics Pharmaceuticals (CRNX, Rahimi, OW)** $350M raise in private placement of shares in March 2024; (9) **BioAge Labs' (Private)** $170M Series D financing in February 2024; (10) **Keros Therapeutics' (KROS, Catanzaro, OW)** raise of $161M in a public offering of stock in January 2024; and others.

EXHIBIT 1

Key Data for Select Completed Deals (US/EU) in the Autoimmune Disease Cell Therapy Space: 3Q23 – September 2024

Source: GlobalData Deals Database: Completed Deals; Q3 2023 – September 2024 (Data Extracted on 09/04/24). Company Materials. Piper Sandler Research.

Deal Flow has Increased in Obesity Therapeutics (Page 1 of 2)

EXHIBIT 2

Select Completed Capital Raising, M&A, and Strategic Alliance Deals Involving Therapies for Obesity: Q3 2023 – 2024 YTD

Date Completed	Deal Headline	Deal Type	Deal Value (US$M)
4 Sep 2024	HAYA Therapeutics Enters Collaboration With Eli Lilly for Up to $1B to Discover Novel Obesity/Metabolic Drugs	Partnership	1,000.00
20 Aug 2024	Ambrosia Biosciences Raises $16M in Series A Financing	Venture Financing	16.00
14 Aug 2024	OrsoBio Raises $40M in Equity Financing	Equity Financing	40.00
26 Jul 2024	Confo Therapeutics Raises $65.08M in Series B Financing	Venture Financing	65.1
24 Jul 2024	Skye Bioscience Enters into Collaboration Agreement With Beacon Biosignals	Partnership	N/A
28 Jun 2024	Zealand Pharma Raises $1B in Private Placement of Shares	Equity Offering	1,005.76
25 Jun 2024	NeuroBo Pharma Raises $17M in Private Placement of Shares	Equity Offering	17.00
25 Jun 2024	NeuroBo Pharma Raises $3M in Registered Direct Offering	Equity Offering	3.00
17 Jun 2024	Immunis Raises $15.79M in Equity Financing	Equity Offering	15.79
12 Jun 2024	Flagship Pioneering Enters into Research Agreement with ProFound Therapeutics	Partnership	N/A
7 Jun 2024	Structure Therapeutics Raises $547.41M in Upsized Public Offering of American Depositary Shares	Equity Offering	547.41
30 May 2024	CinRx Pharma Raises $73M in Financing Round	Venture Financing	73.00
22 May 2024	SixPeaks Bio Raises $30M in Series A Financing	Venture Financing	30.00
20 May 2024	Hercules CM Enters into Licensing Agreement with Jiangsu Hengrui Medicine	Licensing Agreement	6,000.00
9 May 2024	Aardvark Therapeutics Raises $85M in Series C Financing	Venture Financing	85.00
9 May 2024	Flagship Pioneering and Metaphore Biotechnologies Enters into Research Agreement with Novo Nordisk	Partnership	600.00
7 May 2024	HK inno.N Enters into Licensing Agreement with Sciwind Biosciences	Licensing Agreement	56.00
1 May 2024	Elevai Labs Enters into Licensing Agreement with MOA Life Plus	Licensing Agreement	N/A
3 Apr 2024	Metsera Raises $290M in Venture Financing	Venture Financing	290.00
27 Mar 2024	AstralBio Enters into Licensing Agreement with IBio	Licensing Agreement	N/A
26 Mar 2024	Serina Therapeutics Merges with AgeX Therapeutics	Merger	N/A
12 Mar 2024	Arecor Therapeutics Enters into Agreement with TRx Biosciences	Partnership	N/A
4 Mar 2024	Viking Therapeutics Raises $632.5M in Public Offering of Common Stock	Equity Offering	632.50
1 Mar 2024	Crinetics Pharmaceuticals Raises $350M in Private Placement of Common Shares	Equity Offering	350.00
13 Feb 2024	BioAge Labs Raises $170M in Series D Financing	Venture Financing	170.00
6 Feb 2024	Fractyl Health Raises Approximately $110M in IPO of Shares	Equity Offering	110.00
2 Feb 2024	Corbus Pharma Raises $94.50M in Public Offering of Common Stock	Equity Offering	94.50
31 Jan 2024	Adipo Therapeutics Raises $1.9M in Seed Financing	Venture Financing	1.90

Source: GlobalData Deals Database: Completed Deals; Q3 2023 – September 2024 (Data Extracted on 09/04/24). Company Materials. Piper Sandler Research.

Deal Flow has Increased in Obesity Therapeutics (Page 2 of 2)

EXHIBIT 2

Select Completed Capital Raising, M&A, and Strategic Alliance Deals Involving Therapies for Obesity: Q3 2023 – 2024 YTD (Continued)

Date Completed	Deal Headline	Deal Type	Deal Value (US$M)
29 Jan 2024	Roche Acquires Carmot Therapeutics for $3.1B	Acquisition	3,100.00
23 Jan 2024	Novo Nordisk Enters into Licensing Agreement with EraCal Therapeutics	Licensing Agreement	255.97
12 Jan 2024	Zealand Pharma Raises $213.3M in Private Placement of Shares	Equity Offering	213.27
9 Jan 2024	Keros Therapeutics Completes Public Offering of Common Stock for $161M	Equity Offering	161.00
4 Jan 2024	Novo Nordisk Enters into Research Agreement with Omega Therapeutics	Partnership	532.00
4 Jan 2024	Resalis Therapeutics Raises $11M in Series A Financing	Venture Financing	11.00
14 Dec 2023	Deep Apple Therapeutics Raises $52M in Series A Financing	Venture Financing	52.00
6 Dec 2023	Enterin Raises $5M in Equity Financing	Equity Offering	5.00
9 Nov 2023	AstraZeneca Enters into Licensing Agreement with Eccogene	Licensing Agreement	2,010.00
7 Nov 2023	OrsoBio Raises $60M in Series A Financing	Venture Financing	60.00
17 Oct 2023	Amplifier TX Raises Funds through Series A2 Financing	Venture Financing	N/A
30 Aug 2023	Novo Nordisk Acquires Embark Biotech for $16.25M	Acquisition	16.26
28 Aug 2023	i2o Therapeutics Acquires Pipeline Assets from Intarcia Therapeutics	Asset Transaction	N/A
28 Aug 2023	i2o Therapeutics Secures $46M in Series A Venture Funding	Venture Financing	46.00
18 Aug 2023	Skye Bioscience Acquires Bird Rock Bio for Approximately $20M	Acquisition	20.00
15 Aug 2023	Skye Bioscience Raises $12M in Private Placement of Shares	Equity Offering	12.00
14 Aug 2023	Eli Lilly Acquires Versanis for Up to $1.925B	Acquisition	1,925.00

Source: GlobalData Deals Database: Completed Deals; Q3 2023 – September 2024 (Data Extracted on 09/04/24). Company Materials. Piper Sandler Research.

What Does it Take for an Obesity Asset to be Acquired?

EXHIBIT 3

Overview of Key Elements That We Believe Pharma Companies are Looking at to Rationalize Investments in Obesity Agents

While we recognize that each pharma company has its own internal criteria and priorities, below we highlight some key elements that we believe strategics will consider to rationalize their investment in anti-obesity medications.

1

Drug Demonstrates a Robust Safety & Tox Package

This is a crucial point of consideration as concerning safety signals would be a non-starter in obesity. Given the size of the market, the FDA is cognizant that any drug toxicity (even rare) could pose a serious threat/overwhelm the healthcare system. We think Pharma is looking to see breadth and depth of pre-clinical tox data conducted in multiple species models to have confidence that the drug is viable and safe for humans.

2

Optimizing the Balance Between Weight Loss & Safety/Tolerability

For companies intending to acquire assets around Phase IIb, we believe the dosing and titration schedule is top of mind and should provide clarity around the optimal dose that maximizes safety and efficacy/tolerability. Considering that GI tolerability is the primary tolerability concern for currently-marketed agents, we think that agents with a track record of strong tolerability would be especially compelling, even if this sacrifices a modest amount of weight loss efficacy.

3

Potential for Differentiation Within the Obesity Market & Addressing Comorbidities for Competitive Positioning

Obesity is a massive opportunity that will inevitably demand a range of MoAs and administrations, considering that different segments of patients will respond better to different agents. We believe that Pharma will be considering the totality of a drug's profile, with an emphasis beyond weight loss alone given obesity's strong association with different comorbidities. Drugs bringing additional efficacy benefits to certain comorbidities may be well positioned to target specific segments of the market.

4

Competitive Weight Loss & Other Drug Attributes

However, for a given drug to be competitive, the weight loss does not need to be exactly equal to or exceed the currently approved options. Provided that there is clear weight loss benefit in the approximate ballpark of other agents, we believe the specific drug attributes will ultimately be more important considerations (e.g., MoA, ability to modify other comorbidities, form of administration, tolerability profile).

5

IND is Cleared, Taking Some Risk Off of Pharma

We believe that some strategics will want to see that the IND is cleared for the drug to enable seamless transition into subsequent clinical trials. This allows Pharma to maximize efficiency and thus provide the greatest return on this investment. On the other hand, companies such as NVO (not covered) have expressed particular interest in early-stage assets, and thus IND clearance may not be a requirement for them.

Source: Piper Sandler Research.

Big Pharma Investments Continue to Grow in Obesity Space (Page 1 of 3)

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Tracking Big Pharma's obesity footprint: key takeaways from 2Q24 earnings calls. We listened to 2Q24 Big Pharma earnings to understand how industry leaders are planning to develop assets in the obesity space. As expected, **LLY** and **NVO (not covered)** continue to lead in the obesity market with tirzepatide and semaglutide and potential indication expansion (OSA, CKD, HFpEF, and MASH). Further, we highlight a focus on oral therapies with **AZN's (not covered)** AZD5004 (oral GLP-1) and AZD0780 (oral PCSK9), **LLY's** orforglipron (oral GLP-1), **RHHBY's** CT-996 (oral GLP-1), **NVO's** amycretin (oral GLP-1/amylin), **NVS'** DFV890 (oral NLRP3i), and **PFE's (not covered)** danuglipron (oral GLP-1). A common thread besides a growth in development of oral therapies is the desire for highly tolerable, combinable, and novel MoA assets with distinct benefits beyond weight loss (e.g., lean mass preservation). While **BMY (not covered)** did not provide in-depth obesity discussion, it continues to monitor the growing obesity space. Lastly, **GSK (not covered)**, **JNJ (not covered)**, and **SNY (not covered)** did not comment with respect to obesity.

- **AZN (not covered)** is advancing its weight management portfolio strategy with a catalyst rich 2H24 (*note here*). Specifically, AZN's weight management pipeline includes AZD5004 (oral GLP-1), AZD9550 (SC GLP-1/Glucagon), AZD6234 (SC long-acting amylin), and AZD0780 (oral PCSK9). Mgmt believes these assets have strong potential in three major market segments: (1) simple weight management for people with BMI <28-30 - a group of patients who may need to lose just a few pounds and could have other risk factors (e.g., dyslipidemia); (2) significant weight loss for obese patients (BMI >30), who are in need of agents that can be titrated higher in combination with other MoAs to improve weight loss quality (e.g., lean mass preservation) with a tolerable profile; and (3) patients with traditional diabetes. While mgmt stated that the obesity space is heterogeneous, they noted that >60% of patients have ≥1 weight-related comorbidity, further speaking to the individual needs of different subgroups. AZN remains confident in AZD5004 (GLP-1) given its QD dosing, positive PK/PD profile, and no safety warnings (PhI data expected at a conference later this year). AZN believes that amylin will be a crucial component to promote safety/lean mass preservation, further bolstering its confidence in its obesity strategy.
- **BMY (not covered)** provided minimal commentary on the obesity space. On BMY's 2Q24 earnings call (*note here*) when asked about interest in the obesity space mgmt noted they continue to monitor the obesity market, though with respect to business development they are focused on other strategic areas: hematology, oncology, CV, immunology, and neuroscience.
- **LLY (not covered)** is committed to orforglipron (daily oral GLP-1R agonist), with a data outpour expected in 2025 (*note here*). LLY reported strong sales growth with Mounjaro achieving $3.2B in global sales ($2.4B in the US) and Zepbound achieving >$1.2B in sales in 2Q24. LLY mgmt highlighted that underlying revenue was driven by ramped-up production, expanded formulary coverage and access in the US (with >50% of employers opting into anti-obesity medicine coverage). LLY continues to invest into manufacturing with the announcement of an additional $5.3B investment in Lebanon, IN in May 2024, bringing its total investment to $9B, in addition to ramping up production at other sites. LLY mgmt also highlighted that its Concord, NC site is progressing well, with initial production expected by YE24. LLY mgmt also emphasized the importance of oral therapies and its implications

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Big Pharma Investments Continue to Grow in Obesity Space (Page 2 of 3)

on manufacturing to open the door and address the high unmet need and demand for anti-obesity products. To this end, LLY intends to start reading out data across its ACHIEVE and ATTAIN programs, which should provide further clinical evidence towards LLY's goal of achieving an oral therapy with an injectable-like efficacy and strong tolerability. Moreover, LLY detailed that therapeutics with novel MoAs are a central part of LLY's strategy for next-generation metabolic therapeutics. First, glucagon remains a key target for LLY, with LLY expanding its retatrutide TRIUMPH and TRANSCEND programs and the mazdutide (GLP-1/Glucagon) PhII (NCT06124807) in 165 obese/overweight adults with primary endpoint of % change in BW currently enrolling patients. Second, LLY is also evaluating differentiated weight loss, with development ongoing for DACRA QW II (dual amylin and calcitonin receptor agonist) and bimagrumab (ActRII mAb inhibitor), with potential for combination with tirzepatide. Lastly, LLY is also running two studies with eloralintide (amylin agonist LA), further substantiating the company's strong high interest in this MoA and the obesity space in general.

- **MRK (not covered)** is highly interested in the obesity space in the context of a cardiometabolic pipeline (*note here*). MRK communicated its consistent BD strategy where the approach is to focus on the science where the market opportunity is best aligned with its existing portfolio and skill set. MRK is especially focused on second- or third-generation obesity agents as it views first generation agents as no longer viable. MRK's focus for a next-generation agent prioritizes assets with the following characteristics: (1) oral; (2) high tolerability; (3) potential for use in combination; and (4) muscle mass preservation. We believe these comments emphasize mgmt's continued interest in the obesity space, with particular interest in next-generation oral agents.
- **NVO (not covered)** is committed to maintaining its leading position in obesity and diabetes (T2D; *note here*). The company highlighted that it holds market leadership in T2D, with 34.1% share (driven by North American and international sales growth). As such, NVO mgmt detailed its enthusiasm for CagriSema's 68-week PhIII REDEFINE 1 trial (NCT05567796) in 3,400 overweight or obese patients, with primary endpoint of relative change in BW and achievement of ≥5% weight reduction, which has been guided to readout in 4Q24. NVO mgmt further detailed that upon readout of REDEFINE 1, the company will discuss how it intends to position this asset. Importantly, NVO is fully ready to scale CagriSema production with a dual chamber injector for both cagrilintide and semaglutide, based on its learnings with semaglutide, where NVO is also currently evaluating a fixed dose combination to enhance scalability for this therapeutic asset. With respect to semaglutide, NVO is on track to present topline data for Part 1 of the ESSENCE trial (n=~800 patients), which will serve as part of the data package for regulatory submission in 4Q24, with the full 1200 patients and hard outcomes data to follow. In addition, NVO provided additional regulatory updates, including the withdrawal of its HFpEF application and resubmitting a filing in the beginning of 2025 to increase the likelihood of hard endpoints on the label. Lastly, when asked about the average duration of use for Wegovy, mgmt noted that the current average of 6 months is due to supply constraints, where they expect this number to be more reflective of the clinical profile of 12 months and beyond in the near-term future.

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Big Pharma Investments Continue to Grow in Obesity Space (Page 3 of 3)

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- **NVS (not covered)** is focused on next-generation medicines to address obesity or related CV conditions (*note here*). NVS mgmt articulated how the success of semaglutide and tirzepatide in the obesity market will limit the success of modestly-differentiated therapies due to substantial rebate wall and portfolio blocks expected toward the end of the decade. Therefore, NVS is focused on developing next-generation assets to address obesity or related CV conditions, with potential as a monotherapy and/or combination therapy. NVS highlighted its interest in therapies based on potentially much longer-acting agents, biologics, or siRNA, along with other new MoAs that provide dosing advantages, tolerability advantages, or the ability to preserve muscle mass. NVS is currently assessing DFV890's (NLRP3 inhibitor) potential to reduce hsCRP, IL-6, and IL-18 across multiple indications such as coronary heart disease, CHIP, osteoarthritis, low risk myelodysplastic syndromes, and low risk chronic myelomonocytic leukemia. Taken together, we believe NVS' focus on second-generation obesity products providing benefit beyond weight loss supports the continued development of novel MoAs in the cardiometabolic space, especially if these agents produce added benefit to current approved incretins.
- **PFE (not covered)** is making progress to advance QD danuglipron (oral GLP-1R agonist) into the clinic (*note here*). PFE mgmt articulated that given the data seen thus far with a QD modified-release formulation, it has identified a formulation with an ideal target product profile, with dose optimization studies to kick off in 2H24. The PK data have been guided to be read out in 1Q25, where mgmt noted that these data will help guide a PhIII registrational program, pending alignment with the FDA for QD danuglipron. In parallel, PFE is working on advancing PF-06954522 (oral GLP-1R agonist), which is currently under investigation in PhI. PFE is also committed to developing PF-07976016 (MoA undisclosed), which mgmt believes has the potential to be combined with an oral GLP-1, and that these early stage assets will be valuable for lifecycle management and putting PFE back on the map in the competitive landscape of obesity.
- **RHHBY (not covered)** continues to be focused on building an obesity/CV franchise (*note here*). Mgmt provided positive commentary regarding its substantial interest in the obesity opportunity, which they believe will be a key value driver. Recall that the company acquired Carmot's entire portfolio (including CT-388, CT-868, and CT-996), and also an entire array of molecules to explore other/potentially novel MoAs. Mgmt believes there is strong combination potential with other assets within RHHBY's own pipeline to comprehensively build out a robust obesity platform. The team also continues to look out for any opportunities with new agents in the space, but remains diligent when assessing the potential to ensure the right value for the market with the underlying science to support it. While mgmt pointed to last year's Carmot acquisition when asked about how they are thinking about future obesity development, any future strategic decisions for obesity will ultimately depend on the availability and price tag to ensure the company is staying disciplined.

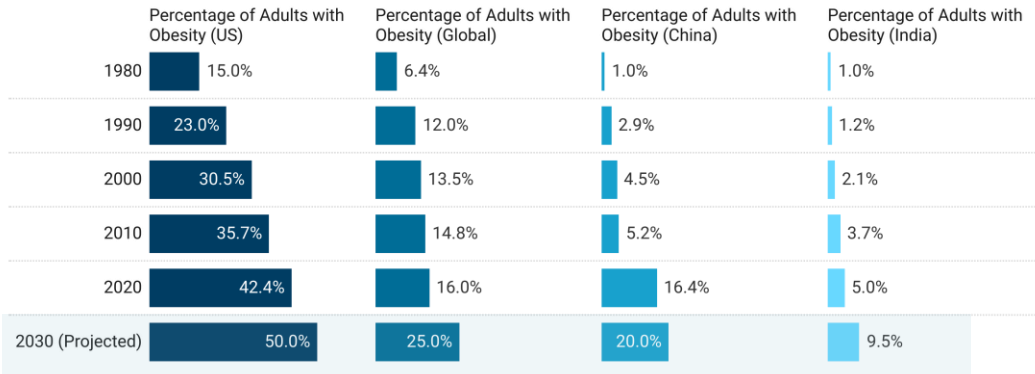
Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

The Global Obesity Epidemic is a Growing Problem

The global health and economic consequences of obesity are enormous and are projected to grow significantly, requiring large-scale interventions – including anti-obesity medications – aimed at promoting weight loss. Obesity – defined as a **body mass index (BMI) of 30 or more** – is a global health epidemic that is associated with increased risk of serious and chronic conditions (cardiovascular diseases, cancer, type 2 diabetes, sleep apnea, and many others) among those affected, causing significant morbidity and mortality and substantial economic costs. Lifestyle modifications may be helpful to treat obesity but alone are often insufficient. This is typically due to weight regain that is caused by physiological changes that slow metabolism and increase appetite. **Obesity's global prevalence more than doubled (to 16%) between 1980 and 2020**, and there are currently ~1B obese people aged 5+ years across the world. **The US has been particularly hard hit:** 42.4% of adults (~138M people) were obese in 2020 (up from 15% in 1980), and ~9% are severely obese (BMI of 40+). According to the CDC, ~1 in 5 US children and adolescents (~15M youths) are obese. Furthermore, obesity disproportionately affects Hispanic and non-Hispanic Black people in the US, and its prevalence is inversely correlated with socioeconomic status. Obesity is also surging in developing countries such as China and India, driven by economic growth, urbanization, and dietary and lifestyle changes. Emphasizing the magnitude of the problem of obesity, **it is projected that by 2030 25% of the global population and 50% of US adults will be obese**. The **economic burden of obesity is also considerable**: the global economic costs associated with obesity and overweight were estimated to be ~$2T annually in 2020, and will exceed $3T by 2030 and $4T by 2035 (~3% of global GDP). In the US, the total cost of chronic diseases driven by obesity/overweight was ~$1.7T in 2016 (~9% of US GDP). This includes direct healthcare costs (~$500B) as well as indirect costs due to lost economic productivity (~$1.2T), and is expected to continue to grow with the rising prevalence of obesity and the cost of treating it.

EXHIBIT 4

Obesity Has a Very Large & Growing Global Health & Economic Footprint: One in Two US Adults & One in Four Adults Globally Will be Obese by 2030



Source: Lim HJ et al. Global Trends in Obesity; in: *Handbook of Eating and Drinking*; 2020:1217-1235. Sung M et al. *BMC Public Health*. 2024;24:1322. Pan XF et al. *Lancet Diabetes & Endocrinol*. 2021;9:373. Hemmingson E. *Int J Obesity*. 2021;45:921. Cawley J et alCDC.gov. WHO.int. Our World in Data: Obesity. Graph created with Datawrapper. Piper Sandler Research.

Currently-Available Anti-Obesity Therapies

Multiple obesity treatment guidelines recommend the use of anti-obesity medicines (AOMs) in combination with lifestyle modification (diet, exercise, behavior) to achieve and sustain a sufficient degree of weight loss that can reduce or resolve obesity-related complications. Currently, a number of AOMs are indicated for the treatment of obesity through chronic weight management: (1) in adults with a body mass index (BMI) of 30 or more; (2) in adults with a BMI of 27 or more and weight-associated comorbidities, including type 2 diabetes (T2D), hypertension, and/or dyslipidemia; and (3) in adolescents (12+ years of age) with BMI at or higher than the 95% percentile for their age and sex. AOMs are not indicated for use in children <12 years of age at this time.

Currently-approved anti-obesity medicines (AOMs) can be classified into three groups according to their MoA: (1) intra-gastrointestinal drugs (e.g., orlistat); (2) centrally-acting drugs (e.g., phentermine, phentermine-topiramate, naltrexone-bupropion); and (3) nutrient-stimulated hormone-based drugs (e.g., liraglutide, semaglutide, tirzepatide) (**Exhibit 5**, below). The latter group (i.e., incretins/GLP-1s) has received a lot of patient, physician, and investor interest in recent years due to them producing unprecedented levels of weight loss in obese individuals, while also mitigating health risks associated with certain comorbid conditions, such as cardiovascular disease.

EXHIBIT 5

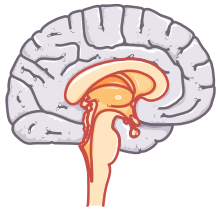
MoAs & Adverse Effects of the Three Classes of Approved AOMs: Centrally-acting Drugs, Nutrient-simulated Hormone-based Drugs, & Intra-gastrointestinal Drugs

Centrally-acting AOMs

- Phentermine: induces release of norepinephrine in the hypothalamus. *Adverse effects*: xerostomia, insomnia, headache, constipation
- Phentermine-topiramate: increases norepinephrine, augments GABA, and blocks excitatory glutamate receptors to reduce appetite. *Adverse effects*: paresthesia, xerostomia, constipation, dysgeusia
- Naltrexone-bupropion: stimulates proopiomelanocortin neurons, blocks reuptake of dopamine & norepinephrine in different brain regions (e.g., mesolimbic reward pathway) to reduce appetite. *Adverse effects*: nausea, constipation, headache, vomiting, dizziness, insomnia, xerostomia

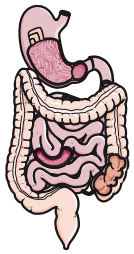
Nutrient-stimulated Hormone-based AOMs

- Mimic the effects of enteropancreatic hormones via action on the gut-brain axis, act to reduce appetite
- *Adverse effects*: nausea, diarrhea, vomiting, constipation, abdominal pain
- GLP-1 receptor agonists: liraglutide (Saxenda), semaglutide (Wegovy, Ozempic): act centrally in the brainstem, hypothalamus, and brain reward centers to promote insulin secretion, block glucagon secretion, and delay gastric emptying
- GIP/GLP-1 dual receptor agonist: tirzepatide (Zepbound): enhance appetite suppression via dual MoA



Gut-brain Axis

A two-way "communication system" between the CNS and gastrointestinal tract that uses neuroendocrine pathways to regulate processes relevant to obesity, including hunger, satiety, food cravings, gut motility, digestion, metabolism, and more



Intra-gastrointestinal AOMs

- Orlistat: blocks pancreatic and gastric lipases (enzymes that promote fat absorption by the small intestine), produces a calorie deficit but does not reduce appetite. *Adverse effects*: oily fecal spotting, fecal urgency, steatorrhea
- Oral cellulose-citric acid hydrogel: taken before meals, acts to expand and "fill" the stomach (~25% of stomach volume), creating a feeling of fullness and increasing satiety. *Adverse effects*: diarrhea, abdominal distension, constipation, flatulence, nausea, abdominal pain

Source: Gudzune KA and Kushner RF. *JAMA*. 2024; doi:10.1001/jama.2024.10816. Sharaiha RZ et al. *J Clin Gastroenterol*. 2023;57:967. Cleveland Clinic: The Gut Brain Connection (Accessed 31/7/24). Servier Medical Art. Piper Sandler Research.

A Look at the Current Market for Anti-Obesity Medications: Aggregate Sales of Wegovy & Zepbound Could Exceed $120B Each by 2030

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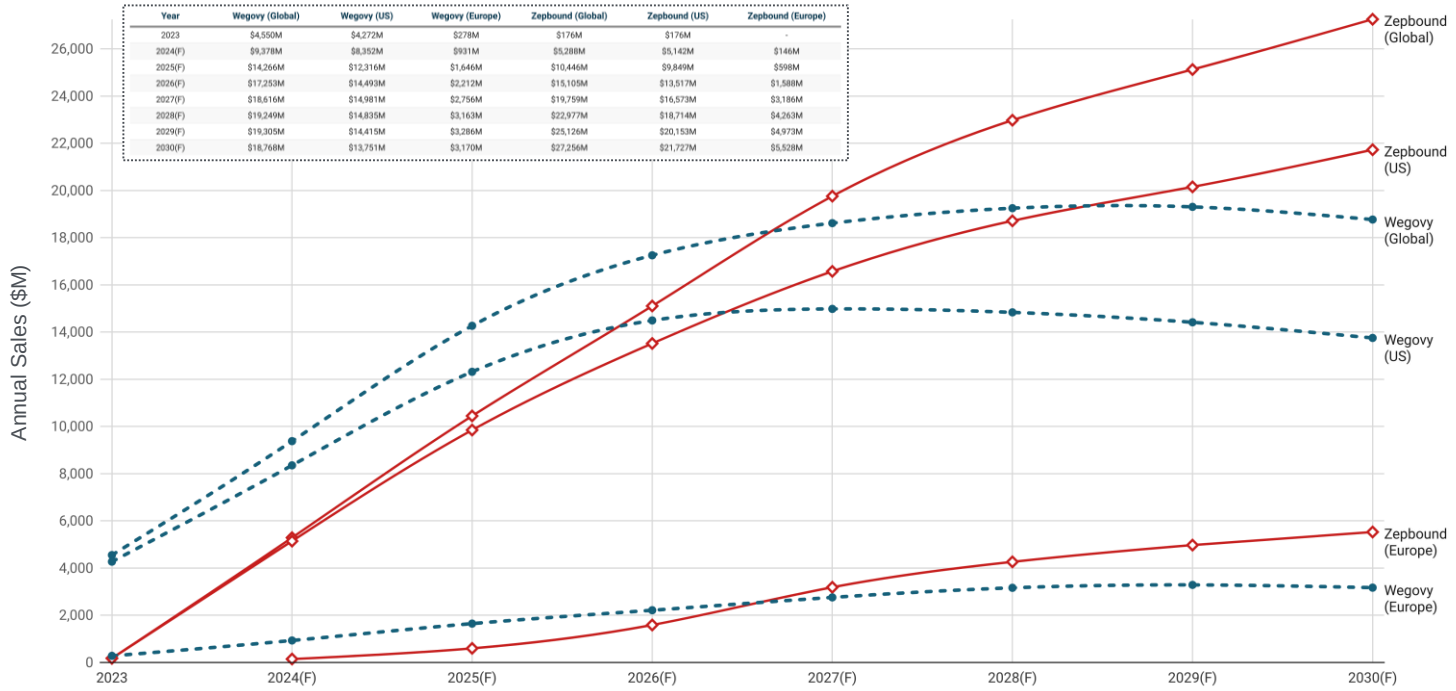
Wegovy and Zepbound are "mega-blockbuster" drugs for obesity: there is a *very* large market opportunity for rivals to take aim at. Analysis of actual and forecast sales figures from GlobalData's Drugs Database for currently approved anti-obesity medications highlights that **NVO's** Wegovy and **LLY's** Zepbound are the clear market leaders. Aggregate global sales to 2030 for each of these two drugs for treatment of obesity are projected to exceed $120B ($121B for Wegovy, $126B for Zepbound), with the US being the dominant market. Projected peak global sales are $19.3B for Wegovy (in 2029) and $27.3B for Zepbound (in 2030). While emerging anti-obesity medications that follow Wegovy and Zepbound to the market will have significant ground to make up, they can also become blockbuster drugs in their own right if they are able to capture even just a fraction of the market share from these currently-leading medicines.

EXHIBIT 6

Actual & Forecast Sales for NVO's Wegovy & LLY's Zepbound for Obesity, 2023-2030 (Per GlobalData's Drugs Database)

Year	Wegovy (Global)	Wegovy (US)	Wegovy (Europe)	Zepbound (Global)	Zepbound (US)	Zepbound (Europe)
2023	$4,550M	$4,272M	$278M	$176M	$176M	-
2024(F)	$9,378M	$8,352M	$931M	$5,288M	$5,142M	$146M
2025(F)	$14,266M	$12,316M	$1,646M	$10,446M	$9,849M	$598M
2026(F)	$17,253M	$14,493M	$2,212M	$15,105M	$13,517M	$1,588M
2027(F)	$18,616M	$14,981M	$2,756M	$19,759M	$16,573M	$3,186M
2028(F)	$19,249M	$14,835M	$3,163M	$22,977M	$18,714M	$4,263M
2029(F)	$19,305M	$14,415M	$3,286M	$25,126M	$20,153M	$4,973M
2030(F)	$18,768M	$13,751M	$3,170M	$27,256M	$21,727M	$5,528M



Source: Novo Nordisk & Eli Lilly Company Materials. GlobalData Drugs Database: sales data extracted July 30, 2024. Graph created with Datawrapper. Piper Sandler Research.

Regulatory Path in Obesity: Inexpensive in Early Development, But Costly in Late Stages (Page 1 of 3)

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Overview of the regulatory path in obesity based on FDA's guidance. The most up-to-date regulatory draft guidance for obesity drug development is the FDA's "*Developing Products for Weight Management, Revision 1*" (link here). It should be recognized that this is draft guidance and only provides a framework of suggestions to sponsors. Here, we summarize key topics from this guidance related to running initial Phase I/II trials, suggestions for pivotal Phase III trials, considerations for statistical analyses, weight-related comorbidities, and combination therapy potential.

Phase I and II studies should focus on understanding the full dose range to select an optimal dose/titration scheme. Prior to any pivotal study, the document states that the purpose of Phase I and II trials should be to characterize the drug's PK profile and assess the differences in efficacy across all active doses vs. placebo. Moreover, FDA recommends testing the drug across a broad range of BMIs (e.g., 27 kg/m2 to 35 kg/m2), to understand if excess adipose tissue has any influence on metabolism or PK profile. That said, earlier (Phase I) trials should be designed to identify the lower and upper bounds of the dose range from no effect to maximally tolerated doses, whereas the focus for subsequent PhII studies shifts to characterization of the dose-response curve (in the context of weight loss efficacy). Overall for the initial PhI/II development program, the document recommends including patients with a BMI ≥30 kg/m2 or ≥27 kg/m2 plus a weight-related comorbidity, and the primary efficacy endpoints should assess: (1) the change from baseline in body weight (BW) between drug vs. placebo (either mean absolute or percent change), and (2) the proportion of patients with ≥5% weight loss from baseline. *The draft guidance does not provide any color on PhI/PhII trial duration or secondary endpoints*.

Key elements for PhIII trial design are outlined in the draft guidance:

1. **Randomized placebo-controlled design in obese patients (or overweight with comorbidities).** The document emphasized that PhIII trials should be randomized, double-blind, placebo-controlled in patients who are at significant risk for weight-related mortality/morbidity. Lifestyle modification programs used in the studies should be relevant to potential real-world usage and effectively balance effectiveness and simplicity. Similar to the earlier trial populations, the recommendation is to enroll patients who are either obese (BMI ≥30 kg/m2) or overweight (≥27 kg/m2) and have weight-related comorbidities (e.g., T2D, HTN, dyslipidemia, sleep apnea, CVD). Ultimately, when planning for enrollment, the draft guidance urges sponsors to include a diverse and representative sample of various demographics, ethnicities, and racial groups – considering where obesity prevalence is the highest – in addition to including patients with the most extreme forms of obesity (e.g., severe obesity, with BMI ≥40 kg/m2).

2. **Phase III program should include at least ~4,500 subjects out to 1 year.** To demonstrate efficacy, the draft guidance recommends that the pivotal program include ~4,500 total participants (~3,000 subjects randomized to active dose(s) and no fewer than 1,500 randomized to placebo), measured out to 1 or more years of treatment. Using these numbers as an example, this would provide 80% power to rule out ~50% increase in the incidence of AEs that occur at 3% in the placebo arm (for example, 4.5% vs 3%), with 95% confidence. This should enable sufficient power and sample size to assess both efficacy and safety, as well as conduct subgroup analyses (sex, ethnicity, baseline BMI, etc.).

Source: FDA: Guidance for Industry – Developing Products for Weight Management; Draft Guidance, Feb 2007 (FDA.gov). Piper Sandler Research.

Regulatory Path in Obesity: Inexpensive in Early Development, But Costly in Late Stages (Page 2 of 3)

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3. **Primary endpoint for PhIII studies should measure weight loss, whereas key secondary endpoints should capture additional metabolic parameters.** The document suggests that the primary endpoint should assess both the *mean* ("difference in mean percent loss of baseline body weight in the active product versus placebo-treated group") and *categorical* ("proportion of subjects who lose at least 5% of baseline body weight in the active product versus placebo-treated group") changes in weight loss. The FDA provides examples of some potential secondary measures that may include (but are not limited to): changes from baseline in BP, HR, lipoprotein lipids, fasting glucose, insulin, HbA1c (for patients with T2D specifically), QoL measures, and waist circumference. Regarding measurement of waist circumference, the guidance points out that this is used in clinical practice as an indirect measure of visceral fat content (which is strongly associated with metabolic abnormalities), but does not serve as a surrogate of visceral fat in clinical trials. Thus, waist circumference reductions may provide confirmation of potential improvements in metabolic parameters, especially when paired with CT or MRI that provides more insight into visceral fat content.

4. **Efficacy bar for success is stat sig ≥5% placebo-adjusted weight loss, or ≥35% of patients with ≥5% weight loss at 1 year.** The guidance document highlights that the PhIII weight loss benchmark for consideration as an effective weight management drug is to achieve – at 1 year – either a stat sig ≥5% placebo-adjusted weight loss, or to show ≥35% of patients achieved ≥5% weight loss from baseline. Secondary endpoints (BP, lipids, glycemia, etc.) should improve with effective obesity drugs. Changes in weight-related comorbidities can also be considered when assessing the overall totality of data/efficacy profile.

5. **Additional considerations for patients with T2D and other weight-related comorbidities.** To begin with, the FDA's guidance document asserts that patients enrolled in a PhIII study who have weight-related comorbidities (e.g., T2D, HTN, dyslipidemia, poor glycemic control) should be treated with SoC during the trial. That said, the regulators recognize that many overweight/obese patients also present with T2D, which typically responds less favorably to weight-management products. Consequently, there is the potential for T2D-specific safety issues, such as higher risk of sulfonylurea-induced hypoglycemia occurring once the patient has lost a significant amount of body weight (particularly, if the dose of sulfonylurea was not appropriately lowered or discontinued in response to the weight loss). Therefore, the draft guidance recommends that sponsors should run a dedicated overweight/obese *with* T2D trial (i.e., separately from overweight/obese patients *without* T2D).

   The FDA provides additional suggestions for the design of T2D-dedicated trials as follows: (1) enroll patients with baseline HbA1c levels between 8%-10%; (2) exclude patients with fasting glucose levels >270 mg/dL; (3) study protocols should include escape criteria for poor glycemic control; (4) study protocols should include an algorithm for patients who lose clinically-significant amounts of weight to lower or discontinue oral hypoglycemia or insulin doses based on fasting glucose levels and/or HbA1c; (5) patient randomization should be stratified by baseline anti-diabetic drug (e.g., metformin vs. sulfonylurea vs. thiazolidinedione vs. insulin), and by baseline HbA1c level (such as ≤9% vs.>9%); and (6) hypoglycemia should be carefully monitored for safety.

Source: FDA: Guidance for Industry – Developing Products for Weight Management; Draft Guidance, Feb 2007 (FDA.gov). Piper Sandler Research.

Regulatory Path in Obesity: Inexpensive in Early Development, But Costly in Late Stages (Page 3 of 3)

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Statistical considerations include discussions on sample size, handling missing data, data analysis, and graphical methods. The FDA's draft guidance includes an in-depth section outlining the key statistical components. Starting with sample size, calculations should be based on at least 80% with two-sided tests of significance at the 5% level, and ultimately, effect sizes should represent clinically-meaningful differences. As for ways to manage/prevent missing data due to subject discontinuation, the document prefaces this by noting that, historically, subject withdrawal rates in long-term weight management product studies have been low. However, to ensure a true intent-to-treat (ITT) analysis, sponsors should still obtain body weight measurements from all subjects who prematurely withdraw from late-stage pre-approval trials around the same calendar date at which they were scheduled to complete the trial. For instance, a participant who withdraws from a 12-month study at the 6-month mark should get a body weight measurement at the time this subject was supposed to complete the 12-month study. Regarding statistical analysis methods, the regulators suggest running a sensitivity analysis where subjects who were treated, drop out, and do not have full post-baseline data are considered treatment failures. That said, analysis of percent weight change from baseline should use ANOVA or ANCOVA, where baseline weight serves as a covariate in the model. Specifically, this should be applied to the last observation carried forward on treatment in a modified ITT population (subjects receiving ≥1 dose of study drug and have ≥1 post-baseline body weight assessment). Importantly, any imputation strategy should be pre-specified and account for anticipated dropout patterns (where the ultimate goal is to keep dropout rate – and thus missing values – to a minimum). If the study achieves stat sig on co-primary endpoints of mean and categorical weight loss, Type 1 error should be controlled across all key secondary efficacy endpoints that are intended for inclusion in product labeling. Lastly, the regulators want to see cumulative distribution plots showing response rates across different definitions of categorical response, based on percent of participants achieving weight loss at specific thresholds as the x-axis. The draft guidance document encourages the use of additional graphical presentations to best illustrate the investigational drug's efficacy.

How do the regulators think about specific language for obesity drug labels? As a generalization, the document reflects that assessing the impact to weight-related comorbidities is a key consideration when reviewing weight management agents. As such, the overall benefit-risk profile can be included as a part of the Clinical Studies section in a subsequent approval label. However, even if the pre-specified secondary efficacy endpoints control for Type 1 statistical error as previously discussed, this does not automatically mean that these data will also be in the label (i.e., if treatment effect vs. placebo only achieved nominal stat sig, the FDA would then want to look at the consistency/clinical meaningfulness of the data to discern whether there is merit to include these secondary endpoints in the label's Clinical Studies section). There is also the potential for addition of stand-alone indications for the prevention/treatment of weight-related comorbidities, provided that the drug produced improvements in these parameters (e.g., BP, HR, lipids, glucose, insulin, etc.) via a mechanism that works independent of weight loss. This is also the case across all these secondary parameters if the drug is targeting a broad metabolic syndrome indication in the label.

Source: FDA: Guidance for Industry – Developing Products for Weight Management; Draft Guidance, Feb 2007 (FDA.gov). Piper Sandler Research.

2.2. What are the Most Pressing Questions in the Obesity Market?

A Closer Look at Key Challenges Facing Obesity Therapeutics

Barriers facing existing and emerging anti-obesity drugs. While semaglutide and tirzepatide have produced unprecedented weight loss to unlock the obesity market opportunity, a number of important challenges remain. In this section, we review these barriers and examine strategies to mitigate their impacts on anti-obesity therapeutics.

What do physicians think about the obesity therapeutics space? We discussed some of the most important challenges facing anti-obesity drugs with an endocrinology doc who treats ~1,000 obesity/T2D patients with weight-related comorbidities. ***See pages 25-28 for key takeaways.***

Pushing the needle for reimbursement: how will coverage of anti-obesity medications be expanded? At this time, the limited and variable coverage and high cost of anti-obesity drugs leaves gaps in who can be treated. Expanding reimbursement to close gaps in coverage is key to fully capturing the obesity market opportunity. ***See pages 29-30.***

How can supply constraints for currently-approved anti-obesity medications be alleviated, and what does this mean for the development of novel drugs? Unprecedented global demand for incretin medicines for weight loss has led to significant and ongoing shortages in the supply of these drugs in the US and EU. Despite Novo Nordisk and Eli Lilly each investing billions of dollars to expand manufacturing output, the near to mid-term outlook is for GLP-1s to remain in short supply as demand continues to outpace production. Addressing supply constraints is crucial to sustaining the market growth of these agents, but also highlights a wider challenge facing emerging anti-obesity drugs. ***See page 31.***

Why do patients discontinue treatment with GLP-1s and how can this be overcome? Obesity is a chronic condition that requires chronic treatment to achieve and maintain meaningful weight loss. However, many obese patients will discontinue GLP-1R agonist therapy (e.g., ~45-50% of patients will stop therapy by 12 months), due to a combination of clinical, demographic, and financial factors. Discontinuation of GLP-1R agonist therapy is associated with rapid and substantial weight regain (i.e., the benefits of therapy are lost), which has important implications for health of patients as well as insurance/reimbursement. ***See pages 32-34.***

Balancing quality and quantity of weight loss: what can be done to mitigate loss of lean (muscle) mass in patients receiving GLP-1s? Despite producing unprecedented weight loss, multiple studies show that GLP-1s can exert significant negative effects on lean mass/volume – a surrogate for muscle mass. For example, in the STEP-1 trial of semaglutide (NCT03548935), 45.2% of total weight loss was attributable to loss of lean mass. This can impact a patient's function and QoL, but also their health, metabolic profile, and weight regain. Some patients (e.g., older adults, post-menopausal women) may be particularly vulnerable to loss of lean mass caused by GLP-1s and experience falls, fractures, slowing of metabolism, and frailty. Within the obesity therapeutics space there is significant need for novel agents that can spare muscle mass during weight loss; these could be used either as monotherapies or in combination with GLP-1s (i.e., to offset the loss of lean mass they cause). To better understand this challenge, we also discussed the issue of lean mass preservation with a KOL who is an expert in obesity research and clinical trials. ***See pages 35-39.***

Source: Piper Sandler Research.

What Do Physicians Think About the Obesity Therapeutics Space? (Page 1 of 4)

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Key insights on the obesity therapeutics space from an endocrinologist KOL. Recently, we discussed a number of important topics in the obesity space with an endocrinology doc who treats ~1,000 obesity/T2D patients with weight-related comorbidities. The KOL's feedback is summarized below **(*and see note here*)**.

#1. Breakdown of GLP-1 utilization in the KOL's practice: semaglutide is most-used, but demand for tirzepatide is strong. The doc offers these medications to almost every single patient in the clinic (8/10 patients are on GLP-1; 2/10 are not due to contraindications or other reasons). 60% of his patients are on semaglutide vs. 40% on tirzepatide, with this difference being due to the later approval of tirzepatide and the effects of this on insurance reimbursement, prior authorization, and prescribing workflow. However, the doc sees preference among patients for tirzepatide (10 mg) due to more robust (16-18%) weight loss vs. semaglutide (2 mg; 14-15% weight loss). The doc also noted that patients who switch from semaglutide to tirzepatide after reaching a weight loss threshold continue to lose a few more pounds.

#2. What did our KOL view as the most interesting at ADA and why? Among the data presented at the recent ADA meeting, the doc highlighted (1) Eli Lilly's tirzepatide SURMOUNT-OSA sleep apnea study, and (2) Novo Nordisk's semaglutide FLOW study in chronic kidney disease (CKD) as the top two presentations that stood out to him. The doc stated his view that physicians want to see more data of the effects of GLP-1/GIP medications on weight-related comorbidities, since there is already extensive data to support effective weight loss.

#3. SURMOUNT-OSA could drive more use of tirzepatide over semaglutide. A key finding presented at ADA related to SURMOUNT-OSA, a study to determine whether tirzepatide can provide a clinically meaningful improvement in obesity-related obstructive sleep apnea (OSA). Notably, the study achieved its primary endpoint: reduction in apnea-hypopnea index (AHI) from baseline (-55% in Study 1 and -62.8% in Study 2). The KOL highlighted the significance of 43.0% and 51.5% of participants that received the highest dose of tirzepatide achieving disease resolution, given their BMI of 30+ and AHI of 15+ is comparable to ~70% of the patients he treats. The doc therefore can speak to his patients about using tirzepatide for OSA vs. other GLP-1s such as semaglutide, especially considering that these patients have similar characteristics to the SURMOUNT-OSA study and a significant portion of individuals in his clinic have issues with using a CPAP machine, have difficulties with sleep leading to poor QoL, and also have high CRP and rates of atrial fibrillation, which are cardiometabolic risk factors. While having specific data on a particular indication will increase the level of prescriptions of tirzepatide in the doc's view, he also described that while he will still prescribe semaglutide, there are sometimes challenges choosing one agent over another with respect to insurance coverage, where payers first require use of semaglutide before tirzepatide. The doc expects these data will enable tirzepatide coverage on day 1 rather than going through other channels.

#4. 30-40% of the doc's diabetic patients have chronic kidney disease (CKD), with FLOW validating GLP-1 use for this indication. At ADA, Novo Nordisk presented full data for its event-driven Phase III study (n=3,533 T2D with impaired kidney function patients), with medium f/up time of 3.4 years. Patients treated with semaglutide achieved stat sig separation vs. placebo across outcome events, with a 24% kidney event (3-year NNT: 20), 1.16 mL/min/1.73m2/year estimated treatment difference in annual eGFR change (total slope), 18% RRR in MACE (3-year NNT: 45),

Source: Piper Sandler Research.

What Do Physicians Think About the Obesity Therapeutics Space? (Page 2 of 4)

and 20% RRR in all-cause death (3-year NNT: 39). The doc highlighted that although the patients in his clinic are based on referrals, at least 30-40% of his patients with diabetes have some evidence of CKD. Moreover, the KOL highlighted that the patient population in the study is very similar to what he sees day to day, with patients in the FLOW study having mean eGFR of 47 mL/min/1.73 m2 and 68% having macroalbuminuria (≥300 mg/g). As such, the doc noted that this patient population is at high risk for CVOT events and renal deterioration.

#5. 80-90% of supply issues have been solved with 60-70% of prescriptions approved by reimbursement. With supply constraints for incretin medicines a key topic, the KOL emphasized that compared to 2023, supply has dramatically improved in his eyes. Supporting this observation, the doc noted that the number of phone calls and complaints from his patients about having their prescription filled at another pharmacy has dramatically been reduced and mostly resolved. Regarding insurance and coverage, between off-label use and the regular indication for both semaglutide and tirzepatide, the doc is presently getting 60-70% approval. Notably, when asked about renewal for prescriptions, the KOL highlighted that he is writing scripts for up to a year and has not had any issues renewing or having any difficulties thereafter.

#6. What do next-gen obesity products need to show? The doc outlined that one concern for new obesity products is the *quality* of weight loss, where questions remain on how much lean body mass is lost compared to fat mass. In particular, when patients discontinue incretins, the doc emphasized that most of the weight regained is fat mass. As such, new options that can preserve muscle mass and have a positive metabolic benefit are of more interest, compared to an absolute weight loss of 15-18%. Moreover, positive benefits on metabolic markers such as insulin resistance, lipid profiles, and glycemic parameters such as HbA1c, and preventing cardiovascular events are also areas of higher importance that need to be addressed. Interestingly, beyond novel MoAs the doc noted that the combination of a GLP-1 therapy with a digital platform to help patients monitor food intake and exercise may be beneficial in helping patients lose weight at lower doses of tirzepatide or semaglutide, and could play a role in better outcomes.

#7. NAFLD is a key comorbidity of obesity to address. When asked about comorbidities that could benefit from incretin treatment, our doc highlighted that we still do not have the full picture of GLP-1s in fatty liver disease. Importantly, the doc discussed that while we know incretins drive weight loss in patients, we have not seen the same clear impact on the liver. The doc noted that he is interested in seeing how therapies can save pancreatic beta cells and prevent patients from chronic use of insulin or avoid using insulin entirely. Further, the KOL emphasized a greater focus on changes in metabolic markers in NASH or NAFLD and wants to see a direct reflection of ~10% weight loss in an ultrasound of a fatty liver.

#8. Our doc is positive about different novel MoAs. When asked *which MoAs have the greatest potential*, our doc highlighted: (1) **ZEAL's (not covered)** petrelintide (amylin analog), specifically noting that amylin analogs have the potential for complementary impact with GLP-1s, depending on the longer term safety profile; (2) **AMGN's (Raymond, OW)** AMG133 (GLP-1/GIP), noting that dosing Q4W may positively impact compliance issues; (3) **ALT's (Rahimi, OW)** pemvidutide (GLP-1/Glucagon), due to the recent positive weight loss and lean mass preservation

Source: Piper Sandler Research.

What Do Physicians Think About the Obesity Therapeutics Space? (Page 3 of 4)

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data; and (4) **LLY's (not covered)** retatrutide (GLP-1/GIP/Glucagon), with the triple G MoA demonstrating best-in-class weight loss of ~20%. Importantly, the doc discussed the benefit of combination MoAs, as detailed above, given their inherent ability to have positive effects outside of weight loss, with potential for metabolic marker effects, lean mass preservation, CV benefit, and improvement of a patient's lipid profile. Further, the doc described that while it is still early to declare an MoA a clear front-runner, differentiated approaches such as amylin analogs and glucagon agonists have shown benefits in areas where GLP-1s are lacking, such as lean mass preservation.

#9. Lean mass preservation is key and our doc's view on the path forward. When asked about our doc's main concern with incretin therapeutics, he noted current therapies (tirzepatide and semaglutide) have already demonstrated beneficial weight loss (~16-18%), yet it remains unclear how much is due to lean body mass or fat mass loss. The doc also pointed out that when patients stop taking incretin therapies, they often regain the weight as fat mass with a lower baseline lean mass, demonstrating a distinct unmet need. As such, the doc reiterated his interest in the development of therapeutics, such as ALT's pemvidutide, which have demonstrated lean mass preservation with a greater metabolic impact on the body in terms of lipid profile. Further, the doc pointed out that drugs in development that affect muscle cells and the growth of muscle mass, such as amylin analogs and some glucagon receptor agonists, do appear to preserve muscle mass when compared to GLP-1 and GIP products. In terms of the regulatory path forward for lean mass preservation drugs, our doc noted that he does not know how the FDA considers the endpoint, but does see beneficial effects on insulin sensitivity, glucose uptake, lipid profile, and exercise through preservation of muscle mass. He was optimistic on lean mass preservation improving the obesity space, with the hope for more data to demonstrate translation to clear metabolic marker benefit.

#10. Amylin analog MoA has potential for robust weight loss. Our doc sees amylin analogs as very promising, especially in light of ZEAL's recent petrelintide topline data for the 16-week Phase I/Part 2 (NCT05613387) in 48 healthy patients, with primary endpoint of safety and tolerability. Of note, ZEAL's poster presentation at ADA 2024 showed 16-week QW petrelintide produced robust weight loss up to -8.6% (vs -1.7% placebo) from baseline, with a clean safety profile (no serious or severe AEs reported) and all GI AEs mild/moderate in severity. Accordingly, the doc highlighted the mean baseline BMI of patients in the petrelintide trial was 29.2 kg/m2, compared to 37.8 kg/m2 for QW 2.4 mg semaglutide (STEP 1; NCT03548935) and 38.1 kg/m2 for QW 15 mg tirzepatide (SURMOUNT-1; NCT04184622). The doc emphasized that if petrelintide is able to demonstrate a placebo-adjusted change in BW of -6.9% in a population of patients with lower baseline BMI, one would expect to see more robust results with similar target populations to semaglutide and tirzepatide trials (i.e., with baseline BMI ~37-38 kg/m2). As such, the doc was intrigued by the novel MoA and is interested to see more data on the safety profile (GI tolerability) to further substantiate its potential as a comprehensive obesity therapeutic.

#11. Triple G MoA has significant potential with impressive weight loss. Further, our KOL highlighted LLY's retatrutide (GLP-1/GIP/Glucagon) as an impressive therapeutic in development which demonstrated up to ~-24.2% weight loss at 48-weeks. Recall, LLY ran a 48-week Phase II trial (NCT04881760) in 338 obese or

Source: ClinicalTrials.gov. Piper Sandler Research.

What Do Physicians Think About the Obesity Therapeutics Space? (Page 4 of 4)

overweight patients with primary endpoint of mean % change from baseline in BW. While the doc recognized the significant weight loss, he posed the question of how much weight loss is actually necessary for a patient to benefit. Given that retatrutide addresses different axes of treatment, the doc believes that it provides more options for patients, though more data is needed to understand the full benefit. Moreover, the doc was interested in further understanding its safety profile, especially when comparing GI tolerability to GLP-1 and GLP-1/GIP therapies.

#12. Doc's thoughts on oral GLP-1s & utility. Finally, when asked about oral GLP-1 therapies, our doc highlighted that primary care doctors are more comfortable prescribing oral medications, and he would expect greater uptake and utilization of oral GLP-1s compared to a QW SC injection. Additionally, while the doc noted ~80% of his patients are comfortable on QW SC therapies, there is a large population (~10-15%) of patients who refuse to use an SC therapeutic. The doc recognized the potential of oral therapies, such as LLY's orforglipron, to significantly penetrate the market, especially if it demonstrates weight loss near ~15-16%. Of note, the doc is interested to know if there will be any food or liquid requirements when taking an oral therapeutic, which will become clearer with additional data. Moreover, an interesting point that came up during the call was the potential of oral therapeutics to be used for maintenance of weight loss following SC injection treatment. Accordingly, the doc saw potential in this unique concept and would be open to using a QD oral therapy like any other pill to help patients "keep off the weight" and maintain beneficial metabolic effects. Taken together, our doc reiterated the strength of current anti-obesity medications, while recognizing key shortcomings in regard to lean mass preservation and flexibility, with novel MoAs and oral therapeutics potentially solving these issues.

Source: ClinicalTrials.gov. Piper Sandler Research.

Coverage of Anti-Obesity Drugs Varies Across Key Markets: Who Can be Treated & Who Will Pay?

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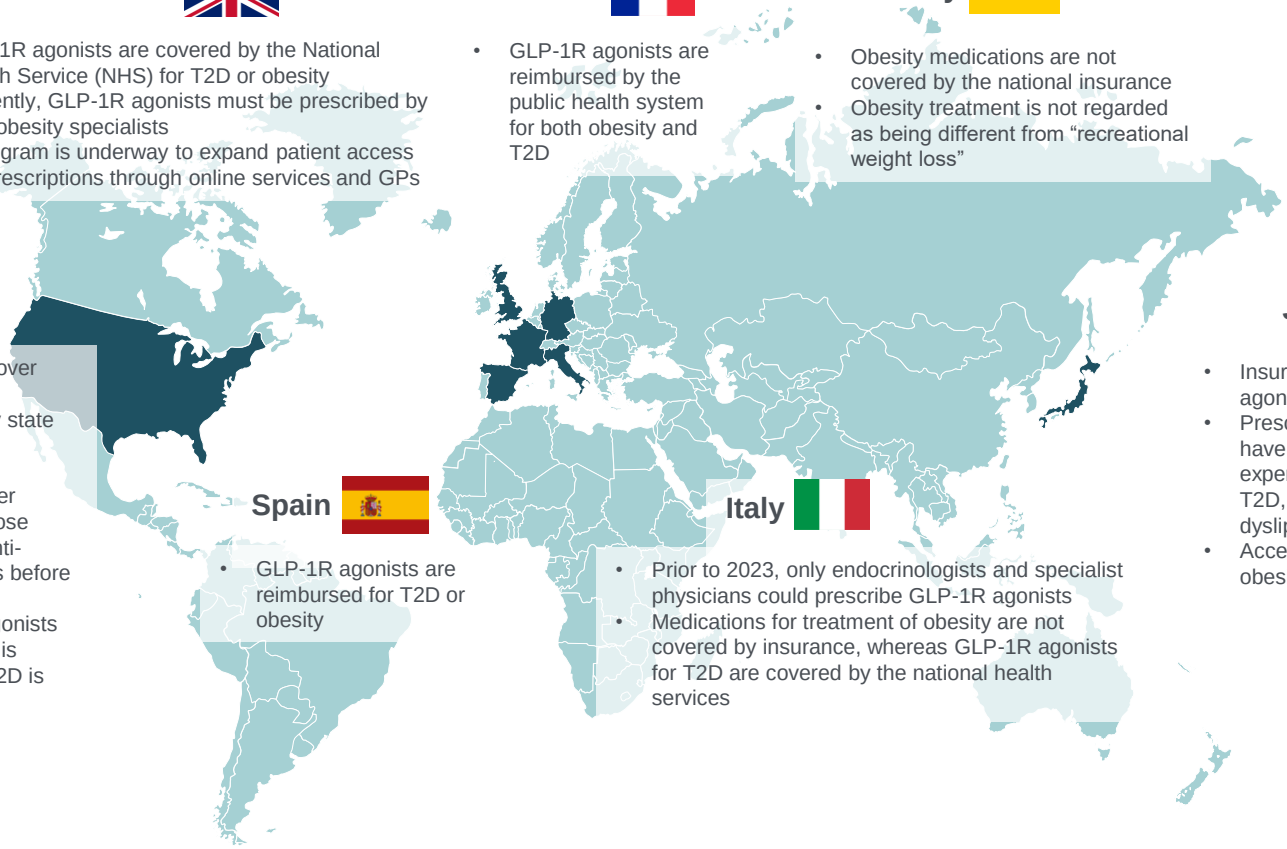
EXHIBIT 7
Summary of Market Access/Reimbursement of GLP-1R Agonists in the Seven Major Markets (7MM; US, UK, France, Germany, Spain, Italy, Japan)



UK

- GLP-1R agonists are covered by the National Health Service (NHS) for T2D or obesity
- Currently, GLP-1R agonists must be prescribed by T2D/obesity specialists
- A program is underway to expand patient access via prescriptions through online services and GPs

France

- GLP-1R agonists are reimbursed by the public health system for both obesity and T2D

Germany

- Obesity medications are not covered by the national insurance
- Obesity treatment is not regarded as being different from "recreational weight loss"

US

- Medicare Part D plans cannot cover anti-obesity medications,
- Coverage by Medicaid varies by state
- A recently-amended form of the **Treat and Reduce Obesity Act (TROA)** directs Medicare to cover obesity treatments for those whose insurance previously covered anti-obesity medications for 1+ years before they enrolled in Medicare
- Overall, coverage of GLP-1R agonists for chronic weight management is limited, whereas coverage for T2D is widespread

Spain

- GLP-1R agonists are reimbursed for T2D or obesity

Italy

- Prior to 2023, only endocrinologists and specialist physicians could prescribe GLP-1R agonists
- Medications for treatment of obesity are not covered by insurance, whereas GLP-1R agonists for T2D are covered by the national health services

Japan

- Insurance covers all GLP-1R agonists
- Prescribers must be certified and have >5 years of clinical experience in treating obesity, T2D, hypertension, and dyslipidemia
- Access is typically more limited for obesity than for T2D

Source: National Council on Aging: Obesity Treatment & Medicare: A Guide to Understanding Coverage (Feb 27, 2024). GlobalData: GLP-1R Agonists 7MM Drug Forecast & Market Analysis (May 2024). House.gov. Servier Medical Art. Wikimedia Commons. Piper Sandler Research.

Pushing the Needle for Reimbursement: How Will Coverage of Anti-obesity Medications be Expanded?

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Limited coverage and high cost of anti-obesity drugs leaves gaps in who can be treated. The scale and impact of the obesity epidemic poses a significant threat to public health: ~70% of US adults are overweight or obese (per Federal government data), and the number of affected is growing. Moreover, >200 diseases (cancer, heart disease, kidney disease, and others) are linked to obesity. Demand for anti-obesity drugs is **unprecedented**: ~50% of US adults are interested in taking a prescription drug for weight loss. If all of the >90M Americans that meet the eligibility criteria for GLP-1 therapy received these medicines, then even with significant price discounts the total annual cost would be ~$600B. This is clearly **unsustainable** as it equals the combined cost of all other US prescription drug spending. Adding to the challenge is that the 2003 Medicare Modernization Act prevents Medicare from covering weight loss medications. Furthermore, many state-run Medicaid programs and commercial health insurance plans do not cover drugs for weight loss.

Reimbursement barriers to uptake of anti-obesity drugs include: **(1) The view among payers that patients can control their weight** ("weight loss stigma") – despite the American Medical Association (AMA) officially recognizing obesity as a chronic, multifactorial disease in 2013. **(2) Exclusion of weight loss medications from benefit** (e.g., Medicare), and the view that incretins (e.g., GLP-1R agonists) are weight loss drugs, despite their utility in other health conditions (e.g., are approved for T2D and show benefit in other conditions). **(3) High per unit price (>$1,000/month) of newer anti-obesity drugs (Wegovy, Zepbound)**, coupled with surging demand. Payers must consider how to manage premiums and affordability given the expansion in patients eligible for anti-obesity medications (as well as surging demand), and must also weigh potential future offsets against the near term financial implications of increasing reimbursement. **(4) High attrition rates** that have been reported among those taking GLP-1R agonists and the resulting **weight rebound**. Payers may be concerned about poor compliance and the likelihood of weight regain. **See payer KOL takeaways from our June 2024 Virtual Obesity Day for more insights into payer perspectives regarding anti-obesity medications.**

Closing the gaps in coverage: is the tide turning? Coverage of anti-obesity drugs may be described as "spotty" (~50M have coverage in the US). Employers and payers are keen to avoid the risk that blanket coverage of weight loss drugs could "break" the system. Instead, we expect a gradual expansion of coverage, with attention also being focused on how Medicare tackles this issue. New data showing that weight loss drugs can improve patient health (i.e., benefits are lifesaving rather than cosmetic) will also drive the trend towards expanded coverage. For example, Novo Nordisk's Wegovy received an additional FDA approval in March 2024 for cardiovascular risk reduction in adults with known heart disease and overweight/obesity. With respect to Medicare, the **Treat and Reduce Obesity Act (TROA)** is one mechanism to expand coverage. The TROA is bipartisan legislation that aims to expand insurance coverage for Medicare beneficiaries by allowing Medicare Part D to cover FDA-approved anti-obesity medications for chronic weight management. In June 2024, the House Ways and Means Committee voted 36-4 to pass a modified version of the TROA covering obesity treatments for those whose insurance previously covered weight loss drugs for 1+ years before enrolment in Medicare. In other words, the TROA can ensure individuals aging into Medicare do not lose coverage for their effective anti-obesity medications. While this may be a fairly small change in the overall scope of coverage, it suggests the reimbursement landscape for weight loss drugs may be shifting.

Source: National Institute of Diabetes and Digestive and Kidney Diseases: Overweight & Obesity Statistics (Sept 2021). House.gov. FDA.gov. ObesityAction.org. Liu B and Rome BN. *JAMA*. 2024;331:1230. Baig K et al. *N Engl J Med*. 2023;388:961. Mozaffarian D. *JAMA*. 2024;331:1007. Piper Sandler Research.

Only So Much to Go Around: Ongoing Shortages Are a Bottleneck to Market Growth of Anti-Obesity Medicines

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Too much success, too quickly? Addressing the shortage of GLP-1 medicines in the face of surging demand. Unprecedented global demand for incretin medicines for weight loss has created significant, ongoing shortages in the supply of these drugs in US and EU. As of July 16, 2024, both semaglutide and tirzepatide show limited availability in the FDA's Drug Shortages Database, and pharmacies across the US are experiencing constraints in filling prescriptions for GLP-1 drugs due to high demand and inadequate supply. This not only limits who can begin taking incretin-based medicines for weight loss, but it can also disrupt treatment regimens for patients already taking these medicines (i.e., causing treatment discontinuation). Limited availability of versions of semaglutide and tirzepatide that are approved for T2D (i.e., Ozempic, Rybelsus, Mounjaro) due to their off-label use for weight loss is also impacting their accessibility to diabetes patients. Another factor to consider is that shortages may worsen as Novo and Lilly pursue global sales of their incretin medicines. Finally, in early 2024 the WHO warned that insufficient supply of GLP-1s to meet demand is resulting in the spread of counterfeit and unregulated versions of these drugs.

What is the near to mid-term outlook for supply of GLP-1s? At the end of 1Q24, Eli Lilly warned that very strong demand for its incretin medicines was outpacing supply increases and leading to wholesaler backorders for the products. While the company is expanding its GLP-1 manufacturing capacity and anticipates significantly increasing its production output in 2H24, in the short to mid-term it expects sales growth for incretin medicines to be limited by the quantity of drug that can be made and shipped. In its 2Q24 earnings call, Lilly said that supplies of Zepbound and Mounjaro have improved, and all dosages are currently listed as "available" on the FDA shortage website (here), as of August 9, 2024. Similarly, Novo Nordisk has stated that overall demand for Wegovy continues to exceed supply, noting that >25,000 new US patients are starting on Wegovy weekly – a number that is growing and is about four times higher than in December 2023. Novo is also expanding its production to meet this strong demand, and supplies of Wegovy and Ozempic have recently improved – as seen with tirzepatide – and the FDA's shortage website currently shows all doses as "available" as of August 9, 2024.

Shortages may be likely to persist – at least for now. Ultimately, even as manufacturing capacity grows (and this will take time to come into effect), we expect supply constraints for incretin-based anti-obesity drugs to persist as increased production is matched or exceeded by very strong demand. In a sense, it is almost impossible to make enough drug to "go around" for the time being – a point that may be illustrated by the significant self-pay/consumer market that exists for weight loss drugs (e.g., among those who do not have insurance coverage for these medicines).

How can demand for anti-obesity medicines be met, and how can emerging obesity players join the race? Lilly and Novo are each investing billions of dollars to expand production of their incretin drugs for obesity/T2D. The emergence of alternatives (e.g., small molecule GLP-1s, but also non-incretin drugs) could ease demand for Wegovy and Zepbound, while also simplifying manufacturing and reducing costs (i.e., small molecules are cheaper and easier to produce than biologic medicines, such as peptides). *We believe that investors should consider how emerging obesity players plan to tackle the question of manufacturing, in order to meet expected demand and capture their own market share*.

Source: FDA.gov. Novo Nordisk and Elil Lilly Company Materials. EMA: Recommendations of Executive Steering Group on Shortages of GLP-1 Receptor Agonists, 12 June 2024. World Health Organization. Ruder K. *JAMA*. 2024; doi:10.1001/jama.2024.13507. Piper Sandler Research.

Discontinuation of GLP-1 Receptor Agonists by Patients is a Major Challenge in the Obesity Therapeutics Space

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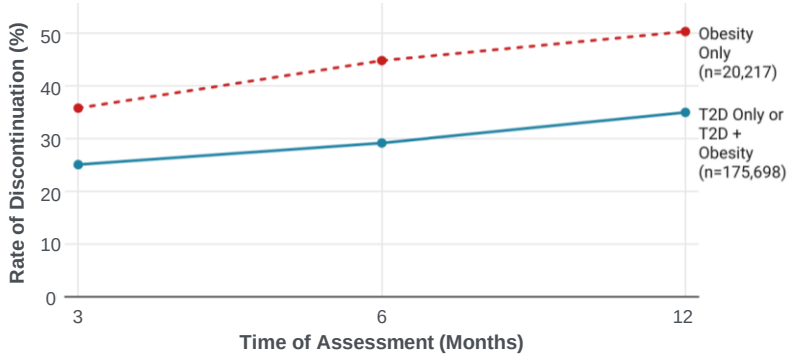
Many patients will discontinue GLP-1R agonist therapy due to a combination of clinical, demographic, and financial factors: the T2D experience. Multiple studies have shown that ~45-50% of T2D patients will discontinue GLP-1 receptor agonist therapy (i.e., dulaglutide, exenatide, liraglutide, or semaglutide) by 12 months. Another study of 4,791 T2D patients found: (1) that the rate of discontinuation (defined as a >90 day gap from the last date of GLP-1R agonist supply to the first date of subsequent prescription claim) was 47.7% at 12 months and 70.1% at 24 months; and (2) that treatment adherence (defined as proportion of days covered from prescription claims > 0.80) was significantly higher among patients receiving weekly vs. daily injections (p<0.001). The latter point (frequency of administration) is important given the emergence of oral small molecule GLP-1s which can be administered daily. A real-world, cross-sectional survey of physicians (n=443) and patients with T2D (n=194) highly a number of factors commonly associated with GLP-1R agonist discontinuation, including poor blood glucose control, nausea/vomiting and diarrhea/gas/bloating (i.e., gastrointestinal side effects), insufficient weight loss, pain or inconvenience of injections, cost, and other causes. Another important point is that discontinuation rates in the real world are consistently higher than those reported in clinical trials, and most T2D patients will discontinue GLP-1R agonist therapy within a period of 24 months.

Discontinuation of GLP-1R agonists may be even more of a problem for obesity than for T2D. A recent study published in *JAMA Network Open* in May 2024 (Do et al) examined the prevalence and causes of GLP-1R agonist therapy discontinuation among patients with obesity only, T2D only, or both (n=195,915 individuals in total). The *overall* prevalence of treatment discontinuation at 3, 6, 12 months was 26.2%, 30.8%, and 36.5%, respectively. However, at each timepoint, **patients with only obesity (i.e., no T2D) had a significantly higher rate of discontinuation than those with T2D only or T2D and obesity** (**Exhibit 8**). Patients were also significantly more likely to discontinue therapy at 12 months if they were Black or Hispanic, male, enrolled in Medicare or Medicaid; resided in areas with very high levels of social needs; had obesity only, heart failure (HF) or other CVD conditions besides HF at baseline; and/or had new gastrointestinal adverse effects at follow-up. Out-of-pocket (OOP) cost was also linked with discontinuation: each 1% increase in OOP cost per 30 day supply of drug was associated with increased odds of discontinuation (odds ratio, 1.02; 95% CI, 1.02-1.03). Importantly, the study did not address the rates of discontinuation among those taking tirzepatide – a newer incretin medication – or whether the higher prevalence of GLP-1R agonist discontinuation seen with obese patients may be due to adverse effects, weight reduction, a lower level of insurance coverage vs. T2D patients, or shortages of GLP-1R agonists.

EXHIBIT 8

Many Obese Patients Will Discontinue GLP-1R Agonist Therapy



Source: Weiss T et al. *Patient Prefer Adherence*. 2020;14:2337. Do D et al. *JAMA Network Open*. 2024;7:e2413172. Graph created with Datawrapper. Piper Sandler Research.

Why Do Patients Discontinue GLP-1R Agonist Therapy?

EXHIBIT 9

Overview of Some Key Factors Associated With Discontinuation & Poor Adherence of GLP-1R Agonist Therapy Among Patients With Obesity

Treatment-related Adverse Effects

- Gastrointestinal issues (nausea, vomiting, diarrhea, constipation) are common side effects: observed in 40-85% of clinical trial patients receiving GLP-1R agonists
- Gastrointestinal side effects due to GLP-1R agonists resulted in up to 6% of patients discontinuing treatment in clinical trials

Limited Insurance Coverage & High Cost of Therapy

- Use of GLP-1R agonists for weight loss is not widely covered by private or public health insurance plans
- Out of pocket costs may be prohibitive for patients without insurance or with limited insurance (e.g., one month's supply of Wegovy can cost >$1,300)

Limited Weight Loss Efficacy

- Patients may discontinue treatment due to insufficient weight loss (e.g., disappointment due to unrealistic expectations, or real world efficacy being less than clinical trials)
- For example, ~30% of obese patients experience <10% body weight reduction with semaglutide 2.4 mg

Ethnicity & Socioeconomic Status

- Black and Hispanic people with obesity are more likely to discontinue GLP-1R agonist therapy
- Higher income is strongly and progressively associated with lower rates of discontinuation

Shortages of GLP-1R Agonists

- In the face of unprecedented demand, both Novo Nordisk and Eli Lilly have warned that they are unable to supply enough Wegovy or Zepbound to patients that want it
- Supply shortages may result in poor adherence or, ultimately, discontinuation

Prescription by Primary Care Physicians

- Most (~90%) GLP-1R agonists for weight loss are prescribed by primary care doctors rather than obesity medicine specialists or endocrinologists
- This is associated with therapy discontinuation

Geography & Rural Status

- Patients in the South of the US are less likely than those in the North-east to remain on GLP-1R agonists
- Those in rural regions are more likely to discontinue treatment than those located in urban/suburban locations

Younger Age

- Obese patients aged between 18 and 34 years are more likely to drop out of treatment earlier than those aged between 35 and 64 years.

Impact of Comorbidities & T2D

- Obese patients with heart failure or other cardiovascular disease conditions are more likely to discontinue GLP-1R agonists
- Obese patients without T2D are more likely to stop therapy than those with T2D

Administration Challenges (e.g., Injections)

- Some patients do not favor regular injections – more so for once-daily injections of Saxenda (liraglutide), but also for weekly injections of semaglutide or tirzepatide
- Some patients may prefer oral administration

Lack of Patient Support

- Insufficient follow-up from healthcare providers is associated with treatment discontinuation
- Obese patients that have regular visits to their healthcare providers show improved medication persistence (odds ratio: 1.57)

Weight Loss Goals Met

- Patients may elect to stop taking GLP-1R agonists once they attain a desired or clinically meaningful reduction in body weight
- Ongoing maintenance of weight loss may be challenging

Source: Gorgojo JJ et al. *J Clin Med*. 2023;12:145. Gudzune KA and Kushner RF. *JAMA*. 2024; doi:10.1001/jama.2024.10816. Do D et al. *JAMA Network Open*. 2024;7:e2413172. Rodriguez PJ et al. *medRxiv*. 2024; doi: 10.1101/2024.07.26.24311058. Lundgren JR et al. *Obesity Science & Practice*. 2020;6:486. Wegovy Product Website. Blue Health Intelligence Issue Brief, May 2024: "Real-World Trends in GLP-1 Treatment Persistence & Prescribing for Weight Management". Piper Sandler Research.

Obesity is a Chronic Condition & Ongoing Treatment is Required to Maintain Efficacy & Prevent Weight Regain

Obesity is a chronic disease that requires chronic treatment to achieve and maintain meaningful weight loss. While drug therapy (e.g., with GLP-1R agonists) is considered an important adjunct strategy for weight loss management (alongside lifestyle changes), current anti-obesity medications must be taken over the long-term to achieve and then maintain a significant reduction in body weight. Notably, data from clinical trials show that obese patients taking GLP-1 drugs should complete at least 12 weeks of therapy – without interruptions – to see efficacy and to achieve clinically meaningful weight loss (i.e., sufficient time is needed to allow weight loss to an extent that can improve a patient's health). As noted earlier, approximately one-third or more of patients taking GLP-1R agonists for weight loss will discontinue the therapy by 12 weeks. Discontinuation of GLP-1R therapy is associated with **weight regain** – even in those patients that continue with lifestyle modifications. Studies consistently show ~50-70% regain of lost weight within 12 months (**Exhibit 10**, top right). This weight regain has implications not only for the health of patients, but is a consideration for insurance/reimbursement. For example, GLP-1R agonists are expensive drugs – what does the reimbursement landscape look like if much of the benefit of GLP-1R agonists is quickly lost after discontinuation?

What causes the weight "rebound" after stopping GLP-1s? Compensatory biological changes during weight loss may confer the rapid weight regain in those that discontinue GLP-1R agonist therapy (**Exhibit 11**, bottom right). These include: (1) hormonal adaptation to weight loss, where caloric restriction causes alterations in leptins, ghrelin, and other hormones, increasing appetite and promoting weight regain; (2) failure of the CNS to control body weight in the absence of GLP-1s; (3) impaired production of insulin by pancreatic beta cells; and (4) alterations in gut microbiota.

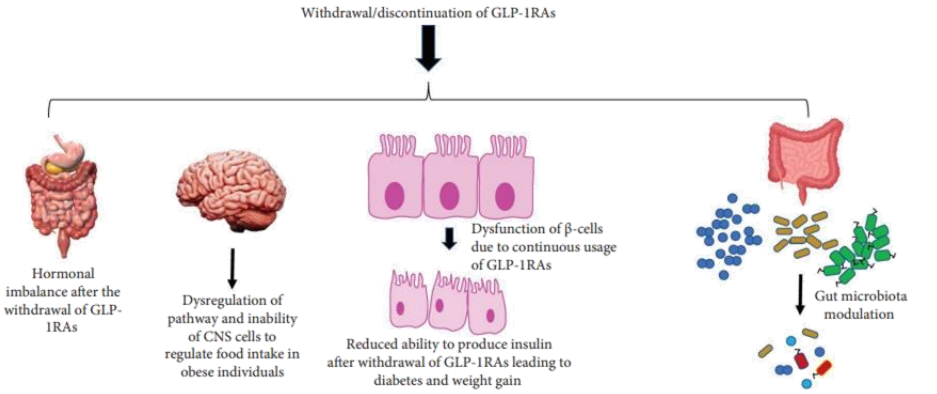
EXHIBIT 10

Examples of Substantial Weight Regain Following Discontinuation of Incretin Therapies in Clinical Trials

Incretin Therapy	Study & Observed Weight Regain	References
Semaglutide	In the STEP 1 trial, study participants (obese with 1+ weight-related comorbidity but without diabetes) that stopped once-weekly SC semaglutide (at 68 weeks) **regained approximately two-thirds of their prior weight loss** in the following year	Wilding JPH et al (2021)
Liraglutide	In the SCALE Maintenance trial, patients that discontinued liraglutide after 52 weeks regained around half of the lost weight in the following year	Wadden TA et al (2013)
Tirzepatide	In the SURMOUNT-4 trial, after 36 weeks of tirzepatide treatment patients were randomized to an additional 52 weeks of either tirzepatide or placebo; those that switched to placebo regained about half of the weight they had lost	Aronne LJ et al (2023)

EXHIBIT 11

Mechanisms Driving Weight Gain After Discontinuation of GLP-1R Agonists



Source: Ahmed IA. *J Obes*. 2024;8056440. Wilding JPH et al. *Diabetes Obes Metab*. 2022;24:1553. Wadden TA et al. *Int J Obes*. 2013;37:1443. Aronne LJ et al. *JAMA*. 2024;331:38. Do D et al. *JAMA Network Open*. 2024;7:e2413172. ClinicalTrials.gov. Piper Sandler Research.

Increased Uptake of Incretins Raises Concerns for Muscle Loss: There is a Need to Maintain a Healthy Body Composition as Patients Lose Weight

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Quantity of weight loss from incretin-based drugs is approaching that achieved with surgery – but what about the *quality* of weight loss? While clinical studies show that agonists of GLP-1R and dual agonists of GIPR/GLP-1R produce robust weight loss in obese patients that exceeds earlier-generation anti-obesity drugs, there is concern over the significant proportion of this weight loss that is attributed to muscle (lean) mass – especially in vulnerable patients (e.g., older adults, post-menopausal women). *Lean mass is used as a surrogate for muscle mass*, and represents the difference between total body weight and body fat weight (i.e., "everything except the fat"). It is important to note that few studies in the field include accurate measurements of muscle mass, and lean mass includes not only muscle but also organs, bone, and fluids. FDA guidelines for evaluating weight loss therapies emphasize that the only acceptable primary efficacy endpoints for trials are those that directly relate to changes in body weight – lean mass and muscle mass are considered to be safety endpoints only and to require small cohorts for testing. Consequently, many Phase III studies of anti-obesity drugs disregard muscle/lean mass changes (or are not adequately powered to assess them), or use fairly crude tools to measure these changes (e.g., dual energy x-ray absorptiometry; DXA) instead of MRI. The FDA guidelines also state that only a very small proportion of patients in Phase III trials should undergo body composition evaluation, and tests of muscle function, strength, or mobility are not needed. This makes it difficult to understand the precise effects of GLP-1s on muscle mass, health, and function in the context of weight loss. Nevertheless, some trials have reported reductions in lean mass/volume for obese patients treated with GLP-1s (examples in **Exhibit 12**, below), which warrants further investigation. For example, in the STEP-1 trial of semaglutide, **the fraction of total weight loss that was attributable to loss of lean mass was 45.2%**.

EXHIBIT 12

Select Clinical Trial Data Illustrating Negative Effects of GLP-1s on Lean Mass/Volume

Incretin Therapy (Study)	Patient Population	Measurement Used	Change in Body Weight from Baseline in kg or liters (%)	Lean Change from Baseline in kg (%)	Fraction Lost (or Gained) of Lean Mass/Volume as a Proportion of Total Weight Loss (%)
Semaglutide (STEP-1)	BMI >30, or BMI >27 + comorbidity; no T2D	DXA (lean mass)	-15.3 (-14.9%)	-6.92 (-13.2%)	**-45.2%**
Semaglutide (SUSTAIN-8)	T2D	DXA (lean mass)	-5.3 (-6.0%)	-2.3 (-4.5%)	**-43.4%**
Tirzepatide (SURMOUNT-1)	BMI >30, or BMI >27 + comorbidity; no T2D	DXA (lean mass)	-22.1 (-20.9%)	-5.67 (-10.9%)	**-25.7%**

Source: Neeland IJ et al. *Diabetes Obes Metab*. 2024;1. Neeland IJ et al. *Lancet Diabetes Endocrinol*. 2021;9:595. Pandey A et al. *J Cachexia Sarcopenia Muscle*. 2024;15:1072. Lundgren JR et al. *N Engl J Med*. 2021;384:1719. FDA.gov. Piper Sandler Research.

Quality Over Quantity? Preserving Lean Mass During Weight Loss

The quality of weight loss is important: why is the loss of lean (muscle) mass a problem? In short, maintenance of lean mass during GLP-1-mediated weight loss is important not only for a patient to maintain normal function (strength, mobility, etc.), but because muscle also has a much higher metabolic rate than fat. Some degree of muscle loss is expected when an obese patient loses weight (given the association between muscle volume and body weight). However, preserving muscle during weight loss can make it easier to *continue* to lose body weight (and to maintain that loss) while receiving anti-obesity medications and after treatment discontinuation. Therefore, the **quality of weight loss** induced by anti-obesity drugs is an important consideration that is based on the impact and clinical significance of reduced lean mass (and muscle mass). In other words, the *quantity* of weight that is lost may not be the only factor to be considered for a given anti-obesity medication – if, for example, much of the weight lost is lean (muscle) mass.

Sarcopenia – loss of muscle mass, strength, and function during weight loss. Sarcopenia is more common in older adults but can be associated with obesity-associated comorbidities (e.g., CVD, CKD, cancer). It is characterized by weakness, fatigue, lack of energy, and difficulty in standing and walking. Sarcopenia is a major cause of falls, which can lead to broken bones and other serious injuries, as well as decreased QoL and more rapid disease progression. Patients that are older, get little or no exercise, have a poor diet, and/or have severe diseases have a higher baseline risk of clinically-significant sarcopenia and impaired muscle function. This should be considered when assessing the suitability of an obese patient for weight loss therapy that is known to adversely affect muscle (e.g., GLP-1R agonists), and strategies to preserve lean mass during weight loss should be considered.

How can lean muscle be preserved during medication-induced weight loss? A number of different strategies may be employed to limit the extent of muscle loss in patients receiving anti-obesity medications. A moderate increase in dietary protein intake may be beneficial, particularly in patients that are more susceptible to loss of muscle mass and sarcopenia (e.g., older adults). This may also be important for patients taking GLP-1-based therapies, who often shift their food preferences away from high nutritional quality proteins when compared to a standard, calorie-restricted diet. A high protein diet can also promote a negative energy balance, which may help patients to maintain weight loss over a longer period of time. There is also a role for exercise during weight loss. Specifically, resistance training exercise can not only help to preserve muscle mass, but it can also increase muscle strength (i.e., it can support normal function). Combining exercise with protein supplementation may produce additional benefits vs. exercise alone in older adults. Furthermore, preclinical studies suggest that combining GLP-1s and exercise may synergistically reduce vascular inflammation and improve insulin action during obesity. One caveat is that some patients taking GLP-1s experience fatigue at a higher level than those receiving a placebo, which may limit the ability to exercise.

Novel agents that can spare muscle during weight loss. Novel MoAs are being leveraged for combination with existing anti-obesity drugs (e.g., GLP-1s) to preserve lean mass, or with fat-selective weight loss activity. Notably, manipulation of **myostatin/activin A signaling** – a master regulator of skeletal muscle mass – is a promising approach to preserve muscle during a period of weight loss. So too is **peripherally-restricted CB1 antagonism**. An overview of these and other approaches is provided in **Exhibit 29** on page 66.

Source: Neeland IJ et al. *Diabetes Obes Metab*. 2024;1. Cava E et al. *Adv Nutr*. 2017;8:511. Piper Sandler Research.

KOL Feedback on Lean Mass Preservation: The Problem and Strategies to Mitigate Loss of Lean Mass (Page 1 of 3)

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As GLP-1s continue their traction in the obesity space, there is unmet need for lean mass preservation. We recently discussed the issue of lean mass preservation with a KOL who is an expert in obesity research, with extensive involvement in multiple clinical trials of both lifestyle interventions and pharmacotherapy for obesity (for more, see our note here).

Low levels of lean mass (muscle) are associated with risk of fractures and falls, and significant weight loss increases these risks even more. Our KOL noted that low levels of lean mass are especially significant in women, who are prone to lower muscle mass, and patients aged 65 years or more, who have progressive slowing of metabolism and loss of muscle mass and are at high risk for frailty. This can lead to fractures/falls, which can create a snowball effect as even more muscle mass is lost during recovery. The KOL suggested that a key ratio for healthy weight loss is that 75% of the weight lost should come from fat and only 25% of the weight lost should come from lean muscle mass. Our KOL referenced a key observation from the Look AHEAD weight loss study, in which **patients who lost weight on treatment subsequently regained primarily fat mass, resulting in a worse body composition at the end of the study vs. placebo, as well as higher risk of frailty-related fractures.**

The efficacy of newer incretin therapies puts these concerns in the spotlight. Prior to semaglutide and tirzepatide, weight loss outcomes were generally not high enough to warrant concern about body composition. Now with the advent of current incretin therapies, the most successful for reducing weight to date, attention has been refocused on maintaining a healthy body composition. Our KOL believes most doctors are not yet paying attention, but healthcare professionals who counsel patients (nurse practitioners, physician assistants) are starting to ring the alarm, and this will be a more talked about issue in the coming years. Our KOL also noted that regulators are starting to pay attention: the revised label for Wegovy (semaglutide) includes language noting an increased incidence of hip and pelvic fractures in women on treatment vs. placebo (1.0% vs. 0.2%, respectively). Although the data is hard to parse through, our KOL noted that body composition outcomes were worse for Wegovy than Zepbound (tirzepatide), possibly due to Zepbound encouraging fat oxidation as a secondary mechanism. In terms of which patients should be eligible for a treatment targeting lean mass preservation, our KOL believes that everyone over 65 years old on a GLP-1 is a good candidate. The KOL also believes that special cases such as women with ovariectomies would also be eligible.

Although lean mass preservation can be addressed with lifestyle intervention (weight training), it is not so straightforward, underscoring the need for additional treatments. Our KOL acknowledged that wrap-around treatment for patients with obesity is important, which includes counseling on diet and exercise. These services are standard for bariatric surgery patients but have not been as widely adopted for GLP-1 patients. Newer recommendations are being developed which more heavily encourage weight training. The doc discussed that while patients who make it to the gym are typically successful, getting patients to the gym in the first place is a high barrier, so additional treatment options are needed.

Figuring out relevant regulatory endpoints for a lean muscle preservation treatment will be difficult. Our KOL discussed that the most important data for a

Source: Piper Sandler Research.

KOL Feedback on Lean Mass Preservation: The Problem and Strategies to Mitigate Loss of Lean Mass (Page 2 of 3)

treatment which preserves lean muscle mass, in her view, is to show that it prevents frailty-induced fractures and falls. However, the KOL conceded that assessing this in a clinical trial setting would be incredibly difficult. Therefore, regulators have the difficulty of figuring out what intermediate endpoints are relevant. The KOL believes that a combination of measuring lean mass plus a functional test like the 6-minute walk test or grip strength could be used, with the caveat that the link between lean muscle mass improvement and functional benefit is assumed rather than clinically established. The KOL likened the story to statins and the SELECT trial for Wegovy, where demonstrating longer-term cardiovascular benefit greatly increased the profile of these drugs. Thus, they expect heightened interest when the therapies show functional benefit in the long term.

Our KOL believes that a lean muscle mass preserving therapy could have additional benefits. The doc explained that the role of muscle in weight regulation is currently underappreciated, but studies of myokines (hormones released in response to muscle use) like leptin show that it is important and can likely increase fat oxidation and suppress appetite. Therefore, lean muscle mass preservation could have additional benefit to overall weight loss as well as metabolic and cardiovascular parameters. In our view, metabolic parameters will likely come into increasing focus as lean mass preservation agents generate more clinical data in obesity, and these may make sense as regulatory endpoints, but again, it remains to be seen how the regulatory landscape for these agents will evolve.

It remains to be seen how these therapies would be positioned in the obesity treatment paradigm. Our KOL believes that data from the FLOW and SELECT trials of semaglutide showing improvements in kidney health and cardiovascular outcomes, respectively, will reinforce that patients should be on GLP-1s for the long term to continue receiving benefit. However, our KOL expressed a need for additional research in younger patients with fewer comorbidities to see if these patients can discontinue a GLP-1 after weight loss, which could require switching to a different therapy. They note that the mechanisms driving weight loss are not necessarily the same as the mechanisms which would drive long-term weight maintenance, and weight maintenance may be better served by a different MoA than just the appetite suppression caused by GLP-1s.

Our KOL believes targeting myostatin/activin A signaling is an important approach. They noted becoming interested in the pathway after seeing bimagrumab (**LLY, not covered**) data for the first time. They briefly reviewed the individual assets in development today, including assets from **SRRK (Bratzel)**, **BHVN (Raymond)**, and **REGN (Raymond)**. However, the KOL did not have a strong opinion about which individual asset might be most efficacious or confer the optimal risk/benefit profile, only that it is important to test each approach, and eagerly awaits clinical data from these programs. The KOL did not have an opinion on whether the activin-sparing approach taken by **SRRK**, **REGN**, **Roche (OTC: RHHBY)** will prove to have better safety and tolerability.

Bimagrumab's Phase II readout is expected to show promising efficacy, but the devil is in the detail, and safety is a major variable. When asked about expectations for bimagrumab's upcoming Phase II readout from the BELIEVE study (in combo with semaglutide, scheduled for late 2024), our KOL believed success

Source: ClinicalTrials.gov. Piper Sandler Research.

KOL Feedback on Lean Mass Preservation: The Problem and Strategies to Mitigate Loss of Lean Mass (Page 3 of 3)

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would be >10% weight loss (preferably 15%), along with a loss of muscle mass <25% compared to semaglutide alone. However, the KOL noted that some specifics like bone mineral density will be important to pay attention to as well. They also discussed that an outcome of less weight loss than semaglutide alone but with better body composition results would be difficult to interpret and would invite discussion on the tradeoffs between more weight loss vs. better body composition. However, the KOL emphasized that the safety results will be key and that any worsening of GI side effects compared to semaglutide alone would almost be a non-starter. They noted that while GI side effects with GLP-1s are common, they are manageable, but any additional AEs may be too much for patients. The previous bimagrumab clinical trial experience has shown frequent GI adverse events including diarrhea and nausea (and, we would note, bimagrumab was also associated with muscle spasms and potential pancreatic and liver safety signals).

Thoughts on the future of obesity treatment: incretin drugs are likely to remain the backbone of anti-obesity pharmacotherapy for the foreseeable future. Although the KOL mentioned in passing some alternative approaches to treating obesity in the pipeline, they were certain that GLP-1s are here to stay. They believe the most interesting area right now is the development of small molecule incretin drugs, since these should be easier to manufacture and thus can expand access for patients. The second area of interest in their opinion is the myostatin/activin signaling landscape, because there is a limit to how far obesity therapy can go with incretins only. The KOL emphasized that incretins mostly work through appetite suppression, but that is not the only way to target obesity and improve overall health.

Source: Piper Sandler Research.

2.3. How do Obesity Therapeutics Affect Other Comorbidities?

It's More Than Just Weight Loss: GLP-1s May Also Treat the Comorbidities of Obesity, With Cardiovascular Risk Reduction Leading the Way

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Obesity is associated with a wide range of comorbidities that cause significant morbidity and mortality, but could be addressed with anti-obesity medications. Obesity is a major public health challenge due not only to its large and growing prevalence (~42% of US adults are obese and ~30% are overweight), but because it also underpins an array of serious health complications (comorbidities) involving multiple organ systems (**Exhibit 13**, next page). These include type 2 diabetes (T2D), cardiovascular disease (CVD), hypertension, dyslipidemia, obstructive sleep apnea (OSA), certain cancers, and many other conditions. For example, obesity significantly increases the risk of CVD and death from CVD: 41% of global BMI-related mortality is linked to CVD. Crucially, weight loss confers improvements in cardiovascular and metabolic profiles in obese/overweight adults, and studies are under way to establish the benefit of anti-obesity medications for other comorbidities.

Anti-obesity medications gain traction in treating obesity-associated comorbidities: Wegovy approved for cardiovascular risk reduction. In March 2024, the FDA approved **Novo Nordisk's** Wegovy (semaglutide) 2.4 mg injection for cardiovascular risk reduction in obese or overweight adults – an indication expansion from its original approval (June 2021) for treatment of adults with obesity. This approval was based on full results from NVO's landmark SELECT PhIII cardiovascular outcomes trial (presented at the 2023 AHA Meeting and published in *The New England Journal of Medicine*) investigating the effects of semaglutide in adults with established CVD and overweight or obesity, but without T2D. The SELECT study enrolled 17,604 adults (BMI of 27+) across 41 countries and >800 investigator sites, who were assigned to receive either once-weekly SC semaglutide (2.4 mg) or placebo. The primary CV efficacy endpoint was a composite of the first occurrence of death from CV causes, non-fatal heart attack, or non-fatal stroke in a time-to-event analysis. Results showed that semaglutide was superior to placebo in decreasing the incidence of primary endpoint events during a mean f/up of ~40 months (P<0.001 for superiority). On safety, more patients discontinued semaglutide than placebo due to adverse events (P<0.001) – an effect that largely attributable to a higher incidence of GI side effects with semaglutide vs. placebo (P<0.001).

Bringing more value to anti-obesity medications: approval for comorbidities will likely be a key driver of market expansion. Looking beyond cardiovascular outcomes, establishing the role of anti-obesity medications in tackling other comorbidities – which may be serious and prevalent – is a critical factor for expanding the reach and impact of anti-obesity medications and for market growth. On this point, we believe that there is a lot of room left for growth in the anti-obesity therapeutics market, and that label expansion will be a key driver of this. Recall that only ~2% of the US adult population was historically treated for obesity with drugs (for a variety of reasons, including limited efficacy, coverage, and awareness, and the perception that obesity was not a disease). We believe the field is at an inflection point, as incretin-based medicines produce unprecedented weight loss among obese patients, leading to increased awareness and demand for these agents and pressure for coverage. On the other hand, emerging data showing that anti-obesity drugs can address significant comorbidities may significantly grow the addressable market for these agents. These data (and approvals) are also likely to shift the perception among payers (as well as physicians) regarding the benefit vs. cost of anti-obesity drugs, which could help to address issues relating to access and reimbursement (i.e., drugs that produce significant health benefits beyond weight loss only are more likely to be covered).

Source: Lincoff AM et al. *N Eng J Med*. 2023;389:2221. FDA.gov. ClinicalTrials.gov. NIH StatPearls: Obesity & Comorbid Conditions; August 28, 2023. Piper Sandler Research.

Obesity Drives an Array of Comorbidities That Represent Opportunities for Label Expansion for Anti-Obesity Drugs

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EXHIBIT 13
Overview of Key Obesity-associated Comorbidities

Neurology & Psychiatric Disorders

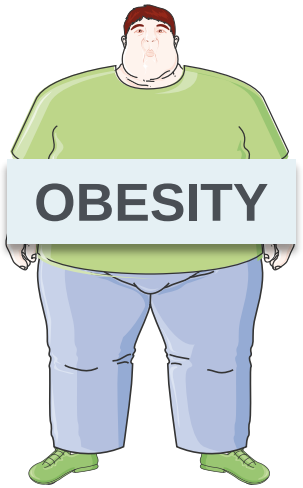
- Depression
- Idiopathic intracranial hypertension (IIH)

Cardiovascular System

- Hypertension
- Coronary artery disease (CAD)
- Heart failure (HF)
- Atrial fibrillation (AF)
- Stroke
- Venous thromboembolism

Endocrinology

- T2D
- Dyslipidemia (high LDLs, low HDLs)
- Metabolic syndrome
- Vit D deficiency



Respiratory System

- Obstructive sleep apnea (OSA)
- Obesity hypoventilation syndrome (OHS)

Gastrointestinal & Urinary Tract

- Non-alcoholic fatty liver disease (NAFLD)
- Gallstones
- Chronic kidney disease (CKD)

Reproductive System

- Irregular menstrual cycles
- Ovulatory dysfunction & infertility
- Increased risk of miscarriage
- Endometrial hyperplasia & malignancy

Other Complications

- Skin disorders (including poor wound healing)
- Increased mortality from infections such as flu or COVID-19
- Obesity-associated cancers (e.g., breast, colorectal, ovarian, endometrial, gastric, esophageal, renal cell, liver, pancreatic, kidney and others)

Source: NIH StatPearls: Obesity & Comorbid Conditions; August 28, 2023. Michos ED et al. *J Am Heart Assoc*. 2023;12:e029282. Servier Medical Art. Piper Sandler Research.

A Closer Look at Anti-obesity Drugs for Cardiovascular Disease: GLP-1s & Other MoAs (Page 1 of 2)

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Building on March 2024's FDA approval of NVO's Wegovy for cardiovascular risk reduction: new CVD indications, new data, and new trials. As mentioned earlier in this section, the FDA approved Wegovy (semaglutide) 2.4 mg injection for cardiovascular risk reduction in obese/overweight adults based on full results from the NVO's landmark SELECT PhIII CV outcomes trial (n=17,604 patients). Following this success, pharma companies are now investigating the role for GLP-1s in other CVD indications and patient groups. **Eli Lilly (LLY, not covered)** released topline data on August 1, 2024 for its PhIII trial of **tirzepatide** (GLP-1R/GIPR SC injectable dual agonist) in individuals with heart failure with preserved ejection fraction (HFpEF) and obesity. Key takeaways from this study are summarized below in **Exhibit 14**, and show that tirzepatide: (1) reduced the risk of heart failure outcomes (i.e., heart failure urgent visit or hospitalization, oral diuretic intensification, or CV death) by 38% vs. placebo; (2) significantly improved heart failure symptoms and physical limitations (as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS)); and (3) produced a 15.7% decrease in BW (vs. 2.2% for placebo) in a pooled group of individuals with or without T2D.

EXHIBIT 14

Key Takeaways From Recent Topline Data From SUMMIT: LLY's PhIII Trial of Tirzepatide in Patients With HFpEF & Obesity (August 1, 2024)

Parameter	Tirzepatide - Phase 3 SUMMIT - (HFpEF and Obesity)
Company	Eli Lilly and Co (LLY, not covered)
Construct	GLP-1/GIP dual agonist
Oral or Injectable	SC injection
Doses	QW 5 mg, 10 mg, 15 mg vs placebo (n=731 total)
Data From:	52-week (up-to 120-week) double-blind, randomized, placebo-controlled Phase 3 SUMMIT (NCT04847557) in 731 obese patients with HFpEF
Weight Loss	**Week 52 (efficacy estimand):** 15.7% (MTD) vs 2.2% placebo **Week 52 (treatment estimand):** 13.9% (MTD) vs 2.2% placebo
When Does Weight Loss Plateau	N/A
GI Tolerability	*Most frequent AEs were GI-related and generally mild-to-moderate in severity *Most common AEs were diarrhea, nausea, constipation, and vomiting in tirzepatide treated patients
Non-GI Safety Reported	*Overall safety profile consistent with previous tirzepatide trials including SURMOUNT and SURPASS
Liver Enzyme Changes	N/A
Lipids	N/A
Additional Data	**Relative risk reduction of HF outcomes (median follow up of 104 weeks):** -38% vs placebo (HR: 0.62; 95% CI: 0.41 to 0.95; p=0.026) **Mean change in KCCQ-CSS from baseline (Week 52; efficacy):** 24.8 (MTD) vs 15.0 placebo **Mean change in KCCQ-CSS from baseline (Week 52; treatment):** 19.5 (MTD) vs 12.7 placebo *all key secondary endpoints met including improvement in exercise capacity as measured by 6MWD and reduction in hsCRP
Discontinuation rate due to AE	N/A
Discontinuation due to GI tolerability	N/A
Reference	**LLY Press Release August 1, 2024**

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

A Closer Look at Anti-obesity Drugs for Cardiovascular Disease: GLP-1s & Other MoAs (Page 2 of 2)

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EXHIBIT 15

Select Clinical Trials to Investigate Anti-obesity Medications in CVD Indications – Including Cardiovascular Outcomes Trials (CVOTs)

Company (Ticker)	Drug	MoA	Phase of Development	NCT Number (ClinicalTrials.gov)	Catalyst
Boehringer Ingelheim (Private) / Zealand Pharma (ZEAL, not covered)	Survodutide (BI-456906)	GLP-1/Glucagon dual Agonist (Ratio of 7.5 (GLP-1): 1 (Glucagon))	Phase III	**Obesity**: NCT06077864 (SYNCHRONIZE-CVOT) (n=4,935)	Primary completion listed as **March 12, 2026** per clinicaltrials.gov
Eli Lilly (LLY, not covered)	Tirzepatide (LY3298176)	GLP-1/GIP dual agonist (Ratio of 1 (GLP-1): 6 (GIP) - 1 (GLP-1): 13 (GIP)	Phase III	**T2D MACE (Major Adverse Cardiovascular Event)**: NCT04255433 (SURPASS-CVOT) n=13,299	LLY guided primary completion **June 2025**
	LA-ANP (LY-3971297)	Long-acting atrial natriuretic peptide	Phase I	**Obesity and Hypertension**: NCT06148272 (n=188)	LLY guided primary completion **February 2025**
Jiangsu Hengrui Pharmaceuticals Co., Ltd. (SHA: 600276)	HRS9531	GLP-1/GIP dual agonist	Phase II	**HFpEF**: NCT06391710 (n=200)	Primary completion listed as **September 2025** per clinicaltrials.gov
Novo Nordisk (NVO, not covered)	Semaglutide	GLP-1 agonist	Phase III	**T2DM**: NCT03914326 (SOUL CVOT) (n=9,642)	NVO guided results in **4Q24**
Rivus Pharmaceuticals (Private)	HU6	Controlled metabolic accelerator	Phase IIa	**Obesity and HFpEF**: NCT05284617 (HuMAIN) (n=62)	PhIIa HuMAIN data at **HFSA (Sept. 27-30, 2024)** and PhIII initiate in **2025**
Ventyx Biosciences (VTYX, Rahimi, OW)	VTX2735	NLRP3 inhibitor (peripheral)	Phase II	**CVD**	VTYX guided Phase II initiation in **2H24**

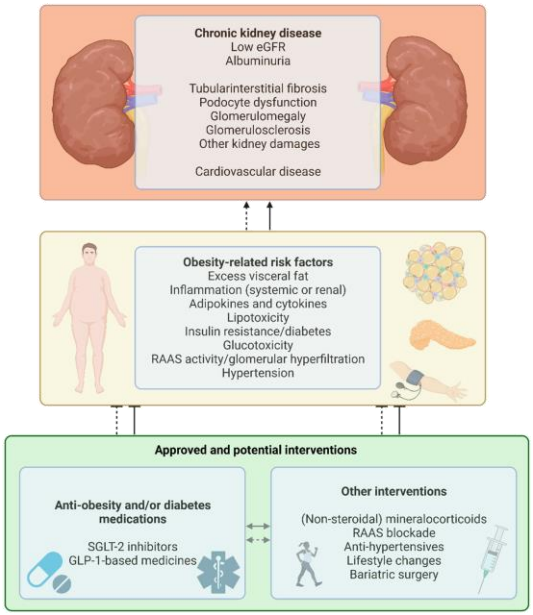
Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

GLP-1s & Chronic Kidney Disease (Page 1 of 3)

Obesity and chronic kidney disease are closely connected. Chronic kidney disease (CKD) is a serious condition with a growing prevalence and is associated with morbidity and early death. CKD is a chronic, progressive disorder that is classified by stages (1-5) according to kidney function (estimated glomerular filtration rate (eGFR)) and damage (graded by the degree of albuminuria, A1-A3). Crucially, obesity is an independent risk factor for CKD, regardless of hypertension, T2D, and other established risk factors. Obesity may cause CKD or could exacerbate pre-existing CKD, and "obesity-related kidney disease" can even be regarded as a possible subtype of CKD. In this regard, key obesity-related factors may drive CKD (**Exhibit 16**). These include visceral adiposity, inflammation and lipotoxicity, RAAS activation and intraglomerular hypertension, and insulin resistance. Due to the high and increasing prevalence of obesity a *Lancet* study projected that by 2040, CKD will be the fifth-leading cause of death globally.

Treatment of obesity-related CKD. Current treatment guidelines target CKD and obesity separately, although some may produce overlapping benefits. Non-pharmacological approaches include lifestyle changes (e.g., diet modifications, increased physical activity) and bariatric surgery. Pharmacotherapies include RAAS blockers (e.g., ACE inhibitors) for CKD patients with albuminuria. SGLT-2 inhibitors and non-steroidal mineralocorticoid receptor antagonists can also be used for CKD to reduce risk of kidney failure and CV events and improve glycemic control, but these agents do not directly impact obesity. With respect to GLP-1s, these therapies are not yet approved for CKD, but in addition to their profound effects on weight loss there is also evidence that they may also exert protective effects on the kidney – suggesting they could offer hope to treat CKD.

EXHIBIT 16
Impact of Obesity-related Factors on CKD (Obesity-related Kidney Disease)



GLP-1s and CKD. Meta-analyses of T2D patients receiving GLP-1 agonists in large CVD outcomes trials suggest these agents may exert a kidney-protective effect. Moreover, data from completed trials for semaglutide provide more insight into the impact of GLP-1s on kidney outcomes. For example, a post-hoc analysis looking at the effects of semaglutide on albuminuria and kidney function based on data from the STEP 1, 2, and 3 trials with once-weekly semaglutide 2.4 mg for weight management in overweight/obese patients (and patients with T2D in STEP 2) found that semaglutide did not impact eGFR vs. placebo, which was likely due to most trial

Source: Kreiner FF et al. *Biomedicines*. 2023;11:2498. Foreman KJ et al. *Lancet*. 2018;392:2052. Piper Sandler Research.

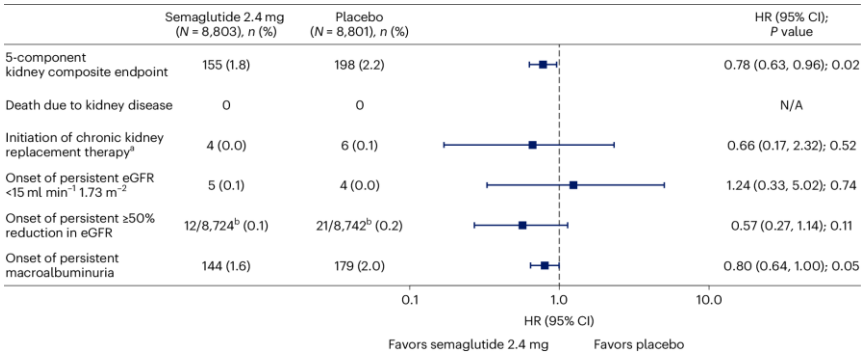
GLP-1s & Chronic Kidney Disease (Page 2 of 3)

participants having normal kidney function. However, semaglutide had an albuminuria-reducing effect in STEP 2. Specifically, in individuals with T2D and overweight/obesity, semaglutide 2.4 mg significantly improved albuminuria, with a 32.9% reduction in the urinary albumin-to-creatinine ratio (UACR) at week 68 vs. placebo (p = 0.003).

Analysis of SELECT data points to improvement in kidney outcomes with GLP-1R agonists. A recent analysis (published in *Nature Medicine*) of long-term kidney outcomes of semaglutide in obesity and CVD from **Novo Nordisk's** completed SELECT trial suggests semaglutide can improve kidney outcomes in overweight/obese individuals without T2D. Recall that the SELECT study demonstrated a 20% reduction in major adverse CV events with semaglutide vs. placebo in overweight/obese patients with pre-existing CVD and no T2D. Importantly, the incidence of the pre-specified main composite kidney endpoint (a composite based on five criteria: death from kidney disease, initiation of chronic kidney replacement therapy, onset of persistent estimated glomerular filtration rate (eGFR) < 15 ml min^{-1} 1.73 m^{-2}, persistent ≥50% reduction in eGFR, or onset of persistent macroalbuminuria) was lower with semaglutide (1.8%) vs. placebo (2.2%): hazard ratio (HR) = 0.78; 95% confidence interval (CI) 0.63, 0.96; *P* = 0.02. The treatment benefit at 104 weeks for eGFR was 0.75 ml min^{-1} 1.73 m^{-2} (95% CI 0.43, 1.06; *P* < 0.001) overall and 2.19 ml min^{-1} 1.73 m^{-2} (95% CI 1.00, 3.38; *P* < 0.001) in patients with baseline eGFR <60 ml min^{-1} 1.73 m^{-2}.

EXHIBIT 17

Semaglutide 2.4 mg Significantly Improves 5-Component Kidney Composite Endpoint in SELECT Trial



FLOW study: semaglutide slows the decline of kidney function in in patients with T2D and CKD. Novo Nordisk's PhIII FLOW trial randomized 3,533 participants in 28 countries to once-weekly semaglutide 1 mg or placebo to look at the effect on progression of renal impairment in subjects with T2D and CKD. The primary endpoint was major CKD events: a composite of the onset of kidney failure (dialysis, transplantation, or eGFR of <15 ml per minute per 1.73 m^2), 50% or more reduction in eGFR from baseline, or death from kidney-related or cardiovascular causes. With a median f/up of 3.4 years, results were similar for a composite of the kidney-specific components of the primary outcome (HR, 0.79; 95% CI, 0.66 to 0.94), as well as for death from CV causes (HR, 0.71; 95% CI, 0.56 to 0.89). Confirmatory secondary outcomes also favored semaglutide: the mean annual eGFR slope was shallower (i.e., a slower decrease) by 1.16 ml per minute per 1.73 m^2 in the semaglutide group (P<0.001), the risk of major cardiovascular events was 18% lower (HR, 0.82; 95% CI, 0.68 to 0.98; P=0.029), and the risk of death from any cause was 20% lower (HR, 0.80; 95% CI, 0.67 to 0.95, P=0.01). Fewer of those in the semaglutide group reported SAEs vs. the placebo group (49.6% vs. 53.8%, respectively).

Source: Perkovic V et al. *N Engl J Med*. 2024;391:109. Kreiner FF et al. *Biomedicines*. 2023;11:2498. Foreman KJ et al. *Lancet*. 2018;392:2052. Colhoun HM et al. *Nat Med*. 2024;30:2058. ClinicalTrials.gov. Piper Sandler Research.

GLP-1s & Chronic Kidney Disease (Page 3 of 3)

EXHIBIT 18
Select Clinical Trials Investigating GLP-1s in CKD

Company (Ticker)	Drug	MoA	Phase of Development	NCT Number (ClinicalTrials.gov)	Catalyst
Novo Nordisk (NVO, not covered)	Semaglutide	GLP-1R agonist	Phase III	**T2DM and Chronic Kidney Disease**: NCT04865770 (REMODEL) (n=105)	Primary completion listed as **October 7, 2024** per clinicaltrials.gov
	CagriSema (Cagrilintide & Semaglutide)	**Semaglutide**: GLP-1R agonist **Cagrilintide**: amylin analog	Phase II	**CKD/T2D/Obesity**: NCT06131372 (n=618)	Primary completion listed as **October 13, 2025** per clinicaltrials.gov
Eli Lilly (LLY, not covered)	Tirzepatide (LY3298176)	GLP-1R/GIPR dual agonist	Phase II	**CKD**: NCT05536804 (TREASURE-CKD) (n=140)	LLY guided primary completion **January 2026**
	Retatrutide (LY3437943)	GLP-1R/GIP/Glucagon agonist (tri-agonist); ratio of GLP-1:glucagon:GIP of 1.7:2.5:0.14	Phase IIb	**Obesity/CKD**: NCT05936151 (n=120)	LLY guided primary completion **November 2025**

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Impact of Anti-Obesity Drugs on Non-Alcoholic Fatty Liver Disease & Non-Alcoholic Steatohepatitis (Page 1 of 3)

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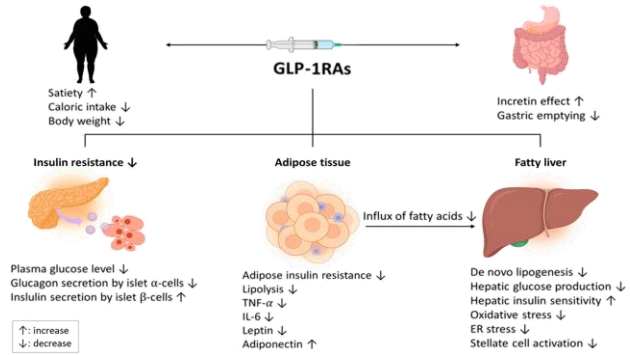
Non-alcoholic fatty liver disease (NAFLD) is characterized by accumulation of fat in the liver (steatosis). It may progress to non-alcoholic steatohepatitis (**NASH, a severe form of NAFLD**), fibrosis, cirrhosis, liver cancer, cardiovascular disease, chronic kidney disease, and death. It is estimated that 9-15M US adults have NASH, and its prevalence is expected to increase by ~60% by 2030 (per Liver Foundation). NASH is also projected to become the leading cause of liver transplantation in the US. Note that the nomenclature for NAFLD was recently changed to **MASLD** (metabolic dysfunction-associated steatotic liver disease) and NASH was changed to **MASH** (metabolic dysfunction-associated steatohepatitis). ***Please email us for our Vol. 5 MASH tracker (note here).***

NAFLD and NASH are driven by obesity, insulin resistance, and metabolic syndrome. This creates an opportunity for anti-obesity/anti-T2D agents – including GLP-1s, but also drugs with novel MoAs – to disrupt NAFLD/NASH pathogenesis (especially in those with underlying obesity and/or T2D) by promoting insulin sensitivity, reducing inflammation, and preventing fat accumulation in liver (**Exhibit 19**). There is significant unmet medical need in the NAFLD/NASH space, with **Madrigal Pharmaceuticals' (MDGL, Rahimi, OW)** Rezdiffra (resmetirom) – a THR-beta-selective agonist – being the only medication currently-approved for NASH with liver fibrosis.

GLP-1s for NAFLD & NASH. A number of studies suggest the beneficial effects of GLP-1R agonists, including liraglutide, semaglutide, exenatide, and dulaglutide, in NAFLD patients. For example, in the Liraglutide Safety and Efficacy in Patients with Non-alcoholic Steatohepatitis (LEAN) study (NCT01237119), the efficacy and safety

EXHIBIT 19

GLP-1s May Address Multiple Pathogenic Mechanisms in NAFLD & NASH



of once-daily liraglutide 1.8 mg was compared to placebo after 48 weeks in overweight patients (n=52) with NASH. The study's primary endpoint – NASH resolution – was achieved in 39% of those receiving liraglutide vs. 9% for placebo (RR = 4.3, 95% CI, 1.0-17.7, p = 0.019). Progression (worsening) of fibrosis was noted in 9% of the liraglutide group and 36% of the placebo group (RR = 0.2, 95% CI, 0.1-1.0, p = 0.04). Patients receiving liraglutide also had significant improvements (vs. placebo) in body weight, BMI, and HbA1c and γ-glutamyl transferase (GGT) levels. GI side effects were more common among the liraglutide group (81%) vs. placebo (65%).

Semaglutide & NASH. Novo Nordisk's 72-week, randomized PhII study (NCT02970942), published in *The New England Journal of Medicine* (Newsome PN et al, 2020), compared the efficacy of once-daily semaglutide (0.1, 0.2, 0.4 mg) to placebo in 320 patients with biopsy-confirmed NASH and liver fibrosis (those with cirrhosis were excluded). The primary endpoint of the study was resolution of

Source: Lee HA and Kim HY. *Int J Mol Sci*. 2023;24:9324. Newsome PN et al. *N Engl J Med*. 2021;384:1113. Liver Foundation. FDA.gov. ClinicalTrials.gov. Piper Sandler Research.

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NASH with no worsening of fibrosis. The confirmatory secondary endpoint was an improvement of 1+ fibrosis stage and no worsening of NASH. On efficacy, the % of patients that had NASH resolution without worsening of fibrosis was 40% (0.1 mg), 36% (0.2 mg), 59% (0.4 mg) with semaglutide, and 17% with placebo (P<0.001 for semaglutide 0.4 mg vs. placebo). Improvement in fibrosis stage was observed in 43% of individuals in the 0.4 mg semaglutide group vs. 33% of the those in the placebo group (P=0.48; not significant). The mean % weight loss for those receiving 0.4 mg semaglutide was 13%, vs. 1% in the placebo group. Regarding tolerability, nausea, constipation, and vomiting were more common in those receiving 0.4 mg semaglutide vs. placebo (i.e., nausea, 42% vs. 11%; constipation, 22% vs. 12%; and vomiting, 15% vs. 2%). Taken together, while semaglutide did not produce significant improvements in fibrosis stage, it did result in a higher percentage of patients with NASH resolution vs. placebo.

EXHIBIT 20

Select Clinical Trials Investigating GLP-1s and Other Agents With Non-incretin MoAs in NAFLD & NASH

Company (Ticker)	Drug	MoA	Phase of Development	NCT Number (ClinicalTrials.gov)	Catalyst
Altimmune (ALT, Rahimi, OW)	Pemvidutide (ALT-801)	GLP-1/Glucagon dual agonist (GLP-1:glucagon ratio of 1:1)	Phase IIb	**NASH**: NCT05989711 (IMPACT) (n=190)	ALT guided enrollment completion in **3Q24** and topline in **1Q25**
AstraZeneca (AZN, not covered)	AZD2693	Antisense oligonucleotide (ASO) targeting PNPLA3	Phase IIb	**NASH**: NCT05809934 (n=175)	AZN guided data in **2025**
Boehringer Ingelheim (Private)	Survodutide (BI-456906)	GLP-1/Glucagon dual agonist (GLP-1:glucagon ratio of 7.5:1)	Phase III	**Obesity and NASH**: NCT06309992 (n=160)	Primary completion listed as **February 16, 2026** per clinicaltrials.gov
	BI-3006337	Undisclosed	Phase I	**Obesity and NAFLD**: NCT05970640 (n=56)	Primary completion listed as **October 13, 2025** per clinicaltrials.gov
Boston Pharma (Private)	BOS-580	Long-acting FGF-21 analog	Phase II	**Obesity and NASH**: NCT04880031 (n=245)	Primary completion listed as **July 2026** per clinicaltrials.gov; Boston Pharma guided advancement to pivotal trials in the **near term**
Eli Lilly (LLY, not covered)	LY3885125	SCAP siRNA	Phase I	**NAFLD**: NCT06007651 (n=112)	LLY guided primary completion **April 2025**
	PNPLA3 siRNA	PNPLA3 knockdown	Phase I	**NASH**: NCT05395481 (n=176)	LLY guided primary completion **December 2025**
Hanmi Pharmaceutical Company (XKRX: 128940)	HM15211	GLP-1/GIP/Glucagon agonist	Phase II	**NASH**: NCT04505436 (n=240)	Primary completion listed as **May 11, 2025** per clinicaltrials.gov

Source: Lee HA and Kim HY. *Int J Mol Sci*. 2023;24:9324. Newsome PN et al. *N Engl J Med*. 2021;384:1113. Company Materials. ClinicalTrials.gov. Piper Sandler Research.

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EXHIBIT 21

Select Clinical Trials Investigating GLP-1s and Other Agents With Non-incretin MoAs in NAFLD & NASH (Continued)

Company (Ticker)	Drug	MoA	Phase of Development	NCT Number (ClinicalTrials.gov)	Catalyst
Merck (MRK, not covered)	Efinopegdutide (MK-6024)	GLP-1/Glucagon dual agonist (GLP-1: Glucagon ratio of 1:1)	Phase IIb	**NASH**: NCT05877547 (n=300)	Primary completion listed as **February 13, 2026** per clinicaltrials.gov
Neuraly (Private)	DD01	GLP-1/Glucagon dual agonist	Phase II	**NAFLD and NASH**: NCT06410924 (n=68)	Primary completion listed as **March 2025** per clinicaltrials.gov
Novo Nordisk (NVO, not covered)	Semaglutide	GLP-1 agonist	Phase III	**NASH**: NCT04822181 (ESSENCE) (n=1,200)	Primary completion listed as **March 25, 2029** per clinicaltrials.gov; NVO guided biopsy topline in **4Q24**
	Semaglutide	GLP-1 agonist	Phase II	**NASH**: NCT04971785 (WAYFIND) (n=457)	Primary completion listed as **November 2024** per clinicaltrials.gov
	NNC0194-0499 & Semaglutide	**Semaglutide**: GLP-1 agonist, **NNC0194-0499**: FGF21	Phase II	**NASH**: NCT05016882 (n=672)	Primary completion listed as **October 31, 2024** per clinicaltrials.gov
Rivus Pharmaceuticals (Private)	HU6	Controlled metabolic accelerator	Phase IIb	**NASH**: NCT05979779 (M-ACCEL) (n=219)	M-ACCEL Study readout **1H25**

Source: Lee HA and Kim HY. *Int J Mol Sci*. 2023;24:9324. Newsome PN et al. *N Engl J Med*. 2021;384:1113. Company Materials. ClinicalTrials.gov. Piper Sandler Research.

A Better Night's Sleep? SURMOUNT-OSA Study Shows GLP-1s Reduce the Severity of Obstructive Sleep Apnea

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Phase III SURMOUNT-OSA: tirzepatide for treatment of obstructive sleep apnea in obese adults. Obstructive sleep apnea (OSA) is a condition in which there are repeated episodes of partial or complete obstruction of the upper airway (leading to disordered breathing) during sleep. While OSA negatively impacts QoL (excessive daytime fatigue, persistent snoring, unrestful sleep, and nighttime awakenings), it also increases all-cause mortality in the first year after diagnosis by almost 40% when untreated. Investigators postulated that **Eli Lilly's** tirzepatide (dual agonist of GLP-1R and GIPR; approved as Zepbound for weight loss) could be a treatment for OSA, given that: (1) obesity is significantly associated with OSA, and (2) earlier studies showed that weight loss (via dietary programs, bariatric surgery, or liraglutide treatment (SCALE Sleep Apnea trial)) can reduce OSA severity.

SURMOUNT-OSA (NCT05412004) consisted of two Phase III, double-blind, randomized, controlled trials in adults with moderate-severe OSA and obesity. Trial 1 included participants that were not receiving positive airway pressure (PAP) treatment (SoC for OSA), whereas trial 2 included those that were receiving PAP therapy at baseline. All participants were randomized at a 1:1 ratio to receive either the MTD of tirzepatide (10 or 15 mg) or placebo for 52 weeks. The study's primary endpoint was the change in the apnea-hypopnea index (AHI) – the number of apneas and hypopneas during an hour of sleep – from baseline. Key secondary end points included the percent change in AHI and body weight (BW), and changes in hypoxic burden, patient-reported sleep impairment and disturbance, high-sensitivity C-reactive protein (hsCRP) concentration, and systolic blood pressure. Regarding efficacy, the mean AHI at baseline was 51.5 events/hour in trial 1 and 49.5 events/hour in trial 2, while the mean BMIs were 39.1 and 38.7, respectively (i.e., participants were obese).

For trial 1 (no PAP), the mean change in AHI at week 52 was -25.3 events/hour (95% CI, -29.3 to -21.2) with tirzepatide, and -5.3 events/hour (95% CI, -9.4 to -1.1) with placebo. This gave an estimated treatment difference of -20.0 events/hour (95% CI, -25.8 to -14.2) (P<0.001). In trial 2 (participants receiving PAP), the mean change in AHI at week 52 was -29.3 events/ hour (95% CI, -33.2 to -25.4) with tirzepatide and -5.5 events/hour (95% CI, -9.9 to -1.2) with placebo, giving an estimated treatment difference of -23.8 events/hour per hour (95% CI, -29.6 to -17.9) (P<0.001). All key secondary endpoints showed improvements with tirzepatide as compared with placebo. The most common AEs reported were GI-related and generally mild-moderate in severity. In conclusion, SURMOUNT-OSA showed that in obese adults with moderate-severe OSA, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure. and improved sleep-related patient-reported outcomes.

What next? Ultimately, GLP-1s can reduce weight and improve airway collapsibility to treat moderate-severe OSA. This could be accomplished either as monotherapy (e.g., in patients unable to tolerate device-based PAP therapy) or with PAP. On the latter point, PAP therapy and weight loss is known to be better at improving moderate-severe OSA vs. either intervention alone. Combined therapy can also offer immediate improvements in OSA severity: PAP gives an instant, complete effect on day 1, whereas weight loss that lowers AHI may take a year or longer, per SURMOUNT-OSA. However, some questions remain. First, since weight regain typically occurs when GLP-1 therapy is discontinued, could this also lead to a resumption of OSA in patients? Second, how applicable are the findings of SURMOUNT-OSA to other OSA patients (e.g., those that are overweight (not obese), have T2D, or mild OSA)?

Source: Malhotra A et al. *N Engl J Med*. 2024; doi: 10.1056/NEJMoa2404881. Malhotra A et al. *Contemp Clin Trials.* 2024;141:107516. Malhotra A et al. *Sleep Med.* 2024;121:26. Buysse DJ. *Sleep*. 2014;37:9. Blackman A et al. *International J Obesity*. 2016;40:1310. Hamilton GS and Edwards BA. *Respirology*. 2023;28:824. ClinicalTrials.gov. Piper Sandler Research.

Protecting the Brain? GLP-1R Agonists May Offer Benefit in Alzheimer's Disease

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Drug "repurposing": incretins may have significant neuroprotective effects for conditions such as Alzheimer's disease and Parkinson's disease. Given the overlapping pathophysiology between T2D and neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD), it has been proposed that anti-diabetic agents – including GLP-1 analog – hold promise as potential therapeutic agents for these disorders. Supporting this concept: (1) epidemiological studies show an increased risk of AD and PD in individuals with T2D; (2) preclinical data indicate that GLP-1R agonists can normalize insulin signaling and protect against progressive neurodegeneration in animal models (e.g., liraglutide prevented memory loss in APP/PS1 mice and could reverse pathological features of established disease); and (3) early clinical trials of anti-diabetic therapies in AD and PD patients (e.g., liraglutide, exenatide, dulaglutide) show some evidence of improvements in disease characteristics (e.g., reduced brain amyloidosis, lower risk of substantive cognitive impairment, etc.). **Novo Nordisk** is currently running two large, Phase III studies, EVOKE (NCT04777396) and EVOKE Plus (NCT04777409), to assess semaglutide in people with early-stage AD, with primary completion for each study estimated for September 2025 (per ClinicalTrials.gov).

A Phase IIb trial suggests liraglutide – a long-acting, once-daily GLP-1R agonist – may protect the brain and slow cognitive decline in AD. Recent clinical data from the Alzheimer's Association International Conference (AAIC) in Philadelphia in July 2024 suggest that the GLP-1 receptor agonist liraglutide (**Novo Nordisk**; marketed as Saxenda for weight loss and Victoza for T2D) slowed cognitive decline. In a randomized, double-blind, placebo-controlled Phase IIb trial, led by Professor Paul Edison at Imperial College London (UK), 204 patients with mild AD each received a daily SC injection of up to 1.8 mg of liraglutide or placebo for one year. All patients underwent baseline MRI imaging to evaluate brain structure and volume, PET scans for glucose metabolism, and rigorous memory testing. This testing was repeated at the end of the study. The primary endpoint was not met – the change in rate of cerebral glucose metabolism in cortical brain regions. However, there was a statistically-significant improvement in the secondary endpoint of change in scores for clinical and cognitive measures, as well as for brain volume (an exploratory endpoint). Specifically, liraglutide reduced cognitive decline by up to 18% after one year of treatment vs. placebo (P<0.01). Cognitive function was determined as a composite score of 18 different tests that assess memory, language, comprehension, and spatial orientation (i.e., ADAS EXEC z score). In parallel, the researchers noted ~50% decrease in loss of volume in key areas of the brain that are typically affected by AD and are crucial for memory, language, and decision-making (i.e., frontal, temporal, parietal, and total gray matter) in those treated with liraglutide vs. placebo, as measured by MRI. As expected, the most common side effects were GI-related (25.5% of all AEs in the liraglutide group). Together, these findings highlight the potential for GLP-1 agonists to protect the brain in neurological conditions such as Alzheimer's disease, possibly by lowering insulin resistance, reducing brain inflammation, potentiating communication between neurons, and/or mitigating the toxic impacts of key AD biomarkers (e.g., tau, amyloid beta). AD lacks effective treatment options and has a large and growing footprint: ~6.9M Americans aged 65 years and over are living with AD in 2024 – a number that is projected to grow to ~13.8M by 2060 – and >55M people have AD worldwide (per WHO). Consequently, AD could represent a very large and significant indication expansion for GLP-1s.

Source: ClinicalTrials.gov. Nowell J et al. *Ageing Res Rev*. 2023;89:101979. Alzheimer's Association. World Health Organization. Piper Sandler Research.

Anti-Obesity Drugs Could Reduce the Risk of Certain Cancers

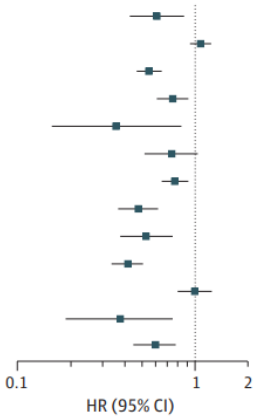
Use of GLP-1R agonists is associated with lower risks of specific obesity-associated cancers (OACs). It has been established that 13 different cancer types are associated with obesity: esophageal, breast, colorectal, endometrial, gallbladder, stomach, kidney, ovarian, pancreatic, and thyroid cancers, hepatocellular carcinoma, meningioma, and multiple myeloma. Specifically, obesity confers a greater risk of developing these cancers and/or having a worse prognosis. Given this, a study published in *JAMA Network Open* in July 2024 addressed the question of whether there is clinical evidence to support the concept that GLP-1R agonists lower the incident risk of OACs. To answer this, researchers performed a retrospective cohort study based on a nationwide database of electronic health records (EHRs) of 113M US patients. This study population included 1,651,452 patients with T2D and no prior diagnosis of OACs at baseline, and who were prescribed GLP-1R agonists, insulin, or metformin between March 2005 and November 2018. First-time diagnosis of each of the 13 OACs during a 15-year f/up period after drug exposure was examined to calculate hazard ratios (HRs), cumulative incidences, and 95% CIs.

Compared with insulin, GLP-1R agonists were associated with a significantly lower risk of 10 of 13 OACs (i.e., HRs were significantly <1.00; **Exhibit 22**): gallbladder cancer (HR, 0.35; 95% CI, 0.15-0.83), meningioma (HR, 0.37; 95% CI, 0.18-0.74), pancreatic cancer (HR, 0.41; 95% CI, 0.33-0.50), hepatocellular carcinoma (HR, 0.47; 95% CI, 0.36-0.61), ovarian cancer (HR, 0.52; 95% CI, 0.03-0.74), colorectal cancer (HR, 0.54; 95% CI, 0.46-0.64), multiple myeloma (HR, 0.59; 95% CI, 0.44-0.77), esophageal cancer (HR, 0.60; 95% CI, 0.42-0.86), endometrial cancer (HR, 0.74; 95% CI, 0.60-0.91), and kidney cancer (HR, 0.76; 95% CI, 0.64-0.91). When comparing risk of OACs between those receiving GLP-1R agonists vs. metformin,

EXHIBIT 22

Lower Risk of 10 of 13 Obesity-associated Cancers in Patients Receiving GLP-1R Agonists vs. Those Receiving Insulin

Outcome (N = 1651452)	Group prescribed GLP-IRAs but not insulin, No (%) (n = 48983)	Group prescribed insulin but not GLP-IRAs, No (%) (n = 1044745)	HR (95% CI)
Esophageal cancer (n = 48437)	49 (0.10)	77 (0.16)	0.60 (0.42-0.86)
Breast cancer (n = 13768)	427 (3.08)	379 (2.94)	1.07 (0.93-1.23)
Colorectal cancer (n = 48443)	223 (0.46)	391 (0.81)	0.54 (0.46-0.64)
Endometrial cancer (n = 25750)	160 (0.62)	210 (0.82)	0.74 (0.60-0.91)
Gallbladder cancer (n = 48587)	<10 (<0.02)	19 (0.04)	0.35 (0.15-0.83)
Stomach cancer (n = 48449)	56 (0.12)	75 (0.16)	0.73 (0.51-1.03)
Kidney cancer (n = 48322)	223 (0.46)	284 (0.59)	0.76 (0.64-0.91)
Hepatocellular carcinoma (n = 48397)	79 (0.16)	167 (0.35)	0.47 (0.36-0.61)
Ovarian cancer (n = 25739)	51 (0.20)	94 (0.37)	0.52 (0.37-0.74)
Pancreatic cancer (n = 48490)	123 (0.25)	290 (0.60)	0.41 (0.33-0.50)
Thyroid cancer (n = 48527)	154 (0.32)	149 (0.31)	0.99 (0.79-1.24)
Meningioma (n = 48518)	11 (0.02)	29 (0.06)	0.37 (0.18-0.74)
Multiple myeloma (n = 48527)	80 (0.17)	131 (0.27)	0.59 (0.44-0.77)



GLP-1R agonist usage was associated with a lower risk of colorectal cancer, gallbladder cancer, and meningioma, but an increased risk of kidney cancer (data not shown here). The study has some limitations: it is a retrospective observational study with potential biases and confounders, cancer diagnoses may not have been reliably captured in patient EHRs, it could not correlate the degree of weight loss with risk reduction, or control for health care utilization, insurance type, or adherence to treatment. That being said, the potential for GLP-1R agonists to prevent OACs warrants further investigation, and could add to the mounting evidence supporting the broader health benefits of these and other anti-obesity medications.

Source: Wang L et al. *JAMA Network Open*. 2024;7:e2421305. Piper Sandler Research.

2.4. What are Upcoming GLP-1 Catalysts & How Does the Incretins Space Currently Look?

Upcoming Data Catalysts (to YE24) in GLP-1 Space (Page 1 of 2)

Email us **for our Vol. 13 obesity tracker,** which captures 300+ obesity catalysts across 125+ agents and plot 92 clinical datasets from 13 oral agents and 17 injectables (*note here*).

Upcoming data catalysts for injectable GLP-1s between now and YE24:

(1) **RHHBY's** CT-388 (QW SC GLP-1/GIP) up to 6-week PhIb (NCT04838405) in n=96 overweight/obese T2D patients with primary endpoint of TEAEs and primary completion for **September 2023** (per clinicaltrials.gov) has data from the added obese T2D cohort guided for **EASD (September 9-13, 2024)**.

(2) **NVO's (not covered)** semaglutide (GLP-1) 52-week PhIII STRIDE (NCT04560998) in n=792 T2D patients with peripheral arterial disease and primary endpoint of change in max walking distance on constant load treadmill test with primary completion listed as June 5, 2024 (per clinicaltrials.gov) and topline guided in **3Q24**.

(3) **NVO's** semaglutide (GLP-1) 52-week PhIII SOUL CVOT (NCT03914326) in n=9,642 Heart Disease T2D patients with primary endpoint of time to first occurrence of a major adverse cardiovascular event (MACE), a composite endpoint consisting of cardiovascular (CV) death/non-fatal myocardial infarction/non-fatal stroke, primary endpoint completion listed Jul. 29, 2024 (per clinicaltrials.gov), and topline guided for **4Q24**.

(4) **NVO's** semaglutide (7.2mg QW) (GLP-1) 72-week PhIII STEP UP (NCT05646706) in n=1,407 obese patients and primary endpoint of relative change in BW and number of patients who achieve BW reduction ≥5% with primary completion guided as September 20, 2024 (per clinicaltrials.gov) and topline guided in **4Q24**.

(5) **NVO's** semaglutide 312-week Phase III ESSENCE (NCT04822181) in n=1,200 MASH F2-F3 patients testing 2.4 mg sc semaglutide QW with SoC with primary endpoints of resolution of steatohepatitis and no worsening of liver fibrosis and improvement in liver fibrosis and no worsening of steatohepatitis, primary endpoint completion listed Jun. 1, 2029 (per clinicaltrials.gov), and topline results guided in **4Q24**.

(6) **NVO's** CagriSema 68-week PhIII REDEFINE 1 (NCT05567796) in n=3,400 obese patients with primary endpoints of change in body weight and proportion of patients with ≥5% weight loss has primary endpoint completion on October 21, 2024 (per clinicaltrials.gov) and completion guided for **2H24**.

(7) **NVO's** CagriSema 68-week PhIII REDEFINE 2 (NCT05394519) in n=1,200 obese T2D patients with primary endpoints of change in body weight and proportion of patients with ≥5% weight loss has primary endpoint completion on December 11, 2024 (per clinicaltrials.gov) and completion guided for **2H24**.

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Upcoming Data Catalysts (to YE24) in GLP-1 Space (Page 2 of 2)

(8) **LLY's (not covered)** tirzepatide (GLP-1/GIP) 72-week PhIII SURMOUNT-5 (NCT05822830) in n=700 obese/overweight patients with weight-related comorbidities and primary endpoint of % change in BW, with primary completion listed as November 6, 2024 (per clinicaltrials.gov) and data guided **2H24**.

(9) **Regor Pharmaceuticals' (Private)** 12-week RGT001-075 (GLP-1) PhII (NCT06277934) in 60 obese patients with primary endpoint completion in June 2024 (per clinicaltrials.gov) and topline guided for **2H24**.

(10) **ZEAL's (not covered)** 13-week dapiglutide (GLP-1/GLP-2) PhIb (NCT06000891) in 84 obese patients with primary endpoint completion on November 15, 2024 (per clinicaltrials.gov) and results guided for **2H24**.

(11) **AZN's (not covered)** AZD9550 (SC GLP-1/Glucagon) has additional data/analysis guided by **YE24**.

(12) **AMGN's (Raymond, OW)** MariTide (AMG 133) (GIPR antagonist/GLP-1R agonist) 52-week PhII (NCT05669599) in 592 overweight/obese patients (w/ or w/o T2D) with primary endpoint of % change from baseline in BW to week 52 has primary endpoint completion on October 4, 2024 (per clinicaltrials.gov) and topline guided for **late 2024**.

(13) **RHHBY's** CT-868 (QD SC GLP-1/GIP) 16-week PhII (NCT06062069) in n=96 overweight/obese T1D patients with primary endpoint of HbA1c and primary completion for October 31, 2024 (per clinicaltrials.gov) has data guided for **2024**.

Upcoming data in the oral GLP-1 space between now and YE24:

(1) **RHHBY's** CT-996 (oral GLP-1) 28-day PhI (NCT05814107) in 118 overweight/obese patients with or without T2D (n=40 in SAD, n=25 obese in MAD) with primary endpoint of TEAEs with primary completion listed for November 2024 (per clinicaltrials.gov) and obese non-diabetic data anticipated at **EASD (September 9-13, 2024)**.

(2) **VKTX's (not covered)** oral VK2735 (oral GLP-1/GIP) 28-day PhI additional dose cohort (80 mg and 100 mg QD) data by **YE24**; initiate 13-wk PhII obesity trial in **4Q24**.

(3) **AZN's (not covered)** AZD5004 (ECC5004; oral GLP-1) 35-day PhI SAD/MAD (NCT05654831) in T2D and HVs with primary endpoint of safety and data guided for a future medical meeting by **YE24**.

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Focus on Development in the Incretins Space for Obesity (Page 1 of 3)

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Beyond Wegovy and Zepbound: a closer look at the rapidly-expanding development landscape of incretin-based drugs for obesity and its related comorbidities.

We identified 29 incretin-based assets in clinical development for treatment of obesity (**Exhibit 23**, below and **Exhibit 24**, starting on the next page). Key trends emerging in the incretin space for obesity include: (1) **a shift from injectable to oral agents** – which may improve uptake and treatment adherence, and could simplify and reduce the cost of manufacturing: 4/5 (80%) of Phase III assets are SC, whereas 10/11 (90.9%) Phase I assets are oral. (2) **LLY's oral GLP-1R agonist – Orforglipron – is the "leader of the pack"** and will likely become the comparator for future oral incretins. (3) **Dual and even triple (tri-) agonist approaches** are under investigation to achieve even greater weight loss efficacy, but also metabolic improvements (e.g., increased energy expenditure) and other clinical benefits.

EXHIBIT 23

Analysis of Select Incretin Assets in Clinical Development for Treatment of Obesity & Associated Comorbidities; by Study Phase & Route of Administration

Phase III: Subcutaneous Administration

- **Novo Nordisk** CagriSema (amylin & GLP-1 analogs)
- **Eli Lilly** Retatrutide (GIP/GLP-1/glucagon tri-agonist)
- **Boehringer Ingelheim** Survodutide (GLP-1/glucagon dual agonist)
- **Sciwind Biosciences** SC ecnoglutide (XW003) (long-acting GLP-1 analog)

Phase III: Oral Administration

- **Eli Lilly** Orforglipron (GLP-1R agonist)

Phase II: Subcutaneous Administration

- **Amgen** MariTide (GIPR antagonist, GLP-1R agonist)
- **Eli Lilly** Mazdutide (GLP-1/glucagon dual agonist)
- **Altimmune** Pemvidutide (GLP-1/glucagon dual receptor agonist)
- **Roche** CT-388 (Dual GLP-1/GIP receptor modulator)
- **Novo Nordisk** NN9542 (GIP/GLP-1 dual agonist)
- **Novo Nordisk** NN9490 (co-agonist of GLP-1 & amylin)
- **PegBio** PB-718 (GLP-1/GCG dual receptor agonist)
- **PegBio** Visepegenatide (PB-119) (GLP-1R agonist)
- **Viking Therapeutics** VK2735 (Dual GLP-1R/ GIPR agonist)
- **Zeal Pharma** Dapiglutide (Dual GLP-1/GLP-2 receptor agonist)

Phase II: Oral Administration

- **Pfizer** Danuglipron (product enhancement) (GLP-1R agonist)
- **Regor Therapeutics** RGT-075 (Selective GLP-1R agonist)
- **Hercules CM NewCo** HRS-7535 (GLP-1R agonist)

Phase I: Subcutaneous Administration

- **AstraZeneca** AZD9550 (GLP-1/glucagon dual receptor agonist)

Phase I: Oral Administration

- **Structure Therapeutics** GSBR-1290 (GLP-1R agonist)
- **AstraZeneca** AZD5004 (GLP-1R agonist)
- **Pfizer** PF-06954522 (GLP-1R agonist)
- **Hercules CM NewCo** HRS-9531 (Dual GLP-1R/GIPR agonist)
- **Roche** CT-996 (GLP-1R agonist)
- **Sciwind Biosciences** XW014 (GLP-1 agonist)
- **Novo Nordisk** NN9847 (co-agonist of GLP-1 & amylin)
- **Terns Pharmaceuticals** TERN-601 (GLP-1R agonist)
- **Sciwind Biosciences** XW004 (GLP-1 analog)
- **Viking Therapeutics** VK2735 (Dual GLP-1R/GIPR agonist)

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Focus on Development in the Incretins Space for Obesity (Page 2 of 3)

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EXHIBIT 24

Select Novel Incretin-based Agents in Clinical Development for Treatment of Obesity & Associated Comorbidities

Company (Ticker)	Asset	Target/MoA	Molecule Type	Route of Administration	Frequency of Administration	Development Stage
Altimmune (ALT)	Pemvidutide	GLP-1/glucagon dual receptor agonist	Peptide	SC	Once-weekly	Phase II
Amgen (AMGN)	Maridebart cafraglutide (MariTide; AMG 133)	Bispecific GIPR antagonist/GLP-1 receptor agonist; differentiated approach is based on the observation that GIP receptor mutations are associated with lower weight	Antibody-peptide conjugate	SC	Once-monthly (also testing less frequent dosing strategies)	Phase II
AstraZeneca (AZN)	AZD5004	GLP-1R agonist	Small molecule	Oral	Once-daily	Phase I
	AZD9550	GLP-1/glucagon dual receptor agonist	Peptide	SC	Once-weekly	Phase I
Boehringer Ingelheim (Private)	Survodutide (licensed from **Zealand Pharma (ZEAL)**)	GLP-1/glucagon dual receptor agonist; acylation for longer half-life	Peptide	SC	Once-weekly	Phase III
Eli Lilly (LLY)	Orforglipron (LY3502970)	GLP-1R agonist	Small molecule	Oral	Once-daily	Phase III
	Retatrutide (triple-G; LY3437943)	GIP/GLP-1/glucagon receptor agonist (GGG tri-agonist)	Peptide	SC	Once-weekly	Phase III
	Mazdutide (LY3305677)	GLP-1/glucagon dual receptor agonist	Peptide	SC	Once-weekly	Phase II
Novo Nordisk (NVO)	CagriSema (cagrilintide + semaglutide)	Combination of amylin analog (cagrilintide) + GLP-1 analog (semaglutide)	Peptide	SC	Once-weekly	Phase III
	OW GIP/GLP-1 (NN9542)	GIP/GLP-1 dual receptor agonist	Peptide	SC	Once-weekly	Phase II
	Subcutaneous amycretin (NN9490)	Long-acting co-agonist of GLP-1 and amylin	Peptide	SC	Once-weeky	Phase I/II
	Oral amycretin (NN9847)	Long-acting co-agonist of GLP-1 and amylin	SNAC Peptide	Oral	Once-daily	Phase I
PegBio (Private)	Visepegenatide injection (PB-119)	GLP-1R (polyethylene glycolated exenatide)	Peptide	SC	Once-weekly	Phase I/II
	PB-718	GLP-1/GCG dual receptor agonist (fixed dose combo of PB-119 [GLP-1R] and PB-722 [glucagon])	Peptide	SC	Once-weekly	Phase I/II

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Focus on Development in the Incretins Space for Obesity (Page 3 of 3)

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EXHIBIT 24

Select Novel Incretin-based Agents in Clinical Development for Treatment of Obesity & Associated Comorbidities (Continued)

Company (Ticker)	Asset	Target/MoA	Molecule Type	Route of Administration	Frequency of Administration	Development Stage
Pfizer (PFE)	Danuglipron (product enhancement)	GLP-1R agonist	Small molecule	Oral	Once-daily	Phase II
	PF-06954522	GLP-1R agonist	Small molecule	Oral	Not disclosed	Phase I
Regor Therapeutics (Private)	RGT-075	Highly-selective GLP-1R agonist	Small molecule	Oral	Once-daily	Phase II
Roche (OTC: RHHBY)	CT-388 (RG6640)	Dual GLP-1/GIP receptor modulator (bias to avoid β-arrestin)	Peptide	SC	Once-weekly	Phase II
	CT-996 (RG6652)	GLP-1 receptor agonist; designed to be a biased GLP-1 receptor agonist that activates cAMP signalling with minimal-to-no beta-arrestin recruitment	Small molecule	Oral	Once-daily	Phase I
Sciwind Biosciences (Private)	SC ecnoglutide (XW003)	Novel, cAMP signaling biased, long-acting GLP-1 analog optimized for improved biological activity	Peptide	SC	Once-weekly	Phase III
	Oral ecnoglutide (XW004)	Oral tablet formulation of the GLP-1 analog XW003 which has been co-formulated with an oral absorption enhancer (PNAC - T2026) to enable oral administration	Peptide	Oral	Once-daily to once-weekly	Phase I
	XW014	GLP-1 agonist	Small molecule	Oral	Once-daily	Phase I
Structure Therapeutics (GPCR)	GSBR-1290	Selective GLP-1R agonist	Small molecule	Oral	Once-daily	Phase II
Terns Pharmaceuticals (TERN)	TERN-601	GLP-1R agonist	Small molecule	Oral	Once-daily	Phase I
Viking Therapeutics (VKTX)	VK2735 (subcutaneous)	Dual GLP-1R/GIPR agonist	Peptide	SC	Once-weekly	Phase II
	VK2735 (oral)	Dual GLP-1R/GIPR agonist	Peptide	Oral	Once-daily	Phase I
Zealand Pharma A/S (ZEAL)	Dapiglutide (ZP 7570)	Dual GLP-1/GLP-2 receptor agonist	Peptide	SC	Once-weekly	Phase II

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

2.5. How Will Future Anti-Obesity Therapies Solve Current Unmet Needs?

Obesity Market Leaders Are Expanding GLP-1 Manufacturing Capacity to Meet Demand

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Build it and they will come: Eli Lilly and Novo Nordisk are aggressively expanding their GLP-1 manufacturing capacities to capitalize on surging demand for GLP-1s. As shown below in **Exhibit 25**, obesity market leaders Eli Lilly and Novo Nordisk are each investing billions of dollars to expand their capacity to manufacture GLP-1s and meet growing demand for these medicines. For example, Novo will acquire three of **Catalent's** fill-finish sites (US, Belgium, and Italy) by late 2024 for $11B to meet very strong demand for its semaglutide medicines Wegovy and Ozempic. Eli Lilly has also invested significantly in production of its anti-obesity medicines and recently announced a new $5.3B commitment to its manufacturing facility in Indiana, taking total investment in that site to $9.0B. In parallel, Eli Lilly acquired a facility in Wisconsin from **Nexus Pharmaceuticals** to boost its production of injectable medicines – including tirzepatide.

How will emerging obesity players tackle the manufacturing issue? Based on experience with Novo and Lilly, Big Pharma players may look to utilize/expand their existing manufacturing infrastructure/capacity, while also engaging with manufacturing partners (CDMOs) to "make up the gap" between supply and demand. Smaller obesity players might be more likely to outsource their manufacturing. The use of third party contract manufacturers will likely be critical to address shortfalls in supply, particularly in the short-medium term, as it typically takes several years to bring a new production facility online. CDMOs are themselves investing heavily to capitalize on demand for GLP-1s. For example, **CordenPharma** – a leading CDMO – is investing ~900M Euros over the next 3 years in a large-scale US/EU expansion of its peptide manufacturing platform to meet increasing demand for GLP-1s.

EXHIBIT 25

Expanding Supply of Anti-obesity Medicines: Select Investments & Deals Related to GLP-1 Manufacturing (Late 2023-2024 YTD)

Date	Investment or Manufacturing Deal
July 15, 2024	• **CordenPharma** – a leading GMP CDMO – invests 900M Euros over the next three years to expand its peptide platform in US and Europe and boost GLP-1 manufacturing capacity
May 24, 2024	• **Eli Lilly** increases its manufacturing investment from $3.7B to $9B at newest US site to boost API production for tirzepatide and other pipeline medicines
April 22, 2024	• **Eli Lilly** acquires a new injectable medicine manufacturing facility in Wisconsin from **Nexus Pharmaceuticals** and estimates that production could start at the facility at YE25
February 5, 2024	• **Novo Nordisk** to acquire three of **Catalent's** fill-finish sites (US, Belgium, Italy) for $11B by late 2024 to meet strong demand for Wegovy and Ozempic
November 23, 2023	• **Novo Nordisk** invests a further ~$2.5B to expand existing production site in France, which includes capacity for GLP-1 products
November 10, 2023	• **Novo Nordisk** invests ~$7B to expand existing manufacturing facilities in Denmark, including increasing capacity of APIs of semaglutide for GLP-1s

Source: FDA.gov. Novo Nordisk and Elil Lilly Company Materials. EMA: Recommendations of Executive Steering Group on Shortages of GLP-1 Receptor Agonists, 12 June 2024. World Health Organization. Ruder K. *JAMA*. 2024; doi:10.1001/jama.2024.13507. Piper Sandler Research.

A Shift From Injectable to Oral Incretins Could Address Manufacturing/Supply & Treatment Adherence Issues: LLY's Orforglipron Leads the Pack

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The emergence of oral incretin-based medicines for treatment of obesity offers many potential benefits, including simplified manufacturing to reduce global shortages. The current market leaders in obesity – NVO's Wegovy and LLY's Zepbound – are biologics (injectable peptides). These are inherently complex and expensive to produce vs. small molecules, with higher requirements for quality and very small margins for error. The emergence of oral incretins for obesity and associated conditions may improve treatment compliance and convenience vs. injectables (e.g., by increasing comfort and use among primary care physicians), and could help to satisfy the strong and growing global demand for weight loss medicines.

LLY leads the pack with orforglipron, but who else is developing oral incretins for obesity? Key players in the oral incretins space are shown in **Exhibit 26** (right). **In particular, we highlight Eli Lilly's orforglipron**, a non-peptide GLP-1R agonist that is the most advanced oral incretin in development, with multiple Phase III studies underway for obesity (ATTAIN-2, NCT05872620; ATTAIN-1, NCT05869903). Other oral incretins in clinical development – most are small molecules, but some are peptide-based – include: **(1) Pfizer's** danuglipron, a GLP-1 agonist in Phase I (NCT06153758), with a modified-release formulation for once-daily dosing; **(2) Structure Therapeutics'** GSBR-1290, an oral, once-daily GLP-1 agonist in Phase I (NCT06139055) to evaluate PK of capsule vs. tablet; **(3) Sciwind Biosciences'** XW004 – an oral tablet formulation of GLP-1 analog XW003 for once-daily to once-weekly dosing in Phase I (NCT05184322) and XW014, an oral, once-daily GLP-1 agonist in Phase I (NCT05579314); **(4) Terns Pharmaceuticals' (TERN)** TERN-601, an oral, once-daily GLP-1R agonist in Phase I; **(5) Viking Therapeutics'** (VKTX) VK2735, a dual GLP-1R/GIPR agonist in Phase I (NCT05203237); and others.

EXHIBIT 26

Select Oral Incretin-based Medicines in Development for Treatment of Obesity

Company (Ticker)	Asset	MoA	Development Stage
Eli Lilly (LLY)	Orforglipron (LY3502970)	GLP-1R agonist	Phase III (ATTAIN-2, NCT05872620; ATTAIN-1, NCT05869903)
Hercules CM NewCo (Private)	HRS-7535	GLP-1R agonist	Phase II (NCT06250946)
	HRS-9531	Dual GLP-1R/GIPR agonist	Phase I (NCT06435676)
Regor Therapeutics (Private)	RGT-075	GLP-1R agonist	Phase II (NCT06277934)
AstraZeneca (AZN); Eccogene (Private)	AZD5004 (ECC5004)	GLP-1R agonist	Phase I
Pfizer (PFE)	Danuglipron (PF-06882961)	GLP-1R agonist	Phase I (NCT06153758) ongoing; Phase IIb BID study completed (NCT04707313)
	PF-06954522	GLP-1R agonist	Phase I
Structure Therapeutics (GPCR)	GSBR-1290	GLP-1R agonist	Phase I (NCT06139055 - formulation bridging and titration study evaluating PK of capsule vs. tablet); Phase II start in 4Q24
Roche (OTC: RHHBY)	CT-996 (RG6652)	GLP-1R agonist (biased to activate cAMP signaling without beta-arrestin recruitment)	Phase I (NCT05814107)
Sciwind Biosciences (Private)	Ecnoglutide (XW004)	Oral formulation of XW003 (GLP-1 analog)	Phase I (NCT05184322)
	XW014	GLP-1 agonist	Phase I (NCT05579314)
Novo Nordisk (NVO)	NN9847	Co-agonist of GLP-1 & amylin	Phase I
Terns Pharmaceuticals (TERN)	TERN-601	GLP-1R agonist	Phase I
Viking Therapeutics (VKTX)	VK2735	Dual GLP-1R/GIPR agonist	Phase I (NCT05203237)

EXHIBIT 27

Key Advantages of Oral Small Molecule vs Injectable GLP-1-based Drugs

- Greater Convenience & Ease of Administration; Simpler Storage/ Shipping
- Can be Combined or Co-formulated With Other Anti-obesity Medications
- Lower COGS: Easier & Cheaper to Manufacture Than Peptides
- Strong Patient Preference for Oral vs Injectable Options

Source: Company Materials. ClinicalTrials.gov. Piper Sandler Research.

Checklist of Differentiated Attributes Crucial in Next-Generation Therapeutics (Page 1 of 3)

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EXHIBIT 28

What are Key Points of Differentiation for New Anti-obesity Agents?

1

Oral Route of Admininstration

- Oral anti-obesity medications would be significantly differentiated as most marketed GLP-1s are SC injectables (e.g., Wegovy, Ozempic, Zepbound, Mounjaro)
- Oral drugs could significantly disrupt the current SoC for obesity, especially if they can provide additional benefits beyond weight loss with a better safety profile
- Our KOL discussions on this subject highlight that:
    1. Patients often prefer an oral option, and oral agents are more scalable due to advantages in distribution and cost (note here)
    2. Payers are highly likely to prefer oral options, given stronger patient adherence rates which can reduce overall costs due to poor compliance (note here)
    3. Oral agents are likely to be covered under a pharmacy benefit, since injectables are self-administered, which further exacerbates adherence challenges

2

Improved GI Tolerability

- Poor GI tolerability is one of the most common AEs for GLP-1-based therapies (i.e., nausea, diarrhea, vomiting, constipation), which creates an opportunity for novel drugs with a cleaner safety profile to differentiate themselves from the current SoC
- In NVO's pivotal 68-week PhIII STEP-1 trial (NCT03548935) assessing QW 2.4 mg semaglutide in 1,961 overweight or obese patients, the most common GI AEs included: (1) 44.2% nausea (vs. 17.4% placebo); (2) 31.5% diarrhea (vs. 15.9% placebo); (3) 24.8% vomiting (vs. 6.6% placebo); and (4) 23.4% constipation (vs. 9.5% placebo), with 4.5% of patients (vs. 0.8% placebo) discontinuing the trial due to GI side effects
- Additionally, in LLY's pivotal 72-week PhII SURMOUNT-1 trial (NCT04184622) assessing QW 5-15 mg tirzepatide in 2,539 overweight or obese patients, the most common GI AEs included: (1) 24.6-33.3% nausea (vs. 9.5% placebo); (2) 18.7-23.0% diarrhea (vs. 7.3% placebo); (3) 8.3-12.2% vomiting (vs. 1.7% placebo); and (4) 11.7-17.1% constipation (vs. 5.8% placebo), with 1.3-2.9% of patients (vs. 0.3% placebo) discontinuing the trial due to GI side effects (nausea, diarrhea, abdominal pain, vomiting)
- As semaglutide and tirzepatide SC injectables *consistently* demonstrate GI tolerability as a leading side effect, products that are able to show competitive weight loss can significantly differentiate themselves from the current SoC with a clean safety profile with minimal GI AEs and low discontinuation rates
- Novel, non-incretin MoAs are also primed to show a differentiated profile, given that they do not target the same gut-derived peptide hormones (e.g., GLP-1) and have the potential to minimize GI-related AEs

Source: ClinicalTrials.gov. Piper Sandler Research.

Checklist of Differentiated Attributes Crucial in Next-Generation Therapeutics (Page 2 of 3)

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EXHIBIT 28

What are Key Points of Differentiation for New Anti-obesity Agents? (Continued)

3

Preserves Lean Mass (Muscle)

- While the extent (or *quantity*) of weight loss is driving interest in current incretin-based therapies, there is a significant focus at this time on the implications of weight loss on body composition and metabolic rate (i.e., on weight loss *quality*). Specifically, there is a great deal of interest in muscle mass composition following treatment, with a goal of maintaining improvement in patients after they come off of treatment
- Novel MoAs such as apelin and CB1 have the opportunity to demonstrate *selective weight loss* within the obesity space, with a focus on muscle mass maintenance. When patients discontinue current incretin treatments they are likely to regain the fat with less muscle mass, which has the potential to negatively affect QoL and overall health
- Lean mass preservation is also associated with an increase in metabolic rate, which has the potential to prevent weight regain after drug treatment
- While the current SoC already shows significant weight loss, new therapies that demonstrate benefit *beyond* weight loss and provide a comprehensive metabolic treatment will have a competitive profile with the ability to actively compete in the obesity space

4

Benefits Beyond Weight Loss Become Important for Obesity-associated Comorbidities

- With current incretin therapies approved for the treatment of T2D and obese/overweight patients, new drugs that target other indications (e.g., NASH, CKD, or HF) through a novel MoA have the potential to provide benefit outside of weight loss
- Both NVO and LLY are assessing whether semaglutide or tirzepatide provide meaningful benefit outside of weight loss, given that comorbidities have a high prevalence within the population and if efficacy is shown, there is potential for label expansion
- Novel MoAs or combination therapies that target distinct pathways (e.g., GLP-1 + glucagon) have the potential to take advantage of GLP-1-driven weight loss, while providing further clinically meaningful benefit
- We believe the future of obesity treatment lies in expanding beyond weight loss as the only relevant metric, which is driving increased interest in MoAs outside the incretin space as viable options for treatment of other indications

Source: Piper Sandler Research.

Checklist of Differentiated Attributes Crucial in Next-Generation Therapeutics (Page 3 of 3)

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EXHIBIT 28

What are Key Points of Differentiation for New Anti-obesity Agents? (Continued)

5

Competitive Weight Loss Does Not Have to be Best-in-Class

- While new anti-obesity therapeutics are expected to show competitive weight loss, they do not need to be best-in-class as long as they clearly demonstrate some added benefit, such as increased GI tolerability or clear comorbidity benefit
- It is important to recognize that the bar for success for weight loss will be based on route of administration, with oral drugs being compared to other oral drugs, and SC injectables compared to other SC injectables, given the distinct difference in level of weight loss
- As an example, GPCR's (Rahimi, OW) management noted when determining a competitive weight loss for GSBR-1290 (an oral agent), they look at LLY's oral orforglipron and think showing >5% weight loss would put GSBR-1290 in the same "zip code" as orforglipron at 12-weeks (note here).
- Consequently, GSBR-1290 would not need to necessarily outperform orforglipron from a weight loss standpoint, given its clean safety profile that primes it for targeted combination therapies.

6

Excellent Safety with Comprehensive Toxicology & In-depth Dataset

- Current approved therapies, such as tirzepatide and semaglutide, have comprehensive toxicology and other data spanning multiple pivotal trials, contributing to a robust safety database
- New treatments will need to show a strong safety profile, backed by multiple animal toxicology studies in order to effectively compete in the obesity space
- Additionally, since >40% of US adults are obese, safety becomes critical with drugs having the potential to scale fast to such a significant proportion of the entire population, highlighting the necessity of understanding the safety profile of a drug prior to authorization

Source: Piper Sandler Research.

Novel Agents in Development to Preserve Muscle Mass During Weight Loss in Obese/Overweight Patients

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Novel approaches in development to preserve lean (muscle) mass in obese/overweight patients undergoing weight loss treatment. Recognizing that while incretins can produce significant and clinically-meaningful reductions in body weight, it is also important to preserve muscle mass and function that is otherwise lost due to these therapies, *companies are developing novel approaches to improve the quality of weight loss*. These agents can either be used alone to produce fat-selective weight loss, or may be combined with other weight loss therapies (e.g., GLP-1R agonists). Approaches in clinical or preclinical development (**Exhibit 29**, below) are primarily focused on **modulating activin/myostatin signaling** – a key regulator of muscle growth and differentiation – or use of **mitochondrial uncoupling** to increase energy expenditure and fat loss, while maintaining muscle mass. Other strategies to retain or improve muscle mass and function during weight loss in obese/overweight patients include activating the apelin receptor (APJ), dual agonism of the GLP-1 and glucagon receptors, peripheral antibody-mediated CB1 receptor blockade, selective androgen receptor modulation, inhibition of acyl CoA synthetase 5, activation of thyroid hormone receptor beta (THR beta), RNAi-mediated suppression of liver inhibin beta E (INHBE), and more.

EXHIBIT 29

Select Agents in Development to Preserve Lean (Muscle) Mass During Weight Loss in Obese/Overweight Patients (Sorted by Development Stage)

Company (Ticker)	Asset	Target/MoA	Route of Administration	Development Stage
Eli Lilly (LLY)	Bimagrumab	Antibody against ActRIIB receptor	IV	Phase II
Biohaven (BHVN, Raymond, OW)	Taldefgrobep alfa	Fusion protein binds at myostatin receptor binding site to block ActRIIB signaling	SC	Phase II
Regeneron Pharmaceuticals (REGN, Raymond, OW)	Trevogrumab	Antibody against mature myostatin	SC	Phase II
	Garetosmab	Antibody against mature activin A	IV	
Scholar Rock Holding (SRRK, Bratzel, OW)	Apitegromab	Selective anti-myostatin antibody	IV	Phase II
BioAge Labs (Private)	Azelaprag	Apelin receptor APJ agonist	Oral	Phase II
Rivus Pharmaceuticals (Private)	HU6	Controlled metabolic accelerator (CMA) - mitochondrial uncoupler	Oral	Phase II
Skye Bioscience (SKYE, Tenthoff, OW)	Nimacimab	Peripherally-restricted antagonistic anti-CB1 antibody	SC	Phase II
Altimmune (ALT, Rahimi, OW)	Pemvidutide	Peptide-based dual GLP-1/glucagon receptor agonist	SC	Phase II
Veru (VERU)	Enobosarm	Selective Androgen Receptor Modulator (SARM) (+ weight loss drugs)	Oral	Phase II
Keros Therapeutics (KROS, Catanzaro, OW)	KER-065	Modified type II activin receptor (ActRII)-derived ligand trap	SC	Phase I
OrsoBio (Private)	TLC-6740	Liver-targeted mitochondrial protonophore	Oral	Phase I
Scholar Rock Holding (SRRK, Bratzel, OW)	SRK-439	Second-generation antibody against pro- and latent myostatin	SC	Preclinical
35Pharma (Private)	HS235	Activin x GDF ligand trap	SC	Preclinical
	HS200	Coformulation of Activin x GDF ligand trap + GLP-1R agonist	SC	Preclinical
Lexicon Pharmaceuticals (LXRX, Rahimi, OW)	LX9851	Acyl CoA Synthetase 5 (ACSL5) inhibitor	Oral	Preclinical
Terns Pharmaceuticals (TERN)	TERN-501	Selective THR-beta agonist	Oral	Preclinical
Arrowhead Pharmaceuticals (ARWR, Tenthoff, OW)	ARO-INHBE	RNAi targeting liver expression of INHBE	IV	Preclinical

Source: Company Materials. Christoffersen BO et al. Obesity. 2022;30:841. Lach-Trifilieff E et al. *Mol Cell Biol*. 2014 Feb;34:606. Heymsfield SB et al. *JAMA Netw Open*. 2021;4(1):e2033457. Piper Sandler Research.

2.6. Beyond Incretins: Which Novel MoAs are on the Rise for Obesity?

Amylin Analogs for Obesity

Amylin is a crucial satiety signal, slowing gastric emptying with potential as a treatment for obesity. Given that obesity is fundamentally caused by appetite dysregulation, resulting in accumulation of adipose tissue (fat) and deterioration of a patient's health, a therapeutic that targets appetite has sig potential in modulating obesity development. Islet amyloid polypeptide (amylin) plays a crucial role in **satiety** (increased feeling of fullness and satisfaction), with receptors located on specific nuclei of the dorsal-vagal-complex located within the hindbrain. Further, amylin is co-released from pancreatic β cells with insulin, modulating glucose homeostasis by slowing gastric emptying, suppressing glucagon secretion, and initiating an anorectic signal, effectively inducing a feeling of satiety. As such, synthetic amylin analogs such as pramlintide are already approved for diabetes and can improve glycemic control and cause sig weight loss. However, the weight loss seen may not be sufficient to reverse obesity complications, positioning second-generation amylin analogs or combination therapies with GLP-1 agonists as potential MoAs that can lead to sig weight loss along with effective appetite and glycemic control.

Synergistic weight loss: dual agonism with amylin and GLP-1s. As weight loss with GLP-1s and amylin analogs is mediated via distinct and overlapping pathways, combining these entero-pancreatic hormones may induce synergistic weight loss (e.g., NVO's CagriSema). PhIb data for CagriSema showed that the combination (cagrilintide 2.4 mg + semaglutide 2.4 mg) resulted in up to 17.1% weight loss vs. 9.5% for semaglutide 2.4 mg + placebo. Similar results were obtained in a PhII study with CagriSema, along with a larger mean reduction in HbA1c compared to semaglutide 2.4 mg only or cagrilintide 2.4 only (~2.2% vs. ~1.8% vs. ~0.9%, respectively).

EXHIBIT 30

Select Amylin Analogs in Clinical Development for Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
AstraZeneca (AZN)	AZD6234	Long-acting amylin analog	Peptide, SC, monthly injection	PhI
Eli Lilly (LLY)	Eloralintide (Amylin agonist LA; fka: LY3841136)	Long acting selective amylin agonist targeting islet amyloid polypeptide (amylin)	Peptide, SC	PhII
Gubra (XCSE: GUBRA)	GUBamy (GUB014295)	Amylin analog	Peptide, SC, once-weekly	PhI
Novo Nordisk (NVO)	CagriSema (cagrilintide + semaglutide)	Combination of amylin analog (cagrilintide) + GLP-1 analog (semaglutide)	Peptide, SC, once-weekly	PhIII
	SC amycretin (NN9490; NNC0487-0111)	Long-acting co-agonist of GLP-1 and amylin	Peptide, SC, once-weekly	PhI/II
	Oral amycretin (NN9847; NNC0487-0111)	Long-acting co-agonist of GLP-1 and amylin	Peptide, oral, once-daily	PhI
	NNC0247-0829	Amylin agonist + GLP-1 agonist	ND	PhI
Zealand Pharma (ZEAL)	Petrelintide (ZP 8396)	Amylin analog (long acting)	Peptide, SC, once-weekly	PhIIb

Source: Dehestani B, et al. *J Obes Metab Syndr*. 2021 Dec 30;30(4):320-325. Züger D, et al. *Physiol Behav*. 2013 Mar 15;112-113:61-9. Mietlicki-Baase EG. *Physiol Behav*. 2016 Aug 1;162:130-40. Smith SR, et al. *Diabetes Care*. 2008 Sep;31(9):1816-23. Company Materials. Piper Sandler Research.

Apelin Receptor Agonists for Obesity

Apelin is crucially involved in adipose tissue regulation and thus is a rational target for obesity. Apelin is a peptide hormone that binds to **angiotensin protein J (APJ) receptor** to mediate a multitude of physiological processes, including regulation of energy metabolism, blood pressure, fluid homeostasis, endocrine stress response, angiogenesis, and cardiac contractility. Specifically, activation of apelin-APJR triggers cAMP reduction and initiates a feedback loop to downregulate subsequent apelin-APJR signaling. Consequently, apelin enhances muscle function by increasing mitochondria biogenesis, autophagy, and activates regenerative pathways in muscle satellite stem cells, in addition to reducing obesity-related insulin resistance. As such, apelin receptor agonism (in combination with an incretin construct to drive weight loss) represents a rational approach for treating obesity by not only driving fat loss, but also selectively preserving lean mass to improve body mass composition while losing weight.

Data support the rationale for APJ receptor agonism, with improvement in various metabolic parameters supporting the potential for monotherapy or in combination with GLP-1 agonists. Specifically, Attane and coworkers showed that apelin treatment of insulin-resistant and obese (high-fat diet) mice resulted in reduced fat mass, glycemia, and protection of plasma triglyceride levels against hyperinsulinemia (vs. control). The metabolic benefits of APJ receptor agonism suggest they could be used in combination with a GLP-1 to protect against concerns of lean mass loss, which could further expand the total addressable market to obese patients who are frail (e.g., with sarcopenic obesity) and those that cannot safely receive GLP-1s on their own.

EXHIBIT 31

Summary of Key Metabolic Effects of Apelin & its Signaling Pathways

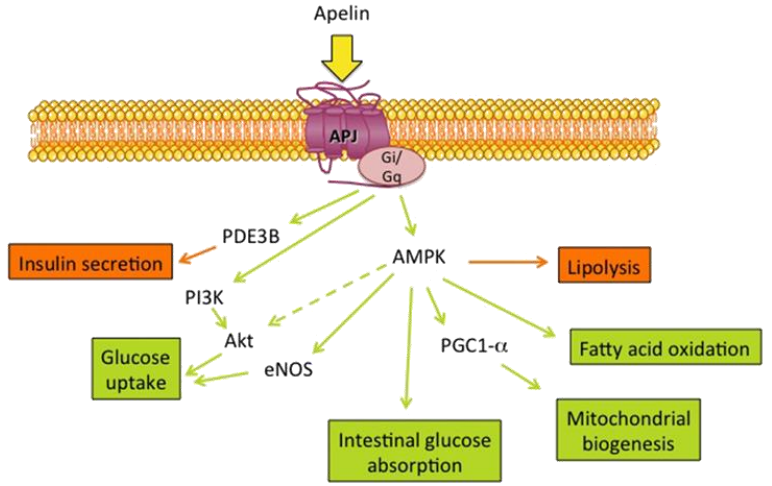


EXHIBIT 32

Select Apelin Receptor Agonists in Clinical Development for Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
BioAge Labs (Private)	Azelaprag (BGE-105) + tirzepatide (dual GLP-1R/GIPR agonist)	Apelin receptor APJ agonist	Small molecule, oral, once-daily	PhII
Structure Therapeutics (GPCR, Rahimi, OW)	ANPA-0073 in combo w/ weight loss medicines	APJR agonist	Small molecule, oral, once-daily	PhII ready

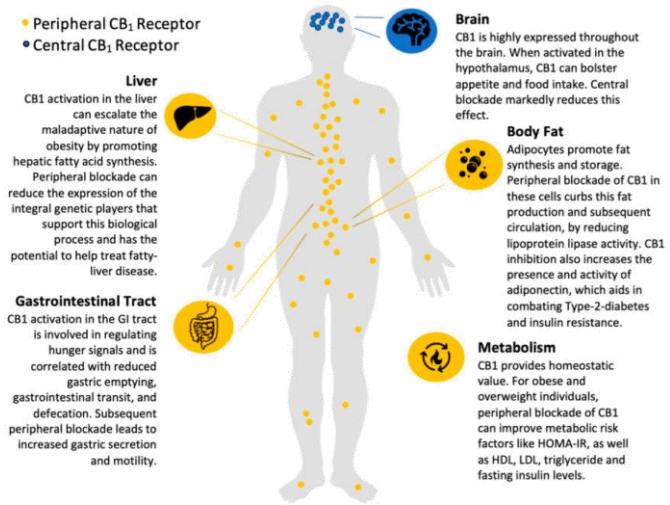
Source: Attane et al., *Diabetes*, 2012; 61(2):310-320. Vinel et al., *Nat Med* . 2018 Sep;24(9):1360-1371. Bertrand C et al. *Front Physiol*. 2015;6:115. Company Materials. Piper Sandler Research.

CB1 Receptor Modulators for Obesity (Page 1 of 3)

What is the rationale for targeting CB1 receptors to treat obesity? Cannabinoid receptor type 1 (CB1) is a G protein-coupled receptor (GPCR) that controls appetite, energy intake and expenditure, and metabolism. CB1 receptors are found centrally in the brain and peripherally in the liver, GI tract, and adipose tissue. Activation of CB1 receptors in the brain drives hunger and promotes food intake. Thus, blocking CB1 receptors can induce weight loss by reducing appetite and over eating. In adipose tissue, CB1 receptors control lipogenesis (fat production) and lipolysis (fat burning). Blocking CB1 peripherally leads to weight loss by reducing fat storage and increasing fat metabolism. CB1 receptor antagonists may also improve the metabolic profile (e.g., insulin sensitivity, glucose metabolism, lipids), which could help in treating obesity-associated comorbidities.

EXHIBIT 33

Metabolic Targets for Central and Peripheral CB1 Receptors



Source: Bosquez-Berger T et al. *Drugs Drug Candidates*. 2023;2:689. Quarta C and Cota D. *Int J Obes*. 2020;44:2179. Company Materials. Piper Sandler Research.

Rimonabant validates CB1 antagonism for weight loss. Rimonabant **(Sanofi SNY, not covered)** is a first-generation CB1 antagonist that caused weight loss in patients in clinical trials. Specifically, four clinical studies established rimonabant's weight loss efficacy and associated metabolic effects (e.g., improvements in CRP, HDL and LDL cholesterol, triglycerides, glucose, insulin, and insulin resistance). Rimonabant consistently induced weight loss of 4-8kg over 6-12 months vs. placebo. On the basis of these findings, *Accomplia* (rimonabant) was approved in Europe in 2006 as a treatment for weight loss. However, rimonabant was rejected by the US FDA due to psychiatric side effects including depression, anxiety, and increased risk of suicide, as well dizziness and nausea. In the CRESCENDO study in patients with cardiovascular disease, rimonabant significantly increased the percentage of patients reporting serious psychiatric side effects from 1.3% to 2.5%, and four of 9,381 (0.04%) patients committed suicide compared to only one on placebo. Approval was withdrawn in Europe in 2008, development of competitor CB1 antagonists was suspended by other companies. The psychiatric side effects are due to the inhibition of central CB1. Rimonabant was shown to cross the blood brain barrier (BBB) and accumulates in the brain over time. The current hope is that peripherally-restricted CB1 blockers will retain beneficial weight loss and metabolic effects of rimonabant with an improved safety profile.

CB1 Receptor Modulators for Obesity (Page 2 of 3)

Targeting peripheral CB1. To avoid neuropsychiatric effects, companies are now developing second-generation antagonists, antibodies, and inverse agonists that do not pass the BBB. However, a key question had to be answered: "Is central CB1 inhibition necessary to cause weight loss?" Multiple preclinical models have shown that peripheral CB1 inhibition is *sufficient* to produce *the same degree* of weight loss and lipolysis that was achieved by rimonabant. Additionally, CB1 inhibition restored leptin and insulin sensitivity, suggesting the cardiometabolic benefits seen in clinical studies with rimonabant will likely be recapitulated with peripherally-restricted agents. Finally, CB1 inhibition had no effect on lean muscle mass, which is critical considering the growing concern regarding muscle wasting with current GLP-1 agonists.

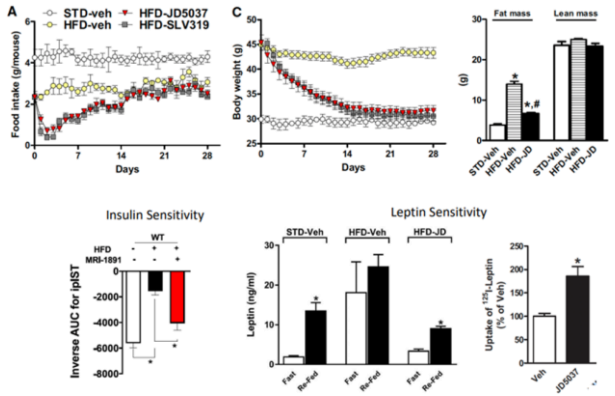
Next-generation small molecule CB1 modulators. One approach has been to develop **peripherally-restricted inverse agonists of CB1**. As the name implies, inverse agonists bind CB1 but induce the *opposite* response to an agonist, whereas an antagonist merely blocks the activity of the receptor. In August 2023, **Novo Nordisk** acquired Inversago for $1.075B for CB1 inverse agonist monlunabant (INV-202) and next-gen INV-347. In a Phase I study in metabolic syndrome patients with glucose intolerance, daily oral 25 mg monlunabant achieved mean weight loss of 3.5 kg (N=20) vs. mean weight gain of 0.6 kg on placebo (N=17) at 28 days. Monlunabant was well tolerated, however 4 participants (20%) reported psychiatric TEAEs vs. only 1 (6%) on placebo. Over time, accumulation of monlunabant may increase the incidence of psychiatric side effects, as was the case with rimonabant. Novo Nordisk is conducting Phase II studies of monlunabant in 240 obese patients, and in 240 diabetic kidney disease patients with data from both studies expected next year. Novo Nordisk has also initiated a Phase I study of INV-347.

Corbus Pharmaceuticals (CRBP, not covered) is also developing CRB-913, a second-generation, peripherally-restricted CB1 receptor inverse agonist for obesity and related conditions.

CB1-targeting antibodies. **Skye Bioscience (SKYE, Tenthoff, OW)** is developing nimacimab, a monoclonal antibody that acts as a non-competitive negative allosteric modulator of CB1 activity, meaning nimacimab retains CB1 blockade despite compensatory increases in endocannabinoids (ECs) that occur in response to inhibition. As a large molecule, nimacimab is unable to cross the BBB and preclinical studies have shown no brain accumulation. Skye recently initiated the Phase II *CBeyond* study of nimacimab in 120 non-diabetic patients; 20 of whom will receive nimacimab + semaglutide to measure additive weight loss of the combination. A key secondary endpoint is body composition to measure muscle preservation. Skye expects to report initial data in 2Q25 and full data in 4Q25.

EXHIBIT 34

Peripherally-restricted CB1 Inhibition Induces Weight Loss



Source: Bosquez-Berger T et al. *Drugs Drug Candidates*. 2023;2:689. Quarta C and Cota D. *Int J Obes*. 2020;44:2179. Company Materials. Piper Sandler Research.

CB1 Receptor Modulators for Obesity (Page 3 of 3)

EXHIBIT 35

Select Agents in Development for Peripheral Targeting of CB1 Receptors for Treatment of Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
Novo Nordisk (NVO)	Monlunabant (f/k/a monlunabant)	Peripherally-acting cannabinoid receptor 1 (CB1) blocker (inverse agonist)	Small molecule, oral, once-daily	Phase II
	INV-347 (NN9441)	Next-generation CB1 receptor blocker (inverse agonist)	Small molecule, oral	Phase I
Skye Bioscience (SKYE, Tenthoff, OW)	Nimacimab (mono and combo with GLP-1 agonist)	Peripherally-restricted CB1 receptor inhibitor (negative allosteric modulator that inhibits CB1 signaling in the periphery); functions as an antagonist (in presence of CB1 agonist w/ B-arrestin) and as an inverse agonist (2x the potency of rimonabant)	mAb (engineered IgG4), SC, once-weekly to once-monthly	Phase II
Corbus Pharmaceuticals (CRBP)	CRB-913	Peripherally-restricted CB1 inverse agonist	Small molecule, oral	Preclinical/ IND-enabling

Source: Company Materials. Piper Sandler Research.

Leptin-Melanocortin Pathway Modulators for Obesity (Page 1 of 2)

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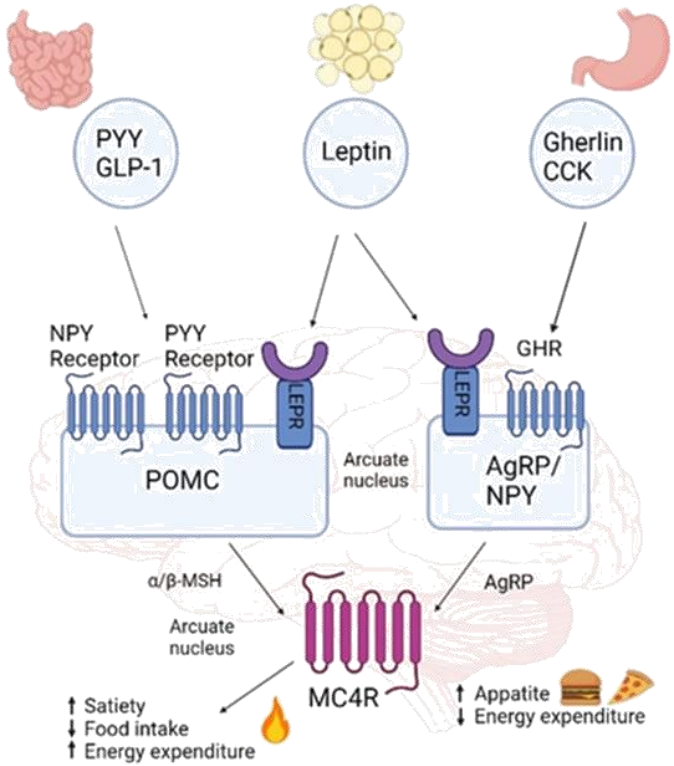
The leptin-melanocortin pathway is a critical regulator of appetite, energy expenditure, and body weight and is a prime target for anti-obesity drugs. Specific gene mutations affecting key components of the pathway – also known as the **melanocortin 4 receptor (MC4R) pathway** (**Exhibit 36**) – are associated with genetic forms of early-onset obesity. These include LOF mutations in leptin, the leptin receptor (LEPR), pro-opiomelanocortin (POMC), prohormone convertase 1 (PCSK1), and the MC4R genes. Consequently, the pathway has emerged as a key target for novel agents that are designed to induce weight loss.

Leptin and gut hormones act on hypothalamic POMC, AgRP, and NPY neurons and produce different effects on energy and weight balance. Leptin is secreted by adipose tissue and signals energy sufficiency to the brain. It binds to hypothalamic receptors, leading to activation of POMC neurons and inhibition of AgRP/NPY neurons. Upon activation, POMC neurons produce α-melanocyte-stimulating hormone (α-MSH), which binds to MC4R in the hypothalamus. This promotes satiety, reduced food intake, and increased energy expenditure. The gut hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) are released in response to food intake and produce a similar effect to leptin – i.e., they act on POMC neurons to activate MC4R and enhance satiety and reduce food intake. Conversely, ghrelin – produced by the stomach – stimulates hunger by activating AgRP and NPY neurons in the hypothalamus, which in turn inhibit MC4R to increase appetite and reduce energy expenditure.

Strategies to modulate the MC4R pathway for weight loss include the use of MC4R agonists, LEPR agonists, PYY analogs (**Exhibit 37**, next page).

EXHIBIT 36

Leptin-melanocortin (MC4R) Pathway Balances Food Intake and Expenditure to Regulate Body Weight



Source: Ayers KL et al. *J Clin Endocrinol Metabol*. 2018;103:2601. Kuhnen P et al. *J Pediatr Endocrinol Metab*. 2020;33:967. Chermon D and Birk R. *Genes*. 2023;14:1996. Company Materials. Piper Sandler Research.

Leptin-Melanocortin Pathway Modulators for Obesity (Page 2 of 2)

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EXHIBIT 37

Select Agents in Clinical Development to Target the Leptin-melanocortin (MC4R) Pathway for Treatment of Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
ERX Pharmaceuticals (Private)	ERX-1000	Leptin sensitizer	Small molecule, oral	Phase I complete
Gila Therapeutics (Private)	GT-001	Topical Lingual PYY	Peptide, topical	Phase I complete
Novo Nordisk (NVO)	NNC0165-1875 (PYY 1875)	PYY analog	Peptide-Ab conjugate, SC	Phase II complete
Palatin Technologies (PTN)	Bremelanotide (co-administered with tirzepatide [GLP-1/GIP])	MC4R agonist	Peptide, SC	Phase II
Regeneron (REGN, Raymond, OW)/ Eli Lilly (LLY)	Mibavademab (combo w/ tirzepatide)	Leptin receptor (LEPR) agonist	mAb, SC	Phase II
Rhythm Pharmaceuticals (RYTM)	Setmelanotide daily formulation (IMCIVREE)	MC4R agonist	Peptide, SC, once-daily	Phase III
	RM-718	MC4R agonist	SC, once-weekly	Phase I
	LB54640 (LR19021)	MC4R agonist	Small molecule, oral, once-daily	Phase II

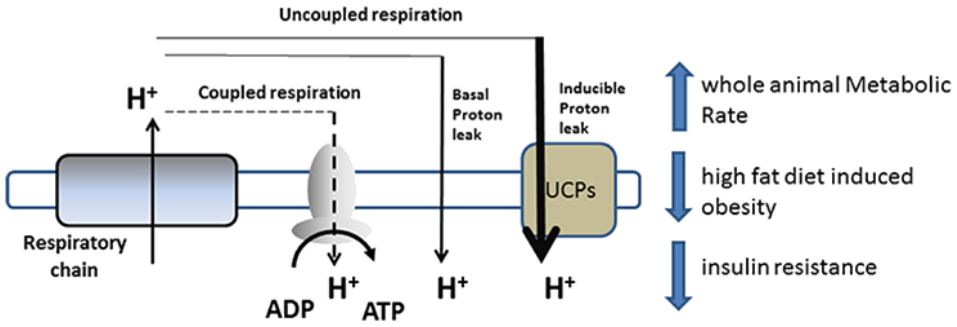
Source: Company Materials. Piper Sandler Research.

Mitochondrial Uncoupling Agents for Obesity

Uncoupling agents have the potential to treat comorbidities associated with obesity. A key function of mitochondria is to oxidize fat by converting fat carbons to carbon dioxide through beta-oxidation and the Krebs cycle, maintaining ATP concentrations. **Uncoupling agents** (aka **controlled metabolic accelerators**, or **CMAs**) increase carbon substrate utilization to maintain ATP concentrations by increasing proton leak via adenine nucleotide translocase. Notably, uncoupling agents have the potential to treat obesity comorbidities, such as NAFLD, NASH, HFpEF, and T2D.

EXHIBIT 38

Uncoupling Agents Activate the Inducible Proton Leak to Alter Metabolism



Mitochondrial uncoupler HU6 is validated in a NASH mouse model and PhIIa, showing benefit in obesity and NAFLD. Previously, HU6 **(Rivus Pharmaceuticals (Private))** was assessed in a diet-induced NASH mouse model (DIAMOND mice), where NASH is driven by insulin resistance, oxidative stress, inflammation, and leaky gut. Treatment with 5 mg/kg or 1 mg/kg HU6 for 8 weeks showed sig reductions in ALT, AST, ALP, ballooning, lobular inflammation, liver transaminotransferase levels, and progression from simple steatosis to NASH. Further, sig reductions in body and liver weight were observed, correlating with decreased hepatic steatosis. Overall, HU6 has the potential to be a novel therapy for patients with obesity and NAFLD (and other metabolic conditions).

EXHIBIT 39

Select Mitochondrial Uncoupling Agents in Clinical Development for Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
OrsoBio (Private)	TLC-6740 (mono or combo therapy)	Liver-targeted mitochondrial protonophore that induces mitochondrial uncoupling to increase energy expenditure	Small molecule, oral, once-daily	PhI
Rivus Pharmaceuticals (Private)	HU6	First-in-class controlled metabolic accelerator (CMA); selectively reduces excess fat via mitochondrial uncoupling	Small molecule, oral, once-daily	PhIIa

Source: Harper JA, et al. *Obes Rev*. 2001 Nov;2(4):255-65. Bertholet AM, et al. *Nature*. 2022 Jun;606(7912):180-187. Noureddin M, et al. *Lancet Gastroenterol Hepatol*. 2023 Dec;8(12):1094-1105. Company Materials. Piper Sandler Research.

NLRP3 Inflammasome Inhibitors for Obesity

Targeting inflammation: NLRP3 is mechanistically rationalized for obesity. Nucleotide oligomerization domain like receptor family, pyrin domain containing 3 (NLRP3) is an inflammasome complex that plays a key role in the innate immune response and thus inflammation signaling upon activation by pathogen-associated molecular patterns (PAMPs)/damage-associated molecular patterns (DAMPs). NLRP3 mediates caspase-1 activation to subsequently drive the secretion of IL-1β and IL-18, which are key proinflammatory cytokines. It has been hypothesized NLRP3 activation plays a crucial role in obesity pathogenesis given that obesity and related metabolic conditions are often correlated to a chronic state of low-grade, systemic inflammation. Specifically, NLRP3 activation is thought to impair insulin sensitivity in diet-induced obesity and give rise to additional metabolic changes, along with adipose tissue inflammation (which further exacerbates insulin resistance) due to the secretion of pro-inflammatory cytokines. In our view, NLRP3 inhibition and mitigation of inflammation that ultimately drives chronic metabolic dysfunction and weight gain makes mechanistic sense.

Early data validates the rationale for NLRP3 inhibition MoA for obesity: (1) **Nodthera's (Private)** NT-0796 (fully brain-penetrant NLRP3i) and NT-0249 (CNS-penetrant NLRP3i) achieved comparable weight loss to semaglutide in mice (Day 28 in hCES DIO mice, NT-0796 showed -19.0% weight loss ($p<0.01$) vs. -21.5% with semaglutide ($p<0.01$), whereas in C57BL/6 DIO mice resulted in -6.8% weight loss ($p<0.0001$) vs. -14.3% with semaglutide ($p<0.0001$)). (2) a clinical observational study in children found statistically significant higher levels of circulating NLRP3 and IL-1β in obese children with insulin resistance and a late insulin peak in response to a glucose tolerance test.

EXHIBIT 40

NLRP3 is a Key Mediator of Inflammation by Promoting IL-1β & IL-18 Secretion

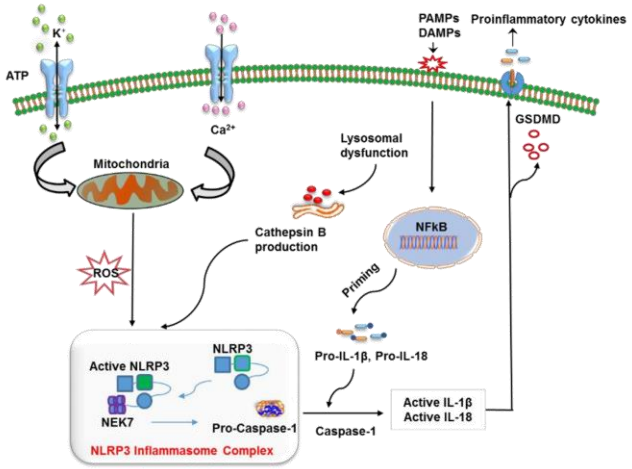


EXHIBIT 41

Select NLRP3 Inflammasone Inhibitors in Clinical Development for Obesity

Company (Ticker)	Asset	MoA/Target	Molecule Type & Route of Administration	Development Stage
Nodthera (Private)	NT-0796	Oral, brain-penetrant NLRP3 inflammasome inhibitor	Small molecule, oral	PhI/II complete, PhII planning
Ventyx Biosciences (VTYX, Rahimi, OW)	VTX3232	CNS-penetrant, potent NLRP3 inhibitor	Small molecule, oral	PhII initiation in 2H24

Source: Pirzada RH et al. *Genes*. 2020;11:131. Belvins et al., *Front Aging Neurosci*., 2022; 14:879021. Jorquera et al., *Int J Mol Sci*., 2021; 22(6):3254. Company Materials. Piper Sandler Research.

INHBE Targeting for Obesity (Page 1 of 3)

Human exosome sequencing identified the hepatokine gene INHBE as a novel target for obesity. In 2022, Deaton and coworkers, in collaboration with **Alnylam Pharmaceuticals (ALNY, Tenthoff, OW)**, published an article in *Nature Communications* identifying INHBE as a gene associated with a lower waist-to-hip ratio (WHR) adjusted for BMI, which is a surrogate measure of abdominal fat. The authors analyzed exosome sequencing and WHR data from 362,679 individuals with European ancestry identifying 12 genes associated with WHR, including 5 that had not been previously linked to obesity: COL5A3, ANKRD12, KEAP1, TRIM40, and INHBE (**Exhibit 42**, below left). Of these, INHBE was the only gene in which loss of function (LOF) variants were associated with lower WHR. The effect size (ß) was similar between men (0.21) and women (0.22). INHBE encodes inhibin ßE, a subunit of hepatokine activin E. While most adiposity-associated genes are expressed in adipose tissue, INHBE is expressed in the liver and can be targeted to treat obesity.

INHBE is a novel target to reduce obesity and related diseases. INHBE was shown to be inversely-related to abdominal fat, as measured by MRI in the exosome sequencing population. High WHR is associated with type 2 diabetes (T2D) and coronary heart disease (CHD). Accordingly, INHBE was negatively-associated with risk for both of these obesity-related diseases (**Exhibit 43**, below right). A phenome-wide association study (PheWAS) showed INHBE LOF mutations were not associated with higher mortality or other diseases. INHBE was associated with higher birth weight and higher circulating levels of INHBC protein, but not with more direct measures of adiposity such as DEXA imaging. The related activin receptor ALK7 was also linked to WHR, and did show a negative relationship with visceral fat and blood pressure. Therefore, it is likely that inhibiting activin signaling may improve adipose distribution. INHBE was shown to be expressed at much higher levels in obese NHP models, and in human data was associated with insulin resistance.

EXHIBIT 42

INHBE Among Genes Identified as Associated With WHR

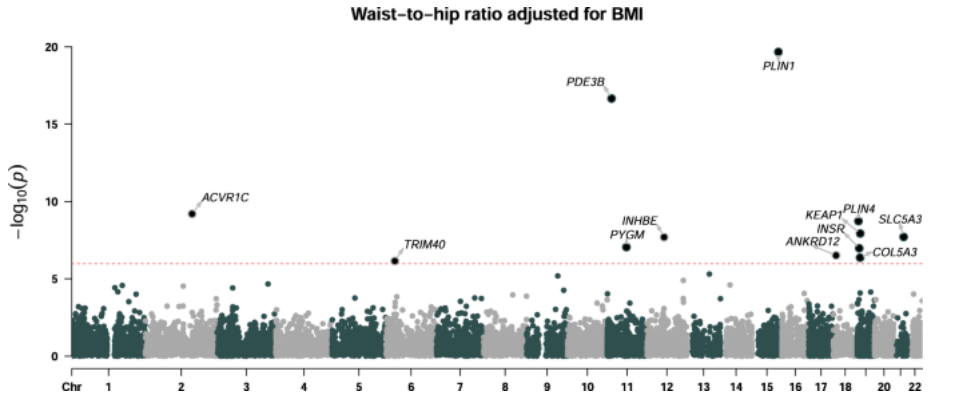
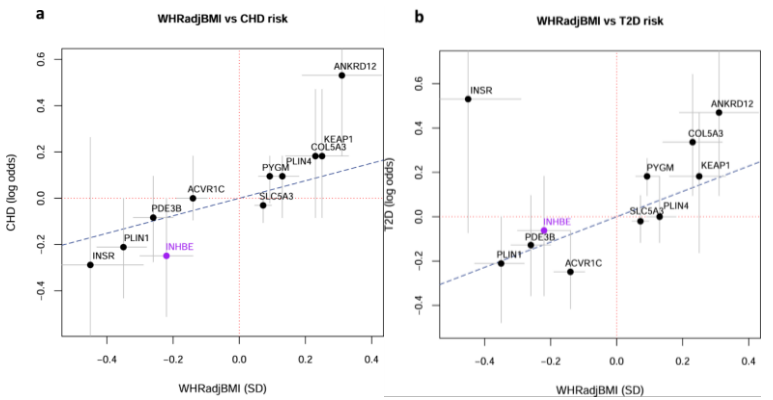


EXHIBIT 43

INHBE is Associated With Risk of CHD & T2D



Source: Deaton, A.M., Dubey, A., Ward, L.D. *et al.* Rare loss of function variants in the hepatokine gene *INHBE* protect from abdominal obesity. *Nat Commun* **13**, 4319 (2022). https://doi.org/10.1038/s41467-022-31757-8
Company Materials. Piper Sandler Research.

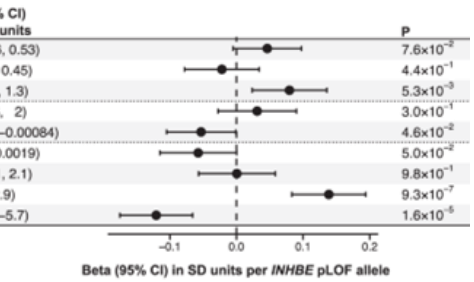
INHBE Targeting for Obesity (Page 2 of 3)

Validation of INHBE's role in fat storage. Shortly after identification, Akbari and coworkers in collaboration with **Regeneron Pharmaceuticals (REGN, Raymond, OW)** replicated the finding that INHBE was associated with fat storage. Importantly, this study included more participants (n=618,375), including 160,058 with non-European (mostly from Mexico) heritage, broadening the applicable population. Exome-sequencing was cross-referenced with GWAS mapping data to assess the impact of individual variants in the identified genes. Visceral:glutofemoral fat ratio measured by MRI was available for 6% of patients in this study, and showed 94% concordance with WHR, with slightly larger effect sizes for MRI vs. WHR (1.3:1 SD). LOF mutations in the gene were associated with larger hip circumference, lower visceral:glutofemoral fat ratio, and lower body fat without changes in lean mass. Additionally, LOF mutations in INHBE were associated with a better metabolic profile, (i.e., higher HDL cholesterol and lower triglycerides) (**Exhibit 44**).

EXHIBIT 44

LOF Mutations in INHBE Are Related to a Better Metabolic Profile

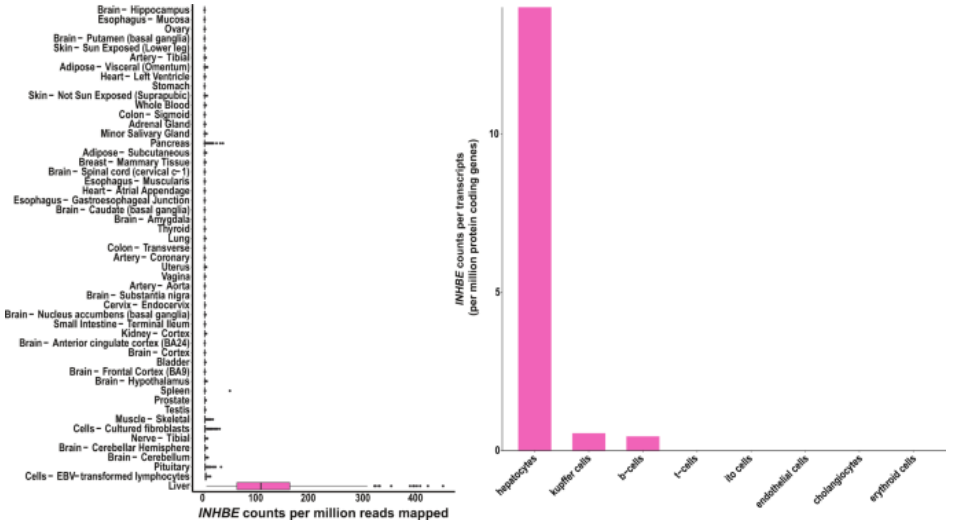
Phenotype, clinical units	Sample size (RR|RA|AA)	Beta (95% CI) in clinical units	P
BMI, kg/m²	644,402|1,224|0	0.25 (−0.026, 0.53)	7.6×10^{-2}
Waist circumference, cm	615,485|1,098|1	−0.29 (−1, 0.45)	4.4×10^{-1}
Hip circumference, cm	615,436|1,098|1	0.76 (0.23, 1.3)	5.3×10^{-3}
Random Glucose, mg/dL	479,380|1,031|0	0.68 (−0.6, 2)	3.0×10^{-1}
Glycated hemoglobin (HbA1c), %	635,948|1,116|1	−0.053 (−0.11, −0.00084)	4.6×10^{-2}
Apolipoprotein B, mg/dL	427,470|967|0	−1.4 (−2.8, 0.0019)	5.0×10^{-2}
Low−density lipoprotein cholesterol, mg/dL	474,864|1,016|0	0.024 (−2.1, 2.1)	9.8×10^{-1}
High−density lipoprotein cholesterol, mg/dL	485,566|1,032|0	2 (1.2, 2.9)	9.3×10^{-7}
Triglycerides, mg/dL	521,444|1,101|0	−10 (−15, −5.7)	1.6×10^{-5}



INHBE LOF mutations prevent protein production in preclinical models. It was found that ~2/3 of influential LOF mutations were caused by a c.299-1 G > C splice acceptor variant. Expression of this gene variant in cells that do not naturally express INHBE resulted in mutant protein expression that was not excreted from the cell. Further, liver biopsies from NASH patients had 60% higher mRNA expression than those from healthy livers ($p = 2.0 \times 10^{-63}$). Importantly, researchers directly confirmed that INHBE is expressed with high selectivity in hepatocytes (**Exhibit 45**), making it an ideal target for siRNA therapy.

EXHIBIT 45

Selective Expression of INHBE in Hepatocytes



Source: Akbari, P., Sosina, O.A., Bovijn, J. *et al.* Multiancestry exome sequencing reveals *INHBE* mutations associated with favorable fat distribution and protection from diabetes. *Nat Commun* **13**, 4844 (2022). https://doi.org/10.1038/s41467-022-32398-7Company Materials. Piper Sandler Research.

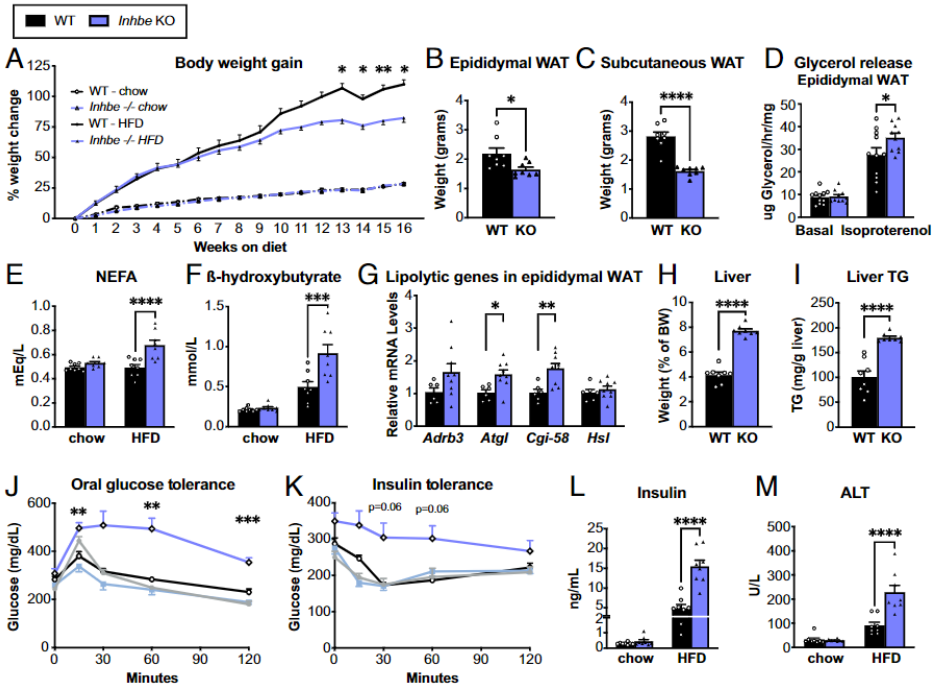
INHBE Targeting for Obesity (Page 3 of 3)

INHBE pathway provides hepatocyte-adipocyte crosstalk; INHBE KO reduces body weight of obese mice. Recent preclinical research by Adam et al., has elucidated the signaling pathway that allows for INHBE to control fat deposition and metabolism. The master transcription factor PPARG controls adipocyte development and metabolism. In the healthy body, burning fat (lipolysis) results in free circulating fatty acids. Hepatocytes respond to increases in fatty acids by increasing INHBE protein expression. INHBE signals at the activin receptor ACVR1C expressed on adipocytes to suppress PPARG. Reduced levels of PPARG curb further lipolysis, limiting the accumulation of fatty acids in the liver. In humans and the high-fat-diet (HFD) model of obesity in mice, levels of INHBE are chronically-elevated. Therefore, lipolysis is harder to induce, and the metabolic function of adipocytes is hindered.

Preclinical models using the HFD mouse model established that chronic overfeeding resulted in decreased levels of genes under the control of PPARG, which are important for adipocyte function, especially metabolism. By knocking out INHBE (or inhibiting ACVR1C (ALK7) with antibodies), it was possible to restore the expression of genes under PPARG control. These genes may also serve as important biomarkers in human studies of INHBE-targeted therapy. In turn, INHBE KO reduced the body weight of mice and generated smaller, more mobile adipocytes. However, abrogating INHBE-ACVR1C signaling also caused insulin insensitivity and liver steatosis after 16 weeks on the HFD. These adverse effects are in line with the normal function of INHBE to limit fatty acid accumulation. Interestingly, human INHBE LOF carriers have not shown significant associations with liver conditions. Insulin sensitivity and liver health will be important safety considerations in the development of INHBE-targeted therapies for obesity.

EXHIBIT 46

INHBE KO is Efficacious for Obese Mice, But With Some Liver Toxicity



Source: Adam RC, Pryce DS, Lee JS, et al. Activin E-ACVR1C cross talk controls energy storage via suppression of adipose lipolysis in mice. *Proc Natl Acad Sci U S A*. 2023;120(32):e2309967120. doi:10.1073/pnas.2309967120.
Piper Sandler Research.

Other Non-Incretin MoAs in Clinical Development for Obesity

EXHIBIT 47

Select Agents With Other Non-incretin MoAs in Clinical Development for Obesity

Company (Ticker)	Asset	Target/MoA	Route of Administration	Development Stage
Biophytis SA (OTC: BPTSY)	BIO101 (20-hydroxyecdysone) + GLP-1 receptor agonists	MAS receptor activator	Small molecule, oral, once-daily	Phase II
Cytoki Pharma (Private)	CK-0045 (In-licensed from Novo Nordisk)	Long-acting analog of interleukin-22 (IL-22), an atypical, non-immunomodulatory cytokine that selectively targets epithelial cells (lipidated IL-22 agonist)	Recombinant protein, SC	Phase I complete
Eccogene (Private)	ECC4703	Liver-targeted THRβ agonist	Small molecule, oral	Phase I
Eli Lilly (LLY)	DACRA QW II (LY3541105)	Dual amylin and calcitonin receptor agonist (DACRA)	Biologic, SC	Phase I
Enterin (Private)	ENT-03	Endogenous, centrally acting mammalian aminosterol with Protein Tyrosine Phosphatase 1B (PTP1B) inhibitory activity (increases insulin resistance and leptin sensitivity)	Small molecule, SC	Phase I
Glaceum (Private)	HSG4112 (Vutiglabridin)	Structural analog of glabridin; anti-obesity drug that improves mitochondrial function via PON2	Small molecule, oral, once-daily	Phase II complete
Glyscend Therapeutics (Private)	GLY-200	Non-absorbed (gut-restricted) polymeric drug that targets and enhances with the mucus membrane in the duodenum and mimics the physiology of bariatric surgery by restoring and activating gut-mediated signaling (e.g., enhanced release of GLP-1 and PYY)	Gut-restricted polymer, oral, twice-daily	Phase II
Kallyope (Private)	K-833	Nutrient receptors agonist (GPR119); targets the body's natural physiology to secrete appetite-suppressing hormones (GLP-1, PYY, CCK, OXM)	Small molecule, oral	Phase II
	K-757 (alone or in combo w/ K-833)	Nutrient receptor agonist (GP40); targets the body's natural physiology to secrete appetite-suppressing hormones (GLP-1, PYY, CCK, OXM)	Small molecule, oral	Phase II complete
Relmada Therapeutics (RLMD)	REL-P11	Novel modified release psilocybin formulation	Not disclosed	Phase I
Scohia Pharma (Private)	SCO-267	GPR40 full agonist (stimulates insulin, GLP-1, GIP, PYY secretion)	Small molecule, oral	Phase I complete
Shionogi (OTC: SGIOY)	S-309309	Oral monoacylglycerol acyltransferase 2 (MGAT2) inhibitor	Oral	Phase II complete
Syntis Bio (Private)	SYNT-101	Duodenal nutrient exclusion - polydopamine coating that blocks absorption in the duodenum; mimics the effects of gastric bypass surgery by transiently blocking nutrient absorption in the upper GI and redirecting absorption to the lower intestines where it stimulates GLP-1 and PYY	Oral, once-daily	Phase I
Xeno Biosciences (Private)	XEN-101	Gut-restricted, non-systemic compound that delivers molecular oxygen to the lower gut in a targeted fashion to modulate the gut microbiome and intestinal environment (intended to be used as a substitute for gastric bypass)	Oral, once-daily	Phase I

Source: Company Materials. Piper Sandler Research.

3. Profiles of Key Companies in the Obesity Therapeutics Space

Obesity Therapeutics Companies Profiled Within This Report

In this section of the report, we provide in-depth profiles for 31 companies with active development programs in the obesity therapeutics space. The companies range from small, private biotechs to larger, publicly-traded companies with assets spanning preclinical and clinical development stages.

Please refer to the hyperlinked list below to jump to a company of interest.

Companies Profiled

35Pharma (Private)
Aardvark Therapeutics (Private)
Altimmune (ALT, Rahimi, OW)
Amgen (AMGN, Raymond, OW)
Arrowhead Pharmaceuticals (ARWR, Tenthoff, OW)
BioAge Labs (Private)
Biohaven (BHVN, Raymond, OW)
Corbus Pharmaceuticals (CRBP)
Crinetics Pharmaceuticals (CRNX, Rahimi, OW)
Fractyl Health (GUTS)
Gila Therapeutics (Private)
Glyscend Therapeutics (Private)
Hercules CM NewCo (Private)
Juvena Therapeutics (Private)
Keros Therapeutics (KROS, Catanzaro, OW)
Lexicon Pharmaceuticals (LXRX, Rahimi, OW)
MBX Biosciences (Private)
MeiraGTx Holdings (MGTX, Raymond, OW)
NodThera (Private)
OrsoBio (Private)
PegBio (Private)
Regeneron Pharmaceuticals (REGN, Raymond, OW)
Rivus Pharmaceuticals (Private)
Scholar Rock Holding (SRRK, Bratzel, OW)
Sciwind Biosciences (Private)
Skye Bioscience (SKYE, Tenthoff, OW)
Structure Therapeutics (GPCR, Rahimi, OW)
Terns Pharmaceuticals (TERN)
Ventyx Biosciences (VTYX, Rahimi, OW)
Viking Therapeutics (VKTX)
Zealand Pharma (ZEAL)

Source: Piper Sandler Research.

35Pharma, Inc. (Private): (Page 1 of 2)

35Pharma is a biotech company developing potent ligand traps for obesity and co-morbid metabolic diseases with HS235 and HS200. The company is focused on TGF-Beta superfamily biology to develop its platform of Activin & GDF ligand traps, which are genetically validated targets implemented in obesity/HF and cardiopulmonary disorders. Starting with Activin, this receptor is crucially involved in body composition and glucose management, where Activin A is associated with Heart Failure (HF). As for GDF (including myostatin), this is involved in skeletal muscle regulation, which is important to drive a lean mass preservation/fat selective weight loss MoA. 35Pharma is developing its lead obesity asset, HS235 (Activin x GDF inhibitor) for obese HFpEF patients, which is on track for IND submission in 2H24. Importantly, HS235 is a differentiated drug due to its dual mode of action that simultaneously targets excess adiposity/increases lean mass and mediating left-heart remodeling. This dual MoA effectively addresses the key underlying disease characteristics/pathogenesis in obese HFpEF, which represents a lucrative market with >3M US patients (>50% of the 6M US HF patients have co-morbid obesity). Beyond this, 35Pharma is also developing HS200, a co-formulation of Activin x GDF trap + GLP-1R agonist. By combining these MoAs into a co-formulated SC administration, HS200 is able to selectively target excess adiposity to drive weight loss and enable lean mass preservation. Therefore, management believes this agent could be particularly compelling for certain subsets of obese populations such as T2D and elderly/sarcopenic obesity as these patients are especially vulnerable to the effects of lean mass loss with incretins alone.

EXHIBIT 48

35Pharma's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obese and Heart Failure with Preserved Ejection Fraction (HFpEF)	HS235 (Activin x GDF trap)	→			
Obese Excess Adiposity	HS200 (Activin x GDF trap + incretin)	→			

Source: 35Pharma Company Materials. Piper Sandler Research.

HS235 IND submission is on track for 2H24 with subsequent clinical trial to start "imminently". As detailed at our recent Obesity Day (here), 35Pharma expects to file its IND in 2H24, with all its necessary preclinical research, tox, and manufacturing steps complete. To bring the IND to finish line, the company is focused on compiling the regulatory package. From there, 35Pharma plans to "imminently" launch its clinical development program, and while specific details are yet to be confirmed, management expects to start by running a SAD/MAD in HVs. There is also the potential to include subsets of obese (based on BMI) and HFpEF patients within the MAD portion. This remains an open discussion with the regulators, although HS235's tox package already satisfies requirements for long-term dosing in both HVs and patients. Ultimately, 35Pharma expects to provide additional color on clinical trial plans as we get closer to the IND filing later this year.

How does HS235 differ from incretins? As a dual Activin x GDF inhibitor, HS235 exerts its effects orthogonally to the incretin MoA. Specifically, HS235 is able to drive weight loss without impacting caloric intake (vs. incretins) and uniquely addresses both "sides" of obese HFpEF by improving metabolic dysfunction (excess adiposity, impaired glucose management, skeletal muscle issues), while also reducing elevated

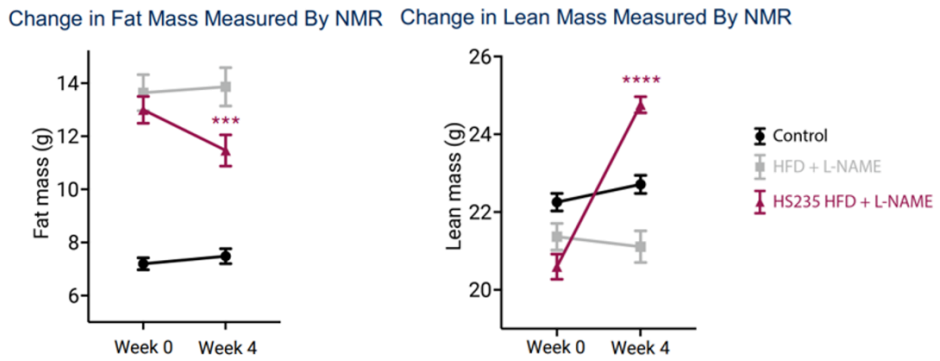
35Pharma, Inc. (Private): (Page 2 of 2)

LV pressures (LV concentric remodeling, cardiac fibrosis). In contrast, GLP-1s only confer moderate impact to metabolic dysfunction by driving weight loss; however, this is associated with substantial lean mass loss and no observed benefits to cardiac remodeling. Accordingly, this provides HS235 with a unique mode of action that could comprehensively capture the needs of obese HFpEF patients where incretins cannot.

Summary of HS235 preclinical data. To date, HS235 has a preclinical package with data across both obese HFpEF and DIO mouse models. Specifically, HS235 at 4 weeks in the obese HFpEF mouse model drove a stat sig decrease in fat mass paired with stat sig increases to lean mass (both measured by NMR) vs control (**Exhibit 49**). HS235 also showed a stat sig reduction (relative to vehicle) across both LVSP and LVEDP at 4 weeks (**Exhibit 50**) and exercise tolerance, which strongly establishes the drug's benefit to cardiac function.

EXHIBIT 49

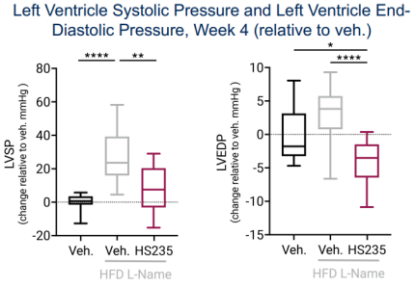
HS235 Drives Stat Sig Body Composition Improvements in Obese HFpEF Mice



Source: 35Pharma Company Materials. Piper Sandler Research.

EXHIBIT 50

HS235 Improved LV Parameters in Obese HFpEF Mice



In a DIO mouse model, HS235 + tirzepatide showed synergy to fat-exclusive weight loss. Specifically, there was 40% greater fat loss in HS235 + tirzepatide-treated mice at 21 days vs tirzepatide alone, with no lean mass changes (**Exhibit 51**).

EXHIBIT 51

HS235 + Tirzepatide Produces Greater Fat Loss & No Lean Mass Changes in DIO Mice

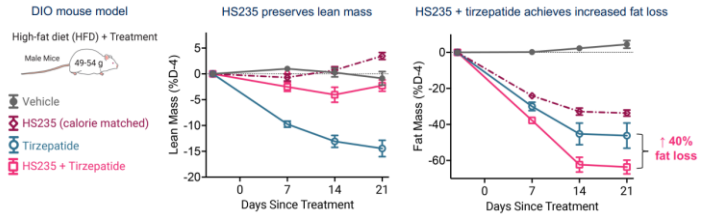


EXHIBIT 52

Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obese HFpEF	**HS235**	IND submission in **2H24**
Obese Excess Adiposity	**HS200**	Co-formulation IND-enabling experiments in **2025** with potential Phase II initiation in **1Q25**

Aardvark Therapeutics (Private): (Page 1 of 2)

Aardvark Therapeutics is pioneering the development of ARD-101, an oral drug targeting obesity and Prader-Willi Syndrome (PWS). Aardvark's potential competitive edge lies in ARD-101's unique MoA, which targets gut Bitter Taste Receptors (TAS2R) to stimulate the local secretion of the satiety hormone cholecystokinin (CCK) in the intestines. Unlike GLP-1s, which affect appetite, ARD-101 addresses hunger through distinct neural pathways. Importantly, ARD-101 avoids the common side effects of nausea and diarrhea associated with GLP-1 use. ARD-101 stimulates local, rather than systemic, release of both GLP-1 and CCK and avoids systemic toxicity. As such, ARD-101 has demonstrated a high safety margin, with >80 patients treated up to 28 days in a twice-daily dosing regimen without any SAEs.

EXHIBIT 53

ARD-101 Development Path

Indication	IND	Phase Ia	Phase Ib	Phase II/IIa	Phase III
First-In-Human study in Healthy Volunteers	Completed				
Prader-Willi Syndrome	Completed				
General Obesity (BMI 30-45 kg/m^2)	Completed				
Post-Bariatric Surgery Patients with Refractory Weight Gain	Completed				

Source: Aardvark Therapeutics Company Materials. Piper Sandler Research.

Phase II trials of oral ARD-101 provided early evidence of reduced hunger in 3 different populations: Prader-Willi Syndrome (PWS), general obesity, and post-bariatric surgery patients. In the Phase II trial that enrolled subjects with PWS, patients experienced an average change of -7.1 in HQ-QT 9, 4 pts had near complete resolution, 8 of 9 patients with analyzed DEXA scans demonstrated a reduction in body fat %, and subjects had less food-seeking behaviors. Subjects with general obesity in the Phase II trial who had stable weight over the prior 6 months experienced a weight loss similar to that achieved with a GLP-1R agonist in 28 days and a reduction in HbA1c and LDL with pathologically-elevated values. Patients in another Phase II who enrolled post-bariatric surgery experienced no weight gain and reduced hunger vs. baseline in an open label 28-day study.

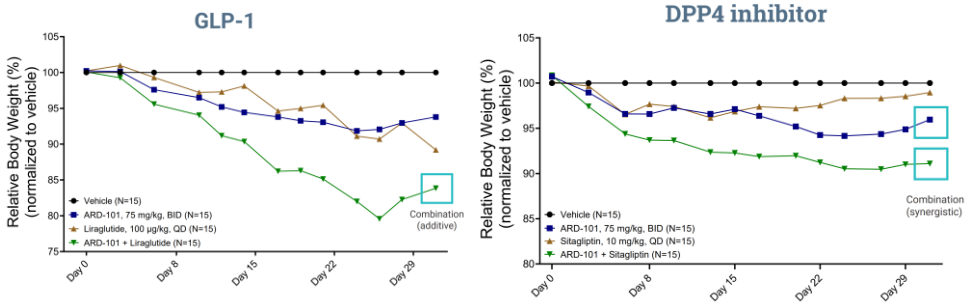
ARD-101 has shown a significant impact on hunger signals. ARD-101 suppresses fasting levels of ghrelin compared to placebo after a 28-day treatment period (p=0.0347). After a single dose, ARD-101 was also found to suppress ghrelin (p=0.0168) in fasted state one hour after the first dose.

What makes TAS2R receptors unique and promising? The TAS2R receptors are seven-transmembrane G protein-coupled receptors that are highly evolutionarily conserved across humans. Found throughout the body, these receptors can modulate the secretion of different enterohormones such as ghrelin, GLP-1, peptide YY, and cholecystokinin. By targeting TAS2R, ARD-101 is able to leverage the body's natural capacity to regulate satiety by stimulating GLP-1 and CCK locally in the gut. This is in contrast to synthetic incretin analogs (e.g., GLP-1R agonists) which mimic the activity of hormones released after eating to suppress appetite.

Aardvark Therapeutics (Private): (Page 2 of 2)

EXHIBIT 54

ARD-101 Shows Additive or Synergistic Potential When Combined with GLP-1R Agonist (Left) or DPP4 Inhibitor (Right), Respectively



ARD-201 is a combination of ARD-101 + sitagliptin (DPP4 inhibitor) with synergistic potential. **Exhibit 54** (above) demonstrates how ARD-101 can display additive or synergistic activities when combined with either liraglutide (GLP-1 agonist) or sitagliptin (DPP4 inhibitor), as shown in a diet-induced obese (DIO) mouse model. In combination with liraglutide, ARD-101 demonstrated additive reductions in body weight, whereas the combination of ARD-101 and sitagliptin resulted in synergistic reductions in body weight. This combination can potentially provide more effective and better tolerated treatment option for patients with obesity and type 2 diabetes, by addressing both blood sugar levels and appetite regulation. As such, Aardvark is advancing ARD-201, a once-daily oral formulation of ARD-101 + sitagliptin, into Phase II clinical development for the treatment of general obesity, post bariatric surgery, and weight rebound.

Source: Aardvark Therapeutics Company Materials. Piper Sandler Research.

The next few years are catalyst-rich for Aardvark. In a Phase IIb weight rebound trial (expected to start in 4Q24), Aardvark plans to enroll ~115 obese patients with GLP-1RA treatment success and evaluate ARD-201 (ARD-101 + sitagliptin) vs placebo over a 12-week treatment period for preservation of weight loss following GLP-1RA discontinuation. Aardvark is also planning a prospective PhIIb trial evaluating ARD-201 +/- GLP-1RA in patients with general obesity over a 6-month treatment period, which is expected to start in 1Q25. In addition, Aardvark plans to initiate a pivotal trial with ARD-101 for PWS in 3Q24 which will evaluate the efficacy of ARD-101 in reducing hyperphagia and other symptoms associated with PWS in ~150 patients.

EXHIBIT 55

Company Pipeline and Upcoming Catalysts

Asset	Indication	Development Phase
ARD-101	Prader-Willi Syndrome	Pivotal Phase III to initiate in 3Q24; Phase II complete
ARD-201 (ARD-101 + sitagliptin)	General Obesity	Prospective Phase IIb trial expected to start in 1Q25; pilot trials at low dose and without sitagliptin
	Post Bariatric	Phase IIa; pilot trials at low dose and without sitagliptin
	Weight Rebound	Phase IIb study expected to start in 4Q24
ARD-501	Autism	Phase IIb
ARD-701	Psoriasis	Phase IIa
ADT-101	Abuse Deterrent	Phase IIa

Altimmune (ALT): Rahimi, OW (Page 1 of 2)

Altimmune is developing the next generation of novel peptide therapeutics for obesity and liver diseases. ALT's next generation peptide molecule Pemvidutide (GLP-1/glucagon MoA) is being developed specifically for obesity and liver-directed co-morbidities. With this MoA, ALT is able to address the powerful GI- and brain-directed effects of GLP-1 to decrease appetite, inflammation, and gastric emptying to drive weight loss, as well as the direct effects on the liver from the glucagon mechanism to drive lipolysis, mobilization of fat, and energy expenditure increases. Taken together, this unique MoA has broad applicability across obesity and liver-directed indications (such as MASLD/MASH).

End of Phase II meeting for obesity program and enrollment completion in Phase IIb IMPACT MASH in 3Q24. Currently, ALT is enrolling a biopsy-driven, randomized, placebo-controlled trial in ~190 MASH subjects with F2 and F3 fibrosis, with and without diabetes. Patients will be randomized 1:2:2 to 1.2 mg Pemvidutide, 1.8 mg Pemvidutide, or placebo. The dual endpoints being assessed are either MASH resolution, or fibrosis improvement at 24 weeks, with patients being followed for an additional 24 weeks for a total of 48 weeks for safety assessment and additional biomarker responses. ALT is planning for completion of enrollment into this Phase IIb study in 3Q24, with topline results expected in 1Q25. In addition, for the obesity program, after the positive results from the MOMENTUM obesity trial as discussed herein, management is planning to have an end of Phase II meeting with the FDA in 3Q24 to plan for subsequent steps moving forward.

EXHIBIT 56
ALT's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity	Pemvidutide				
MASH	Pemvidutide				

Source: Altimmune Company Materials. Piper Sandler Research.

How does it differ from incretins? By having a dual-targeted MoA, Pemvidutide harnesses added benefit on top of the GLP-1 mechanism with the liver-directed effects of the glucagon MoA. Specifically, apart from being able to drive a robust weight loss benefit (mean weight loss of 15.6% on Pemvidutide 2.4 mg at week 48) that continued to have a linear trajectory, Pemvidutide has added effects on lipids (i.e., substantial reductions in total cholesterol, LDL, and triglycerides), as well as clinically meaningful reductions in blood pressure. Moreover, Pemvidutide has been shown to reduce liver fat, inflammation, and fibrosis, driven by the glucagon MoA (and recall that Pemvidutide, in contrast to other GLP-1/glucagon agents, has a balanced 1:1 GLP-1:glucagon ratio). That being said, as we highlighted in our recent note here, investors need to pay attention to the importance of glucagon, especially in MASH, where at EASL this year key data was shared from survodutide (7.5:1 ratio of GLP-1:Glucagon), validating glucagon as the driver of efficacy in MASH (in both fibrosis and cirrhosis patients) with fibrosis benefit. Hence, there is expectation that Pemvidutide's greater glucagon activity should translate to a superior profile, meaning a high PoS in the upcoming IMPACT PhIIb MASH readout in 1Q25.

Summary of clinical data. So far across its clinical programs, Pemvidutide has shown to be highly differentiated for both obesity and MASH, with robust weight loss

Altimmune (ALT): Rahimi, OW (Page 2 of 2)

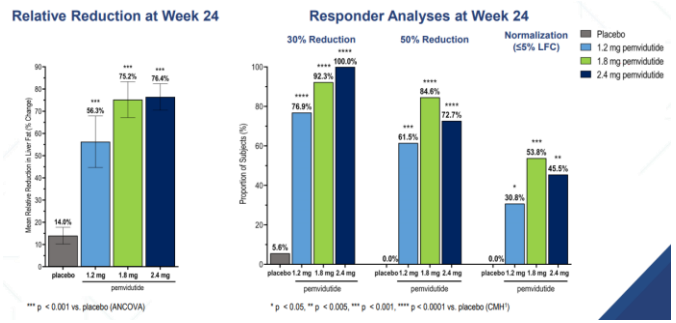
(15.6% on Pemvidutide 2.4 mg at 48 weeks, with over 30% of subjects losing 20% or more body weight), reductions in total cholesterol, LDL, triglycerides, and blood pressure, and rapid and robust reductions in liver fat of 75% at 24 weeks. Specifically, in the Phase II, 48-week MOMENTUM obesity trial in ~391 patients with overweight or obesity, mean weight loss of 15.6% was achieved at week 48 on 2.4 mg Pemvidutide, vs -11.2% at 1.8 mg, and -10.3% at 1.2 mg (vs -2.2% in placebo). More importantly, weight loss was shown to continue at week 48 (with no plateau of effect), which suggests there could potentially be greater weight loss realized with a longer duration of treatment. In addition, the majority of subjects lost 15% or greater body weight on the 2.4 mg dose (51.8% (p<0.0001 vs placebo)), and showed robust weight loss across all Pemvidutide doses. Alongside this there were significant reductions from baseline in serum lipids at week 48 (triglycerides, total cholesterol, LDL, VLDL, and HDL). Lastly, there were improvements in blood pressure without any clinically meaningful increases in heart rate at week 48. On the safety front, there were no AESI or MACE events, no imbalances in cardiac AEs across treatment groups, and only 1 drug-related SAE of vomiting.

Robust liver fat reductions in PhIb NAFLD (MASLD) trial. Pemvidutide also has strong data from ALT's PhIb NAFLD (MASLD) trial in ~94 patients over 12 weeks, which assessed key outcomes of reductions in liver fat content, ALT, and corrected T1 (cT1). As shown in **Exhibit 57**, there were robust reductions in liver fat content at week 24 across all doses tested, including 76.4% at 2.4 mg, 75.2% at 1.8 mg, and 56.3% at 1.2 mg (all p<0.001 vs placebo) vs. 14% for placebo. In addition, looking at the responder analyses at week 24, 100% of patients on the 2.4 mg dose had at least

Source: Altimmune Company Materials. Piper Sandler Research.

EXHIBIT 57

Pemvidutide: Robust Reductions in Liver Fat Content



a 30% reduction in liver fat, compared with 72.7% with a 50% reduction, and 45.5% with normalization (≤5% LFC). Moreover, Pemvidutide treatment resulted in significant cT1 response rates and ALT reductions (which are two independent indicators of reduced liver inflammation).

Key upcoming catalyst of PhIIb IMPACT MASH data in 1Q25. We have high conviction for the PhIIb MASH trial given the strong effects seen thus far with Pemvidutide on liver fat content, which is known to correlate with MASH resolution and fibrosis improvement.

EXHIBIT 58

Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**Pemvidutide**	EOP2 Meeting with FDA on MOMENTUM trial in **3Q24** Present MRI composition PhII MOMENTUM sub-study data at **EASD (September 10, 2024)**
MASH	**Pemvidutide**	Enrollment complete in PhIIb IMPACT **3Q24** and topline data **1Q25**

Amgen (AMGN): Raymond, OW (Page 1 of 3)

Amgen is a premier large pharma focused on transforming biologic insights into novel therapies for bone, cardiometabolic, hematology/oncology, inflammatory, nephrology, neuroscience, and rare diseases. Within Amgen's cardiometabolic portfolio, the company focuses on utilizing multiple modalities to correct the biological underpinnings of disease. Its clinical cardiometabolic pipeline currently contains 3 assets: (1) marketed product evocolumab (Repatha) for hypercholesterolemia, (2) olpasiran for atherosclerotic cardiovascular disease (ASCVD), and (3) maridebart cafraglutide (MariTide) for obesity. MariTide recently garnered significant attention for showing an elevated rate of weight loss compared to competitors in an early stage trial. *For this report, we will focus on the MariTide program*, including the data to date and Amgen's future development plans. We would note that per Amgen's commentary, the company has a robust preclinical pipeline in the obesity space, though few details have been provided around these assets at this point.

EXHIBIT 59

AMGN's Cardiometabolic Pipeline

			Highest Stage of Development			
Drug	**Modality**	**Indication**	**Phase I**	**Phase II**	**Phase III**	**Market**
Repatha	Antibody	Hypercholesterolemia				
Olpasiran	siRNA	ASCVD				
Maridebart cafraglutide (MariTide)	Antibody-peptide conjugate	Obesity				

Source: Amgen Company Materials. Piper Sandler Research.

EXHIBIT 60

Upcoming Catalysts for MariTide

Indication	Drug	Upcoming Catalyst
Overweight/obesity ± T2D	**MariTide**	Phase II study - *ongoing*
Overweight/obesity ± T2D	**MariTide**	Topline data from Phase II study – *late 2024*
T2D ± obesity	**MariTide**	Initiate Phase II study – *late 2024*
Overweight/obesity, obesity-related conditions, and diabetes	**MariTide**	Initiation of global Phase III program – *2025 (PSC est.)*

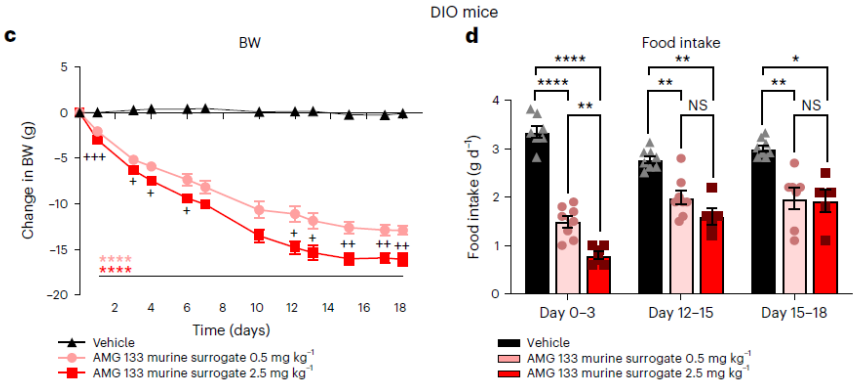
MariTide: a differentiated incretin therapy. Based on Amgen's genomic research, the company has developed maridebart cafraglutide (MariTide; f/k/a AMG-133), a GLP-1R agonist/GIPR antagonist. This bispecific molecule is engineered as a fully human monoclonal GIPR antagonist antibody conjugated to two GLP-1 mimetic peptides using amino acid linkers. The mechanism of GIPR antagonism is in contrast to **Eli Lilly's (LLY, not covered)** approved obesity/T2D therapy tirzepatide (Zepbound, Mounjaro), which is a dual GLP-1 agonist/GIPR agonist. Although it seems contradictory to pursue a somewhat opposing mechanism to an established therapy, there are multiple pieces of evidence which indicate that GIPR antagonism may be a valid strategy for targeting obesity. For example, GIPR knockout mice were observed to be protected from weight gain induced by a high-fat diet, and Amgen's own research in partnership with subsidiary deCode Genetics found that individuals with naturally lower GIP activity tend to have a lower body mass index (BMI).

Amgen (AMGN): Raymond, OW (Page 2 of 3)

Preclinical results show MariTide's promising drug properties. In preclinical studies, MariTide showed potent GLP-1R agonism and GIPR antagonism, as well as favorable PK properties, with a half-life of ~200 hours. In db/db mice injected with 2 mg/kg MariTide, body weight and blood glucose reductions were observed through 216 hours and 144 hours, respectively. Next, diet-induced obesity (DIO) mice (a standard model for obesity) were given a single 0.5 mg/kg or 2.5 mg/kg dose of MariTide and showed significant reductions in body weight, food intake, blood glucose, insulin levels, triglycerides, and total cholesterol, which was maintained for 18 days. These results were also observed in cynomolgus monkeys given either a 0.25 mg/kg or a 0.75 mg/kg dose SC once-weekly, with total body weight reductions of 11% and 13%, respectively, observed at 43 days.

EXHIBIT 61

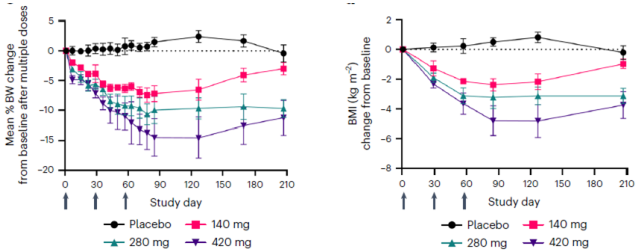
Weight Loss and Food Intake Results for MariTide in DIO Mice



Source: Amgen Company Materials. Véniant et al. *Nat Metab* 6, 290–303 (2024). Piper Sandler Research.

EXHIBIT 62

Body Weight and BMI Reductions After Three Doses of MariTide



MariTide's Phase I results show rapid weight loss. Based on these promising preclinical data, AMGN moved MariTide into a Phase I study in adult obesity patients (N=110). The randomized, double-blind, placebo-controlled, SAD and MAD study aimed to determine the safety, tolerability, PK, and PD of MariTide. 49 patients received a single SC MariTide dose between 21 mg and 840 mg or placebo. MAD cohorts included 26 patients receiving 3 doses of MariTide once-monthly ranging from 140 mg to 420 mg or placebo. Importantly, MariTide led to dose-dependent decreases in body weight (**Exhibit 62**). In SAD cohorts, body weights were reduced up to -8.2% at the highest dose, and reductions were maintained through 150 days in all cohorts except the lowest dose cohort. In the MAD cohorts, mean body weight reductions of -7.8% and -14.5% were observed between days 78-85 in the 140 mg and 420 mg cohorts, respectively. These reductions were maintained through 210 days, 150 days after the last dose. Fasting glucose also showed a treatment-specific reduction through the study. These results caused excitement due to the large weight reduction observed relatively quickly with once-monthly dosing (vs. once-weekly dosing required for Wegovy and Zepbound).

Amgen (AMGN): Raymond, OW (Page 3 of 3)

Broad Phase II study is ongoing. Amgen is currently conducting a randomized, placebo-controlled, double-blind, dose ranging Phase II study of MariTide in patients with overweight or obesity without T2D (Cohort A) or with T2D (Cohort B) (N=592). In Part 1 of the study, patients are randomized to receive MariTide SC in one of seven dose schemes or placebo. The company has been vague about what dose levels and frequencies are being tested, but management has indicated that patients are being dosed once-monthly and possibly even less frequently. Part 1 encompasses 52 weeks of treatment, and the main goal is to determine the optimal dose to bring into Phase III. The company announced in early 2024 that it added a Part 2 to the study to assess weight loss maintenance. Details on Part 2 are also vague, but management commentary indicates that only patients who reach a certain weight reduction threshold in Part 1 are eligible and are re-randomized to receive one of four dose schemes or placebo. The main goal of Part 2 is to assess strategies for long-term weight maintenance on MariTide and durability of weight loss after stopping treatment.

The primary endpoint for the Phase II study is percent change in body weight from baseline at 52 weeks. Key secondary endpoints include: proportion of patients reaching certain weight loss thresholds (≥5%, 10%, 15%, and 20% of body weight); changes in metabolic parameters like HbA1c, fasting serum insulin, fasting plasma glucose, insulin resistance, and beta cell function; PK and laboratory parameters (blood pressure and cholesterol); and body composition as measured by DEXA.

Amgen is gearing up for success. The primary completion date for the Phase II trial is October 2024 (NCT05669599), and **Amgen has guided to a topline data release by the end of 2024.** Interestingly, the company announced in May 2024 that it had completed an interim analysis of the trial, and, based on the strength of the data so far, **the company feels confident in a "differentiated profile" and that planning is already underway for a broad Phase III program across obesity and multiple obesity-related conditions.** Amgen has also begun to ramp up production capacity in anticipation of the Phase III program and commercial launch, but has not provided any additional color as to the results of the interim analysis, nor what a "differentiated profile" entails, but based on this announcement and previous data, dosing frequency and speed of weight loss are likely to be in focus.

From a safety perspective, MariTide has so far shown an acceptable safety and tolerability profile in line with other incretin drugs. In the Phase I trial, there were no clinical abnormalities except for two patients who experienced amylase and lipase elevations that resolved without clinical sequelae. Most common AEs were GI-related, including nausea and vomiting, which were generally mild-to-moderate and resolved within 48 hours. There were no SAEs or TEAEs leading to permanent discontinuation. However, AEs were most significant at the highest dose levels, and only half of the 420 mg MAD cohort completed treatment. Thus, it will still be important to examine the safety profile when the Phase II topline data reads out.

Source: Amgen Company Materials. Piper Sandler Research.

Arrowhead Pharmaceuticals (ARWR): Tenthoff, OW (Page 1 of 2)

PIPER | SANDLER

Arrowhead Pharmaceuticals is developing Targeted RNAi Molecules (TRiMs) to treat a wide range of diseases. Lead candidate plozasiran (ARO-APOC) met the primary endpoint in the Phase III PALISADE trial in Familial Chylomicronemia Syndrome. Arrowhead will file the NDA by YE24, which could result in the company's first drug approval and launch in 2025. Arrowhead is conducting the Phase III SHASTA-3 and SHASTA-4 trials in Severe Hypertriglyceridemia (SHTG), and will start the CAPITAN CVOT trial to potentially broaden the plozasiran label. Beyond CVD, Arrowhead is developing a rich pipeline of TRiM candidates to treat liver, pulmonary, muscle, and CNS diseases (**Exhibit 63**). Arrowhead plans to submit two CTAs for ARO-INHBE and ARO-ALK7 to treat obesity by YE24. Arrowhead is partnered with **Amgen (AMGN, Raymond, OW)**, **Takeda**, and **GlaxoSmithKline**.

EXHIBIT 63

Arrowhead's Clinical TRiM Pipeline

Therapeutic Area		Pre-clinical	Phase 1	Phase 2	Phase 3	Product Rights
Cardiometabolic	Plozasiran (ARO-APOC3) Hypertriglyceridemia					Arrowhead
	Zodasiran (ARO-ANG3) Dyslipidemia					Arrowhead
	Olpasiran CVD					Amgen
	GSK4532990 NASH					GSK
	ARO-PNPLA3 NASH					Arrowhead
Pulmonary	ARO-RAGE Inflammatory					Arrowhead
	ARO-MUC5AC Muco-Obstructive					Arrowhead
	ARO-MMP7 IPF					Arrowhead
Liver	Fazirsiran Alpha-1 Liver Disease					Arrowhead / Takeda
	Daplusiran/Tomligisiran HBV					GSK
Muscular	ARO-DUX4 FSHD					Arrowhead
	ARO-DM1 DM1					Arrowhead
Other	ARO-C3 Complement Mediated Disease					Arrowhead
	ARO-CFB Complement Mediated Disease					Arrowhead

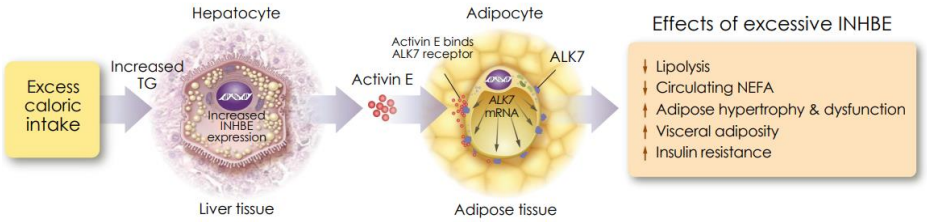
Tissue Targets: Liver, Lung, Muscle

Source: Arrowhead Pharmaceuticals Company Materials. Piper Sandler Research.

INHBE is a novel target for obesity and related diseases. Recent research has elucidated that the INHBE signaling pathway controls fat deposition and metabolism. In healthy individuals, burning fat results in free circulating fatty acids. Hepatocytes respond to increases in fatty acids by increasing INHBE protein expression. INHBE signals at the activin receptor ALK7 expressed on adipocytes to curb lipolysis (**Exhibit 64**). In obese humans, INHBE expression is chronically elevated. Therefore, lipolysis is more difficult to induce, and the metabolic function of adipocytes is hindered. Human genetic studies have validated associations between LOF mutation in INHBE and larger hip circumference, lower visceral:glutofemoral fat ratio, and lower body fat without changes in lean mass. Additionally, LOF mutations in INHBE were associated with a better metabolic profile, i.e. higher HDL cholesterol and lower triglycerides. Similar observations have been made for ALK7. Importantly, many ligands can act on ALK7, potentially with the ability to compensate for the lack of INHBE signaling. Arrowhead is developing ARO-INHBE targeting hepatocytes and ARO-ALK7 targeting adipocytes to treat obesity.

EXHIBIT 64

INHBE is a Target for Treatment of Obesity



Arrowhead Pharmaceuticals (ARWR): Tenthoff, OW (Page 2 of 2)

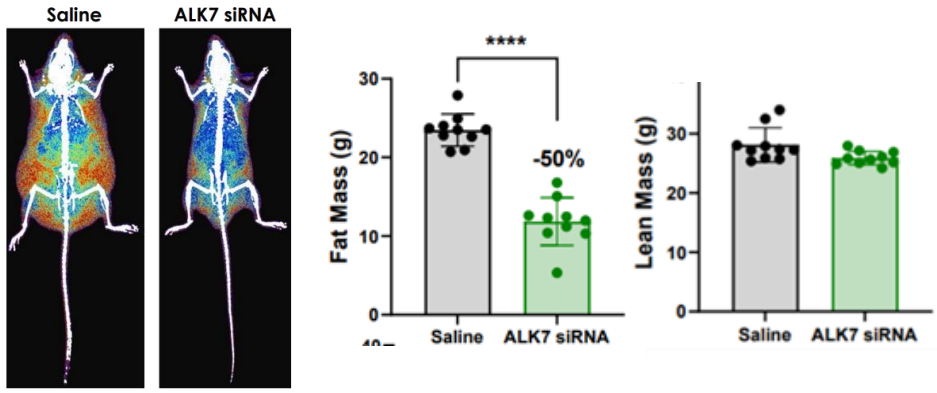
Preclinical validation of INHBE-ALK7 MoA. Research has already demonstrated that knocking down INHBE-ALK7 signaling can limit weight gain in obese rodent models on a high fat diet or reverse adiposity in 'obese' rodents. Arrowhead has replicated these findings with murine ARO-INHBE and ARO-ALK7 molecules. Over ~18 weeks, ARO-INHBE showed a 22% reduction in weight with trends towards increased lean muscle mass (5%) and glucose tolerance (20%). Arrowhead also observed a gene transcript signature indicative of induction of lipolysis. Importantly, liver steatosis was not observed, which has been seen with complete INHBE KO. In fact, liver fat was marginally reduced with ARO-INHBE.

In NHPs, a single dose of 4.5 mg/kg ARO-INHBE was sufficient to reduce circulating INHBE protein by 79% at 30 days. Arrowhead has developed a dual lipid conjugation platform to deliver siRNA to adipocytes and achieved >75% KD of target adipocyte-marker protein at 16 months with a single high 10 mg/kg i.v. dose in NHP. ARO-ALK7 reduced levels of the ALK7 receptor and produced a similar profile to ARO-INHBE, but an even more pronounced 50% reduction in fat mass, and significantly reduced TGs in the liver by 67%. While ARO-ALK7 may have greater efficacy by preventing signaling from multiple ligands, adipocyte delivery is unproven in the clinical setting. In contrast, ARO-INHBE targets hepatocytes with a well-validated delivery vehicle. Therefore, Arrowhead is progressing *both* programs into Phase I studies. A KOL on Arrowhead's R&D day (August 2024) suggested any reduction of weight >10% would be impressive and likely earn a role for ARO-INHBE/ALK7 in combination therapy, while >15% weight loss may set a new bar for 1st-line therapy. While Phase I studies are not long enough or powered to show efficacy, we anticipate Arrowhead may approach these benchmarks in the long run given the strength of preclinical data.

Source: Arrowhead Pharmaceuticals Company Materials. Piper Sandler Research.

EXHIBIT 65

ARO-ALK7 Significantly Reduces Fat Mass, But Preserves Lean Mass



CTA Filings by YE24. Arrowhead is planning Phase I/IIa SAD/MAD studies of ARO-INHBE and ARO-ALK7 in obese patients (BMI>30) with and without T2D. Patients in the MAD cohort will receive two doses (Day 1, Day 29). Part II of the study will evaluate the drugs in combination with a GLP1/GIP agonist. The studies will assess the effects of two different doses of tirzepatide combination on serum Activin E (INHBE) and bodyweight in obese patients. The primary endpoint is safety, and the secondary endpoint is PK. Exploratory endpoints include weight change, waist circumference, body adiposity, and liver fat content. For ARO-ALK7, patients will also undergo pre-dose and post-dose adipose biopsies on days 29 and end of study in the SAD cohort, and on days 57 and 169 in the MAD cohort. Arrowhead expects to file the CTAs by YE24, and report initial results, including biomarker, weight loss, and body composition imaging data, in 2H25.

BioAge Labs, Inc. (Private): (Page 1 of 2)

BioAge Labs is a clinical-stage biotech company developing therapeutic product candidates for metabolic disease. BioAge's lead asset is azelaprag, a potential first-in-class apelin receptor APJ agonist oral small molecule that has shown increased weight loss and improved body composition in combination with incretin therapies. Additionally, BioAge is also developing BGE-100, a novel NLRP3 inhibitor, and multiple preclinical programs aimed at addressing key pathways in metabolic aging.

Azelaprag is in Phase II development for obesity. In October 2023, BioAge announced a collaboration with **LLY (not covered)** and Chorus (operationally-independent clinical development organization in LLY) to run the 24-week PhII STRIDES trial (NCT06515418) of azelaprag + tirzepatide (GLP-1/GIP) in 220 obese patients (age 55+), with primary endpoint of % change in overall weight loss (QD and BID; ~90% power to detect 3.3% improvement in weight loss over TZP mono). Of note, LLY is supplying tirzepatide (Zepbound) and Chorus is providing guidance on clinical trial design and execution. Importantly, BioAge maintains worldwide exclusive rights to develop and commercialize azelaprag for all indications. Further, BioAge detailed secondary endpoints of metabolic parameters, PROs, and QoL will be measured in addition to the collection of aging-related biomarkers from patients.

How is azelaprag differentiated from incretins? It is important to recognize BioAge's azelaprag is a QD orally-available apelin receptor APJ agonist with potential for best-in-class weight loss in obesity. The drug mimics the activity of the exerkine apelin, which is a peptide that is actively released in response to exercise. BioAge designed azelaprag to improve basal metabolic rate, insulin sensitivity, and mitochondrial biogenesis, and to inhibit muscle atrophy and inflammation. In our previous KOL note we hosted an apelin expert who detailed that apelin has impressive effects to treat or restore muscle mass in older patients, with broad expression across tissues. Thus, combined with GLP-1s an apelin agonist has the potential to drive differentiated weight loss through prevention of loss of muscle mass. With this, BioAge believes injectable incretin therapies drive sig weight loss, though performance of oral incretins lags and remains a clear unmet need. As such, BioAge is positioning azelaprag in combination with an incretin therapy with the goal of 20%+ total weight loss at 1 year with potential for differentiated body composition/function, glucose control, and tolerability.

EXHIBIT 66

BioAge's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity	Azelaprag				
Insulin sensitivity	Azelaprag				
Neuroinflammation	BGE-100				

Summary of clinical data. BioAge ran a double-blind, placebo-controlled PhIb trial (NCT06141889) assessing infusions of 240 mg azelaprag over 10-days of bedrest in 21 healthy volunteers aged 65 or older, with primary endpoint of safety and pharmacodynamics. Specifically, key azelaprag takeaways from the PhIb trial were: (1) 100% improvement in thigh circumference ($p<0.001$ vs placebo); (2) 58% improvement in vastus lateralis cross-sectional area ($p<0.05$ vs placebo) and 73% improvement in thickness ($p<0.01$ vs placebo); (3) only 1/11 azelaprag-treated

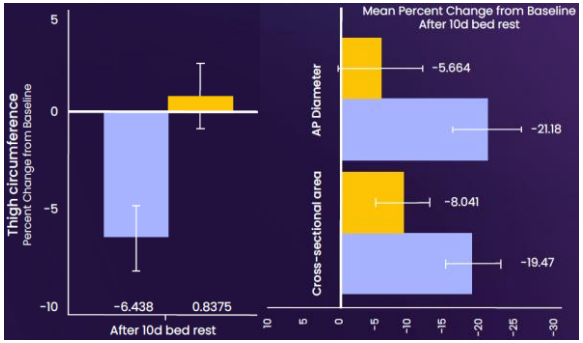
Source: BioAge Labs Company Materials. Piper Sandler Research.

BioAge Labs, Inc. (Private): (Page 2 of 2)

patients (p<0.005 vs. 8 of 10 placebo patients) showed a worsened Goutallier grade (quantifies fatty degeneration in muscle); (4) sig amelioration of reduction in muscle proteins due to bed rest (p<0.005 vs. placebo); and (5) azelaprag was well-tolerated (across 240+ total individuals) and consistent with prior PhI trials conducted by **AMGN (Raymond, OW)**. Taken together, the initial PhIb trial of azelaprag in healthy older volunteers validates the apelin agonist MoA in improving muscle physiology in older adults. Thus, azelaprag is on track for development in obesity with a focus on differentiated weight loss when used in combination with an incretin therapy.

EXHIBIT 67

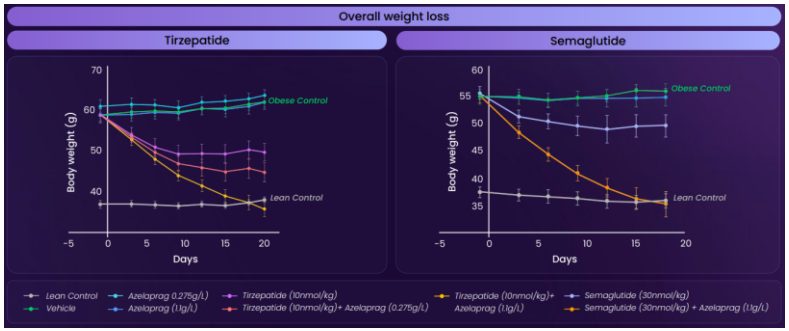
Azelaprag (Yellow) Reduced the Impact of Bed Rest on Muscle Size



Summary of preclinical obesity data. Recently, BioAge presented preclinical data in an obese mouse model that demonstrated the addition of azelaprag to tirzepatide increased total weight loss to ~40% (i.e., ~2X tirzepatide monotherapy) and restored body weight in the range of lean control mice (**Exhibit 68**). Additionally, co-administration of azelaprag w/ tirzepatide was restored body composition and muscle function to control levels. Of note, similar results were seen when azelaprag was combined with semaglutide (GLP-1; **Exhibit 68**). Synergistic weight loss in animals was not due to a decrease in food intake. Taken together, BioAge believes its preclinical results effectively derisk the PhII combination trial being planned to assess azelaprag co-administered with tirzepatide (Zepbound).

EXHIBIT 68

Azelaprag Showed Additive Weight Loss with Tirzepatide (L) & Semaglutide (R)



Upcoming catalysts. BioAge has guided 24-week PhII azelaprag/tirzepatide (Zepbound) STRIDES topline for 3Q25, initiation of a PoC study PhII trial assessing azelaprag in combination with semaglutide in 1H25, trial initiation of a POC study in insulin sensitivity in patients with obesity with prediabetes in 1H25, and IND submission of BGE-100 in 2H25.

EXHIBIT 69

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**Azelaprag/Tirzepatide**	PhII STRIDES 24-week topline data in **4Q25**
Obesity	**Azelaprag/Incretin**	PhII initiation in **1H25**

Source: BioAge Labs Company Materials. Piper Sandler Research.

Biohaven Ltd (BHVN): Raymond, OW (Page 1 of 3)

Biohaven is a clinical-stage company specializing in treatments for both common and rare neurological and neurodegenerative disorders, as well as early-stage programs in immunology and oncology. Key assets for the company include: BHV-7000, a Kv7 ion channel modulator for neuropsychiatric diseases; BHV-2100, a TRPM3 antagonist for migraine and neuropathic pain; taldefgrobep alfa, a myostatin inhibitor for SMA and obesity; BHV-1300, a pan-IgG degrader for inflammatory diseases; and BHV-8000, a TYK2/JAK1 inhibitor for neuroinflammation. *For this report, we focus on the obesity opportunity for taldefgrobep alfa*, but given the breadth of Biohaven's pipeline, we note that multiple catalysts outside this program could drive stock action this year (**Exhibit 70**).

EXHIBIT 70

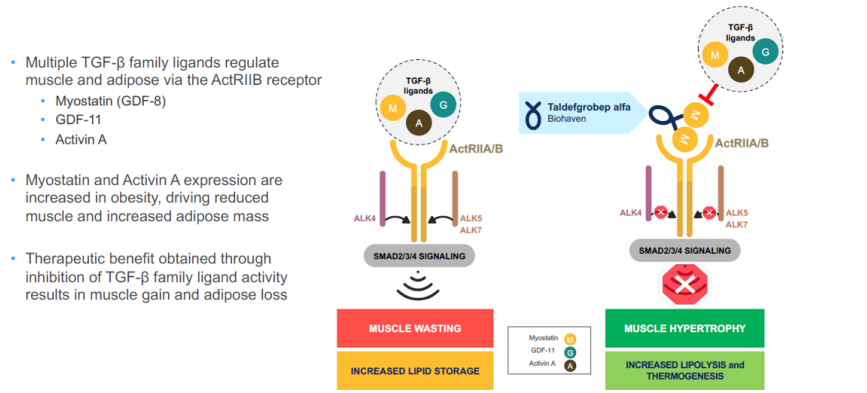
Biohaven's Pipeline and 2024 Catalysts

		1H 2024	2H 2024
Troriluzole | BHV-4157	Obsessive-Compulsive Disorder *2 ongoing trials*	Phase 3 Interim Analysis	
			Phase 3 Interim Analysis
Taldefgrobep Alfa | BHV-2000	Spinal Muscular Atrophy		Phase 3 Topline
	Obesity		Initiate Phase 2
Kv7 Activator | BHV-7000	Focal Epilepsy	Initiate Phase 2/3	
	Generalized Epilepsy	Initiate Phase 2/3	
	Bipolar Disorder	Initiate Phase 2/3	
	Major Depressive Disorder	Initiate Phase 2	
TRPM3 Antagonist | BHV-2100	Migraine		Initiate Phase 2
	Neuropathic Pain		Initiate POC
TYK2/JAK1 | BHV-8000 (brain-penetrant)	Neurodegenerative Disorders		Initiate Phase 2
IgG Degrader | BHV-1300	Rheumatoid Arthritis	Phase 1 IgG Interim Data	SAD Topline
IgG Degrader | BHV-1310	Myasthenia Gravis		Initiate Phase 1
IgA Degrader | BHV-1400	IgA Nephropathy		Initiate Phase 1
β1-AR Degrader | BHV-1600	Dilated Cardiomyopathy		Initiate Phase 1
Trop2 | BHV-1510	Carcinoma	Initiate Phase 1	

Source: Biohaven Company Materials. Piper Sandler Research.

EXHIBIT 71

Schematic of T-alfa's Mechanism of Action



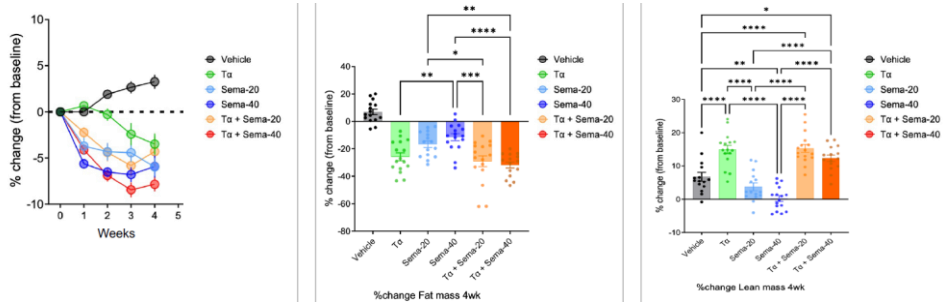
T-alfa for muscle loss prevention. Taldefgrobep alfa (T-alfa) is a fusion protein that targets the myostatin/activin pathway to prevent inhibition of muscle growth. Inhibiting this pathway has been shown to increase muscle mass in severe degenerative disorders like SMA, as well as in models of GLP-1-induced weight loss. T-alfa contains a domain which binds to mature myostatin and inhibits ActRIIB signaling in tissues where myostatin is active (**Exhibit 71**). This approach may enable better efficacy and safety than targeting myostatin alone for several reasons. First, it can disrupt other binding partners to ActRIIB which influence muscle growth, like activin A. T-alfa's specificity for tissues with active myostatin may also prevent off-target action and reduce AEs. Finally, the complex formed by T-alfa and myostatin continues to circulate, potentially leading to a longer duration of effect than an antibody which destroys free myostatin.

Biohaven Ltd (BHVN): Raymond, OW (Page 2 of 3)

Taldefgrobep alfa has shown promising preclinical and clinical results. T-alfa's opportunity in obesity is bolstered by data from a Phase I, randomized, double-blind, placebo-controlled trial in healthy volunteers (N=140). Findings from the MAD portion (N=97) where patients were given taldefgrobep alfa SC Q1W for 29 days include: (1) increased lean mass of 2% at the end of the study, which further increased to ~4% at day 57; (2) reduction in fat mass of ~-4% at the end of dosing and approx. -6% at the end of the study. Taldefgrobep has also been evaluated in multiple clinical trials in Duchenne muscular dystrophy. In each trial, taldefgrobep was generally well tolerated. Additionally, preclinical data in DIO mice in combination with semaglutide show greater reductions in body weight and in fat mass, and increased lean mass compared to semaglutide alone (**Exhibit 72**, below).

EXHIBIT 72

T-alfa's Effects on Body Weight, Fat Mass, and Lean Mass in DIO Mice in Combo with Semaglutide



Source: Biohaven Company Materials. Piper Sandler Research.

EXHIBIT 73

Phase I Data in Healthy Volunteers Show Increases in Lean Mass and Reduction in Fat Mass

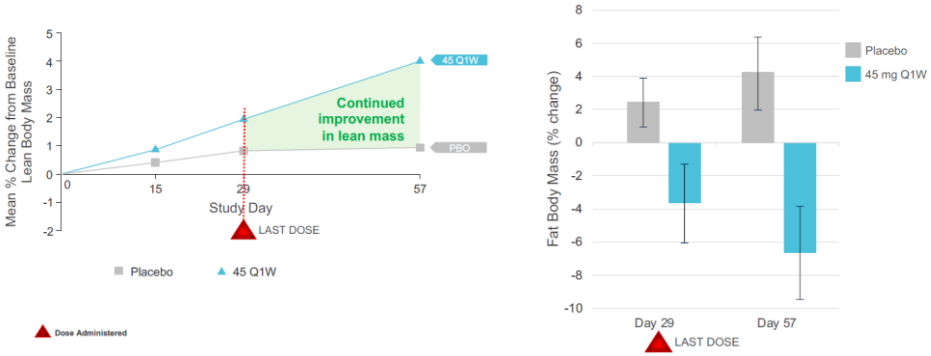


EXHIBIT 74

Safety Data from Phase I Trial

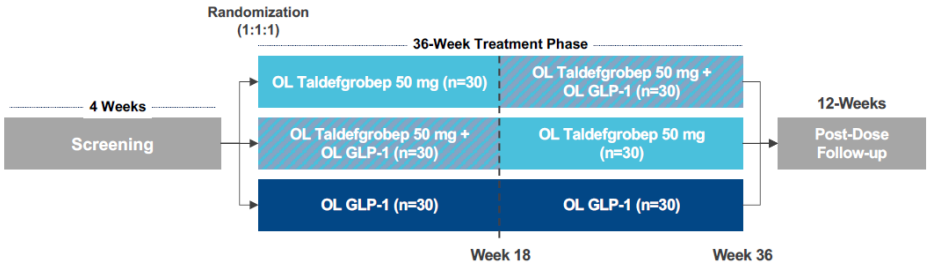
	Phase I: Healthy Volunteers	
	Taldefgrobep alfa (Any Dose)	Placebo
N	72	25
Safety		
Incidence of AEs	60%	44%
Common AEs		
Injection-site erythema	17%	0%
Rash	11%	4%
Upper respiratory tract infection	14%	4%
Abdominal pain	3%	4%
Headache	3%	8%
Muscle spasms	4%	0%

Biohaven Ltd (BHVN): Raymond, OW (Page 3 of 3)

Plans for a Phase II trial to assess T-alfa as a monotherapy and in combination with a GLP-1. The trial aims to recruit 90 patients and will measure the impact of T-alfa monotherapy on changes in body composition, total body weight, and metabolic parameters; the ability of T-alfa to augment fat loss and prevent lean mass loss when used with a GLP-1; and the influence of T-alfa on weight regain following discontinuation of the GLP-1. Patients will receive taldefgrobep alone, semaglutide alone, or taldefgrobep + semaglutide QW for 18 weeks, after which the taldefgrobep monotherapy cohort will add semaglutide, the combo cohort will remove taldefgrobep, and the semaglutide monotherapy cohort will remain on semaglutide monotherapy for an additional 18 weeks (**Exhibit 75**). Biohaven plans to initiate the Phase II study before YE24, but timing on a possible data update remains TBD.

EXHIBIT 75

T-alfa's Phase II Obesity Trial Design



DESIGN	Randomized, open label (OL), active comparator Phase 2 trial
POPULATION	Male and female adults with overweight or obesity
SAMPLE SIZE	90 treated participants, randomized 1:1:1 across treatment groups
TREATMENT	Taldefgrobep alfa (50 mg Q1W) and GLP-1
TREATMENT DURATION	36-week treatment period, 12-week post-dose follow-up
ENDPOINTS	Changes in body composition, metabolic parameters, and total body weight over time, including post-dose follow-up period, PK/PD.

Source: Biohaven Company Materials. Piper Sandler Research.

Corbus Pharmaceuticals (CRBP): Not Covered

CRBP is a clinical-stage biopharma developing CRB-913, a highly peripherally-restricted CB1 inverse agonist for treatment of obesity. In addition to its precision oncology programs (i.e., CRB-701, a Phase I Nectin-4 targeted ADC for solid tumors, and CRB-601, a preclinical anti-αvβ8 mAb for solid tumors), CRBP is developing CRB-913, a highly peripherally-restricted cannabinoid Type-1 receptor (CB1R) inverse agonist for treatment of obesity and related conditions (CRB-913). CRB-913 is currently in IND-enabling studies (enrolment of first Phase I patient expected in 1Q25). CRB-913 is a once-daily, oral small molecule with potential applications as a monotherapy (maintenance or induction) or in combination with SC/oral incretins to enhance efficacy or improve tolerability. In the monotherapy setting, CRBP believes CRB-913 could show weight loss efficacy in line with semaglutide/tirzepatide, but with added benefits: (1) being a once-daily oral therapy (no need to titrate), (2) having improved tolerability, and (3) the ability to reduce weight while preserving lean mass.

EXHIBIT 76

CRBP's Obesity Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity and related conditions	CRB-913	→			

Preclinical data with CRB-913 (mono/combo). In a DIO mouse model, CRB-913 monotherapy significantly reduced body weight without impacting lean mass, and demonstrated enhanced efficacy when combined with incretin analogs (tirzepatide or semaglutide). Improvements were observed across body fat content, leptinemia, insulin resistance, liver triglycerides, liver fat deposits, and liver histology with CRB-913 as a monotherapy and in combination with incretins.

Source: Corbus Pharmaceuticals Company Materials. Piper Sandler Research.

Rationale for CB1 inverse agonist MoA. CB1 is a clinically-validated obesity drug target, but concerns for neuropsychiatric events halted the development of first-gen CB1 blockers, which target the brain. Notably, **Sanofi's (SNY, not covered)** rimonabant (EU approval in 2006) was pulled from the market in 2008 due to concerns related to CNS liabilities (depression/suicide ideation). However, in PhIII, rimonabant decreased weight by -6.6% (placebo-adj) at 52 weeks, without reducing lean mass. To overcome safety concerns, next-generation CB1 blockers such CRB-913 selectively-target CB1 in the periphery to minimize risk of CNS-associated toxicities and enhance efficacy. CB1 blockade works to reduce weight by both reducing food intake and increasing energy expenditure, which also helps to protect against lean mass loss.

Upcoming catalysts. CRBP expects to complete IND-enabling studies in 4Q24 and initiate a Phase I SAD/MAD study in 1Q25, with monotherapy data in 2H25 or 1H26 and combo data in 2H26 or 1H27. Competitors in the CB1 space have upcoming data that will readthrough to CRB-913, including PhII data from NVO's monlunabant (expected in 2H24). NVO's PhI modeling suggests the potential for 16-19% weight loss in PhII, and CRBP believes CRB-913 will be competitive given the higher degree of peripheral restriction vs monlunabant and rimonabant (12x or 21x lower brain concentrations observed with CRB-913 vs monlunabant or rimonabant, respectively).

EXHIBIT 77

Upcoming Catalysts

Drug	Upcoming Catalyst
CRB-913	Complete toxicology and IND enabling studies in **4Q24**
CRB-913	Initiation of Phase I study and first patient enrolled in **1Q25**
CRB-913	28-day monotherapy initiation (3-doses) expected in **2H25** or **1H26**
CRB-913	Combination with incretin analog initiation expected in **2H26** or **1H27**

Crinetics Pharmaceuticals (CRNX): Rahimi, OW

CRNX is leveraging its deep expertise in candidate molecule development and medicinal chemistry to break into the obesity space. CRNX is currently in the discovery and optimization phase to develop oral obesity agents with preferential efficacy/safety profiles. Recall from its current blockbuster programs in acromegaly and carcinoid, CRNX has deep expertise in developing oral endocrinology therapeutics with high clinical success. Therefore, we have conviction as CRNX develops two oral small molecule assets for diabetes and obesity, including a GLP-1 non-peptide and GIP non-peptide, with candidate selection for both on track for 2025. With this, CRNX intends to accelerate development of better GLP-1 and GIP agents that have good drug characteristics and clean safety.

How does it differ from incretins? With the competitive landscape of obesity therapeutics in mind and the potential oversaturation of the GLP-1 class, CRNX believes there still remains major unmet need for oral small molecules with improved characteristics and profile. Specifically, keep in mind that current injectables have supply chain issues, where development of oral small molecules is key, as they require lower capital needs and COGS with regard to manufacturing. This, combined with CRNX's expertise in clean and highly crafted drug candidate development and selection, means there is opportunity to develop better GLP-1 agents with good drug characteristics and clean safety to enter the market.

Candidate selection for GLP-1 non-peptide and GIP non-peptide guided for 2025 could be an important catalyst for CRNX. Importantly, we believe obesity candidate selection of a GLP-1 non-peptide and GIP non-peptide in 2025 could be a key stock moving event for CRNX, presenting an opportunity to unlock the obesity market with an oral agent that has an optimal efficacy/safety profile. The would also represent key value creation for the company, especially given the size of the diabetes/obesity market opportunity, paired with CRNX's ability to develop drugs with a high PoS.

EXHIBIT 78
CRNX's Pipeline

		Stage of Development			
Indication	**Program**	**Discovery**	**Preclinical**	**Phase I**	**Phase II**
Diabetes/Obesity	Oral GLP-1 nonpeptide				
Diabetes/Obesity	Oral GIP nonpeptide				

Source: Crinetics Pharmaceuticals Company Materials. Piper Sandler Research.

EXHIBIT 79
Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Diabetes/Obesity	**Oral GLP-1 nonpeptide**	Candidate selection **2025**
Diabetes/Obesity	**Oral GIP nonpeptide**	Candidate selection **2025**

Fractyl Health (GUTS): Not Covered (Page 1 of 2)

Fractyl's Revita and Rejuva platform technologies are centered on addressing durable weight and glucose control. Fractyl Health (GUTS) is a metabolic therapeutics company focused on developing therapeutics for obesity and type 2 diabetes (T2D). The company has two platform technologies: (1) Revita, and (2) Rejuva to address key unmet needs in these indications. Digging into the details, Revita is a proprietary device and delivery system that enables privileged access to the gut and pancreas to deliver a non-drug alternative via duodenal mucosal resurfacing (DMR), an endoscopic procedure which potentiates improved metabolic parameters and restores insulin sensitivity. This procedure facilitates T2D prevention and weight maintenance through dose-dependent glucose lowering. Rejuva is a pancreatic gene therapy platform crafted for remission of obesity and T2D. It is based on the AAV9 vector, with a human GLP-1 transgene driven by an insulin promoter, delivered through an endoscopic needle directly into the pancreas. As such, Rejuva transduces pancreatic islets via a one-time intrapancreatic administration, with nutrient-responsive GLP-1 expression.

EXHIBIT 80

GUTS' Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Pilot**	**Pivotal**	**Launch**
Weight Maintenance	Reveal-1 (Revita)				
Weight Maintenance	Remain-1 (Revita)				
Insulin-treated T2D	Revitalize 1 (Revita)				
CE Mark	German RW Registry (Revita)				
T2D	RJVA-001				
Obesity	Not Yet Disclosed				

Source: Fractyl Health Company Materials. Piper Sandler Research.

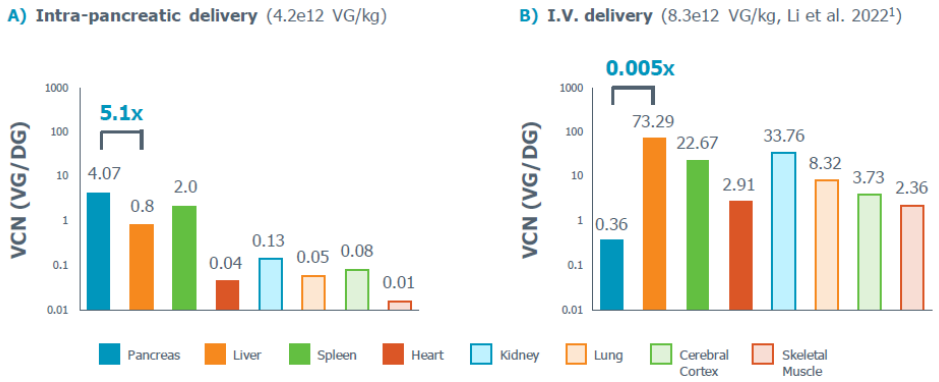
How does it differ from incretins? Current incretin medications deliver a high dose to patients weekly, leading to GI tolerability issues such as nausea and vomiting due to chronic elevation of these hormones. With this in mind, Rejuva gene therapy with an insulin promoter restricts GLP-1 expression to beta cells, which sense nutrient uptake and glucose in a meal-dependent manner to drive secretion of GLP-1. Accordingly, there is an autoregulated and automatic titration mechanism where once blood sugar goes down, the amount of GLP-1 produced will also be effectively reduced in a normal physiologic manner. Considering DPP4i's result in levels of GLP-1 to 10-15 pM (with little to no GI tolerability), whereas injectable incretins lead to GLP-1 levels of 10-20 nM, the company believes it has a wide range to work with its gene therapy on both efficacy and tolerability.

Localized delivery results in low dose with limited systemic biodistribution. GUTS has treated >50 Yucatan pigs with no adverse safety signals to date, with low viral genome dose and limited systemic virus exposure. In particular, with a 5.0e13 VG dose (~5e11 VG/kg human dose), GUTS achieved a 19.8% endocrine eGFP expression, which increased to 41.2% at the 1.5e14 dose. The amount of AAV9 used is 2-3 orders of magnitude lower compared to other marketed products using AAV9 vectors, further substantiating the importance of localized delivery towards achieving low doses.

Fractyl Health (GUTS): Not Covered (Page 2 of 2)

For biodistribution, intra-pancreatic delivery of 4.2e12 VG/kg resulted in a 5.1-fold higher viral copy number in the pancreas compared to the liver (**Exhibit 81**), with low viral copy number in other organs. In contrast, IV delivery administration of 8.3e12 VG/kg resulted in widespread systemic biodistribution, bolstering the rationale for localized delivery of GUTS RJVA gene therapy. Moreover, across 7 days, we highlight that ALT and lipase levels were within the normal range.

EXHIBIT 81
Intrapancreatic Localized Delivery for AAV9



RJVA-001 in a DIO mouse model shows superiority to chronic semaglutide.

In DIO mice treated with semaglutide (10 nmol/kg/d), a single injection of RJVA-001 (1e13 VG), or vehicle control, treatment with RJVA-001 led to weight reductions of 28% vs. 20% with daily semaglutide after a month. Next, half of the mice treated with daily semaglutide were withdrawn from treatment while the other half were given RJVA-001.

Source: Fractyl Health Company Materials. Piper Sandler Research.

As shown in **Exhibit 82**, mice withdrawn from semaglutide regained their weight to baseline (-2% weight body reduction vs. 4% vehicle control) on Day 57. In contrast, mice switched to RJVA-001 achieved robust weight loss (-22% body weight reduction vs. 4% vehicle control), similar to mice treated with RJVA-001 at the beginning of the study (-25% body weight reduction vs. 4% vehicle control), supporting durable weight loss in treatment-naïve mice as well as mice previously-treated with semaglutide.

EXHIBIT 82
Body Weight Change in DIO Mice with RJVA-001 & Semaglutide

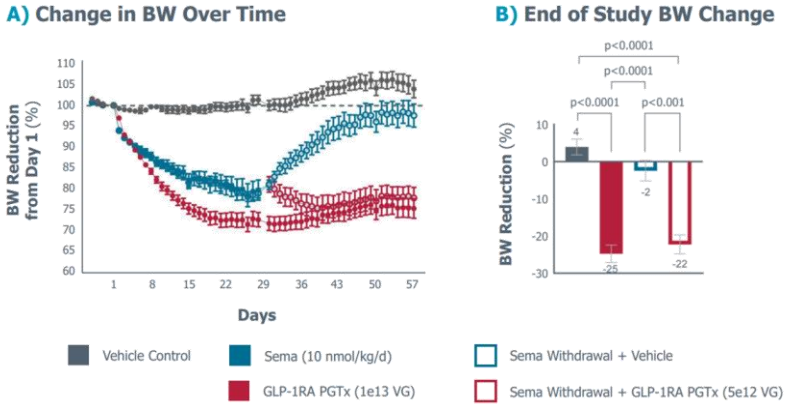


EXHIBIT 83
Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Insulin-treated T2D	**Revita**	Topline data expected in **4Q24**
T2D	**RJVA-001**	Complete IND enabling studies in **2H24** and initiate FIH study **1H25**
Obesity	**-**	Candidate nomination in **2H24**

Gila Therapeutics, Inc. (Private)

Gila Therapeutics is a clinical-stage biotech company pioneering a topical/lingual delivery system for the treatment of obesity and cardiometabolic disorders. Gila aims to use a novel, highly-targeted neural signaling system to treat obesity, T2D, and other metabolic disorders. Of note, Gila's topical/lingual delivery system was developed to activate satiety in the brain without any systemic exposure, through a distinct connection between the tongue and the brain. Thus, the method of delivery effectively avoids systemic dosing and the risks and safety concerns associated with current therapeutics. Gila is running an initial program assessing a topical lingual PYY (GT-001) in obese patients, while also developing multiple targets inclusive of GLP-1, amylin, leptin, and others.

GT-001 completed Phase I development with strong efficacy and clean safety. Gila Therapeutics completed a ~2-week PhI (NCT03490786) assessing GT-001 in 12 obese patients with primary endpoint of safety and other endpoints related to hunger and satiety. Gila has detailed that the PhI was successful with clear efficacy and no treatment-related AEs or SAEs, de-risking the topical/lingual approach.

EXHIBIT 84
Gila Therapeutics' Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity	GT-001				
Undisclosed	GLP-1, Amylin, Leptin, and others				

Source: Gila Therapeutics Company Materials. Piper Sandler Research.

How is Gila's technology differentiated from currently approved incretins? Gila Therapeutics' novel topical lingual/neural signaling platform allows for direct activation of specific brain regions related to metabolic regulation. Accordingly, this novel approach allows for natural peptide hormones to be non-invasively delivered to the brain without systemic dosing and no side effects. Recall, the initial PhI GT-001 trial demonstrated efficacy with zero treat-related AEs or SAEs, supporting Gila's hypothesis of targeted brain dosing. Further, the Catalent Zydis ODT dissolves on the tongue within 3 seconds and evenly disperses the peptide in the saliva and ensures the hormones do not enter the bloodstream. Additionally, extensive toxicology and preclinical studies (ex. dogs and Asian musk shrews) demonstrated no side effects, further validating this novel approach. For reference, typical incretin therapies are delivered systemically throughout the body, exposing other areas to the treatment and most commonly leading to GI side effects (ex. brain's nausea center). By comparison, Gila's topical lingual delivery system enables for hormones to directly bind to oral receptors causing rapid signaling to the brain, stimulating satiety centers in the brainstem and hypothalamus without activating the nausea center.

Next steps. While Gila Therapeutics has not provided formal guidance on further development of GT-001 (PYY) in obesity, it has noted development of multiple topical lingual hormones across GLP-1, amylin, leptin, and other MoAs. With this, Gila recognizes GI-related side effects as a driving cause of incretin discontinuation rates and positions its topical lingual approach as a novel way to treat obesity, T2D, and metabolic disorders without systemic effects.

Glyscend Therapeutics (Private): (Page 1 of 2)

Glyscend Therapeutics is a clinical-stage biopharmaceutical company focused on developing GLY-200, a first-in-class oral polymeric duodenal exclusion drug. Glyscend Therapeutics was founded on research showing the benefits of bariatric surgery: significant improvements in glucose, metabolic regulation, and sustained weight loss. As such, the company aims to replicate the long-term clinical benefits of metabolic surgery and minimize GI side effects through development of non-absorbed and gut-restricted therapies. Importantly, Glyscend's pipeline is driven by an in-house Mucus Complexing Polymer (MCP) platform selecting polymeric compounds that are: (1) effective and drive rapid mucus complexation; (2) GI-targeted (pH-based); (3) soluble and non-viscous; (4) non-absorbed and non-metabolized in the gut; (5) stable to hydrolysis or enzymatic degradation; and 6) naturally eliminated through the GI tract. GLY-200 is Glyscend's novel lead asset in T2D and obesity and is an oral therapy specifically developed to modulate the mucosal barrier in the GI tract and effectively achieve the benefits of gastric bypass surgery without the need for surgical intervention.

GLY-200 is in Phase II development in obesity and T2D. Glyscend is currently running a 16-week PhII PoC trial (NCT06259981) assessing 2.0 g BID GLY-200 vs. placebo in 90 obese patients without diabetes, with primary endpoint of % BW change and % of patients who achieve ≥ 5% BW reduction. Of note, Glyscend completed a 14-day PhIIa (NCT05478525) trial assessing 0.5 g, 1.0 g, and 2.0 g BID GLY-200 (oral duodenal exclusion drug) vs. placebo in 48 subjects with T2D (wash-out metformin for 14-days prior to dosing) and primary endpoint of safety and tolerability, as well as a PhI trial.

Source: Glyscend Therapeutics Company Materials. Piper Sandler Research.

EXHIBIT 85
Glyscend's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity/T2D	GLY-200				

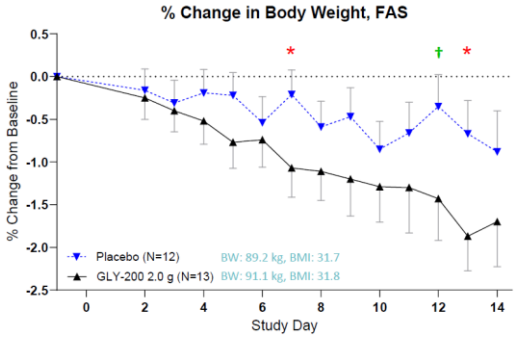
How does GLY-200 differ from incretins? GLY-200 is a first-in-class oral polymeric drug specifically designed to target and enhance the mucus barrier of the duodenum, mimicking healthy physiologic activity and driving duodenal exclusion. Importantly, incretins (exogenous GLP-1 activation) clearly drive weight loss with benefit across comorbidities (OSA, CKD, and CVD), though a significant on-target consequence is GI tolerability issues with increases in satiety driven by non-physiologic nausea. Thus, Glyscend is developing GLY-200 as an oral therapy for better tolerability and replication of gastric bypass surgery benefits, which have demonstrated up to 2.9% reductions in HbA1c and 29% BW reductions (Schauer P et al, 2012 (1-year STAMPEDE Trial report)), with potential T2D remission before weight loss. Additionally, GLY-200 is further differentiated as it is an oral therapy, ensuring streamlined simple manufacturing with low COGS driving development. Further, GLY-200's novel MoA has already shown immediate improvement in metabolic markers and glycemia, with advantages beyond weight loss and lower discontinuation rates (Glyscend expects this to drive sig uptake by PCPs).

Glyscend Therapeutics (Private): (Page 2 of 2)

Summary of clinical data. Glyscend completed a PhI trial in healthy volunteers and a 14-day PhIIa trial in patients with T2D (detailed on previous page). Accordingly, both trials established clinical PoC for GLY-200 and showed: (1) replication of duodenal exclusion biomarkers (decreased glucose and insulin; increased bile acids, GLP-1, glicentin, and PYY); (2) dose-dependent reductions in blood glucose and progressive weight loss in T2D patients; (3) decreased appetite and increased satiety in line with the duodenal exclusion MoA; (4) reductions in fasting and postprandial blood glucose; and (5) up to 30% reduction in LDL and total cholesterol. Notably, GLY-200 showed ~1.5% weight loss at 2-weeks in T2D patients **(Exhibit 86)**, which is consistent with early weight loss seen after Endobarrier placement (duodenal exclusion medical device; Gersin KS, et al. GIE. 2010). Importantly, Glyscend anticipates weight loss in an obese population to be more significant, with the expectation of >10% at 3-months (Schouten et al. Annals of Surg. 2010) and >20% at 12-months (Jirapinyo P, et al. Diabetes Care. 2018), based on its duodenal exclusion MoA.

EXHIBIT 86

Significant Weight Loss in PhIIa T2D Trial



Source: Glyscend Therapeutics Company Materials. Piper Sandler Research.

At ADA 2024, Glyscend presented three posters providing an in-depth overview of the PhIIa T2D trial which we detailed in our Virtual Obesity Day takeaway note. In addition to distinct efficacy in line with duodenal exclusion, GLY-200 was shown to have a strong safety profile with no treatment or dose-related safety signals, no serious or severe AEs (97% of AEs were mild), and tolerability issues were limited to GI events (mild constipation, diarrhea, and nausea were the most common). Glyscend selected the 2.0 g BID GLY-200 dose to move forward into the 16-week Phase II obesity trial, with a 2-week dose titration with 1.0 g BID to minimize nausea at the onset of treatment.

Upcoming catalysts. Glyscend guided enrollment completion and data in 1Q25 for the 16-week PhII trial (NCT06259981) assessing 2.0 g BID GLY-200 vs. placebo in 90 obese patients w/o diabetes, with primary endpoint of % BW change and % of patients who achieve ≥ 5% BW reduction. Importantly, the PhII trial will effectively de-risk GLY-200 development in the obesity indication, with ongoing 9- and 6-month dog and rat tox studies enabling 52-week trials (or longer). Of note, Glyscend is also preclinically assessing GLY-200 with semaglutide in DIO mice, with data expected to be presented at ObesityWeek 2024 (November 3-6) and pilot data showing a clear additive benefit (-9.1% GLY-200, -10.6% semaglutide, and -24.7% GLY-200 + semaglutide vs. +4.2% saline at Day 28).

EXHIBIT 87

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**GLY-200**	Topline PhII obesity data in **1Q25**

Hercules CM NewCo, Inc. (Private)

Hercules is a biotechnology startup backed by life science investors with a weight loss medicine portfolio licensed from Jiangsu Hengrui Pharmaceuticals. Hercules is a newly-established Delaware biotech company with funding from life science investors. In May 2024 Hercules licensed three of **Hengrui's (SSE: 600276)** GLP-1 drugs: (1) HRS-7535 (GLP-1); (2) HRS-9531 (GLP-1/GIP); and (3) HRS-4729 (metabolic target). Specifically, Hengrui will receive an upfront payment of $110M ($100M + $10M tech transfer milestone), clinical development and regulatory milestone payments of up to $200M, sales milestones of up to $5.725B, low single to low double digit sales royalties, and a 19.9% equity stake in Hercules.

HRS-9531 is in Phase II development. At ADA 2024, data was presented from the 24-week placebo-controlled PhII (NCT05881837) assessing QW SC 1.0-6.0 mg HRS-9531 in 249 obese adults without diabetes and primary endpoint of % change in BW from baseline to week 24. Adults aged 18-65 years with a BMI of 28-40 kg/m2 were randomized into the double-blind treatment period.

EXHIBIT 88

Hercules' Pipeline

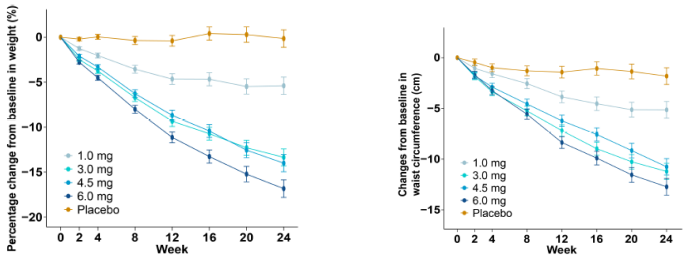
	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity/Diabetes	HRS-7535				
Obesity/Diabetes	HRS-9531				
Obesity/Diabetes	HRS-4729				

Source: Hercules CM NewCo Company Materials. Piper Sandler Research.

HRS-9531 demonstrated stat sig, dose-dependent reductions in body weight at 24 weeks. At the highest 6.0 mg dose, HRS9531 drove stat sig ($p<0.0001$) weight loss at -16.7% placebo-adjusted (-16.8% (95% CI: -18.8% to -14.9%) vs -0.1% (95% CI: -2.1% to 1.8%) placebo. As shown in **Exhibit 89**, all doses hit stat sig, and the proportion of patients with ≥5% weight reduction was 41.8-81.8% placebo-adjusted (52.0-92.0% vs 10.2% placebo), ≥10% was 11.9-71.5% (18.0-77.6% vs 6.1% placebo), and ≥15% was 3.9-49% (8.0-53.1% vs 4.1% placebo). Moreover, **Exhibit 89** shows that HRS9531 also reduced waist circumference by up to -12.7 cm at 6.0 mg (vs -1.8 cm for placebo), as well as improvements across other metabolic parameters like BP, HbA1c, insulin resistance, lipids, and liver enzymes.

EXHIBIT 89

HRS-9531 Drove Dose-dependent Reductions in Weight & Waist Circumference



HRS-9531 showed a clean safety profile with GI AEs most common. SAEs came in at 0-3.9% vs. 6.1% placebo), and only 2 AEs led to dropout (vs. n=1 placebo). Most common GI AEs were nausea (14.3-32.7% vs. 8.2% placebo), diarrhea (10.2-33.3% vs. 8.2% placebo), vomiting (6.1-28.6% vs. 2.0% placebo), abdominal distension (2.0-17.6% vs. 0% placebo), eructation (0-8.2% vs. 0% placebo), dyspepsia (0-7.8% vs. 0% placebo), and abdominal pain (0-6.0% vs. 0% placebo).

Juvena Therapeutics, Inc. (Private): (Page 1 of 2)

Juvena Therapeutics is a clinical-stage biotech company leveraging its AI-enabled platform to advance tissue-restorative biologics to tackle chronic muscle and metabolic diseases. Juvena's obesity candidate, JUV-112, is based on a novel secreted protein with an orthogonal, non-appetite-suppressing MoA (non-GLP-1/GIP mediated) for improved fat metabolism, including insulin sensitivity and adipose regulation. It was discovered using Juvena's platform, JuvNET, a fully integrated, end-to-end platform which combines AI, quantitative proteomics, high content imaging, and multi-omics to map stem cell-secreted proteins to specific disease phenotypes, followed by translating them into engineered biologics for specific diseases. JUV-112 is currently in lead optimization with IND-enabling studies anticipated in 2025. In addition to JUV-112, its lead asset is JUV-161, a muscle-regenerating biologic entering Phase I in 2H24. Juvena is also identifying muscle pro-metabolic and hypertrophic secreted proteins for obesity in its M11 program.

What differentiates Juvena's approach to tackling obesity? Juvena's non-protonophore biologic, JUV-112, works to promote lipolysis by altering lipid droplet surface proteins to induce triglyceride metabolism and drive fat-specific weight loss. It has pronounced effects in attenuating fatty liver and fibrosis. This mechanism is non-appetite suppressing, muscle sparing, and muscle force preserving. JUV-112 also provides significant metabolic benefits to glucose metabolism and insulin tolerance, equivalent to that of GLP-1/GIP receptor agonists like tirzepatide. JUV-112 fits into the obesity space as a monotherapy for subpopulations in early stages of obesity progression, those that are genetically predisposed to metabolic dysregulation without extensive subcutaneous fat accumulation, or who have reached a

EXHIBIT 90
Juvena's Pipeline

	Stage of Development				
Indication	**Program**	**Discov.**	**Preclin.**	**Phase I**	**Phase II**
Myotonic Dystrophy Type 1	JUV-161				
Obesity	JUV-112				
Obesity	M11				

maintenance phase of treatment, seeking to avoid further side effects following GLP-1/GIP agonist therapies. JUV-112 also has potential for use in combination with incretin-based therapies.

Summary of preclinical data. In diet-induced obesity mice (DIO), JUV-112 treatment induces weight loss by the second week, reaching over 11% BW loss ($p<0.0001$) and over 15% fat mass loss compared to vehicle by week 4 ($p<0.0001$; **Exhibit 91**). Further, JUV-112 was shown to maintain muscle force (~1048 mN vs. ~1038 mN vehicle) and food intake (~11.7 mg vs. ~11.4 mg vehicle) in contrast with tirzepatide that showed sig worsened muscle force (~909 mN vs. ~1038 mN vehicle; $p<0.001$) and food intake (~8.3 mg vs. ~11.4 mg vehicle; $p<0.01$), supporting JUV-112's differentiated effects (**Exhibit 91**). Of note, Juvena detailed that improvements in body composition and metabolic regulation are achieved and sustained despite caloric intake (60% high-fat diet), with biomarkers in fat pads supporting enhanced lipophagy and activation of AMPKa. Accordingly, the preclinical data supports JUV-112's

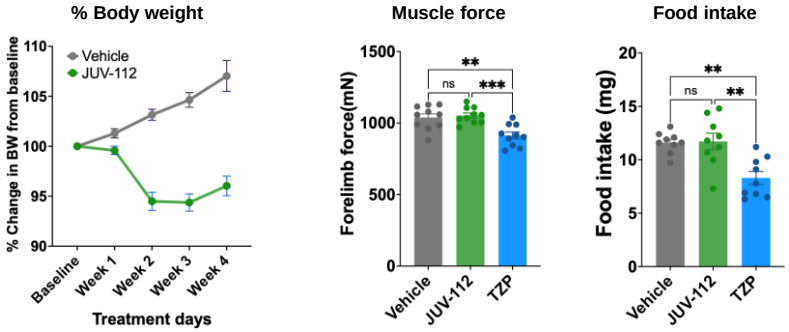
Source: Juvena Therapeutics. Company Materials. Piper Sandler Research.

Juvena Therapeutics, Inc. (Private): (Page 2 of 2)

differentiated profile through weight loss driven by a factor other than decreased food intake. Additionally, given that JUV-112 drives reduction in intramuscular and intrahepatic fat (>57%) it has also been shown to provide metabolic improvement in glucose metabolism (-42.53% AUC OGTT; p<0.05; **Exhibit 92**) and insulin tolerance (-31.55% AUC). Further, in DIO mice JUV-112 was shown to reduce liver triglyceride levels by -57% (p<0.0001) and reduce fibrosis by -59% (p<0.001), demonstrating its ability to potentially attenuate fatty liver symptomology. Taken together, JUV-112 is a novel obesity target that: (1) drives non-incretin mediated weight loss without appetite suppression and promotes triglyceride breakdown (non-protonophore MoA); (2) promotes adipocyte health through increased lipolysis, decreased fat droplet number, and improved metabolism in DIO mice (detailed above); (3) has an optimized molecular form with distinct structure activity relation (SAR) and optimal dosing regimen for concentration and frequency. Ongoing studies are further validating JUV-112's development in obesity.

EXHIBIT 91

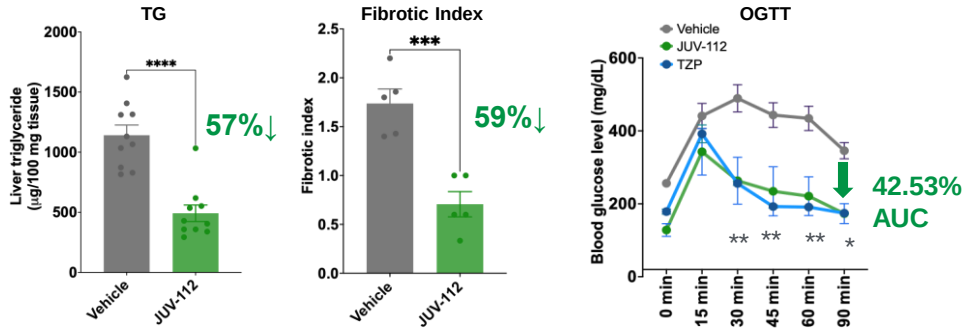
JUV-112 Increases Lipolysis & Spares Muscle Function w/o Affecting Appetite



Source: Juvena Therapeutics. Company Materials. Piper Sandler Research.

EXHIBIT 92

JUV-112 Attenuates Fatty Liver & Fibrosis & Improves Glucose Tolerance



Upcoming catalysts. Juvena has guided IND submission for JUV-112 is expected in 2026. Further, management detailed the FIH SAD/MAD trial is expected to be a double-blind, placebo-controlled, randomized, single-center, parallel study with endpoints of safety/tolerability, PK, PD, immunogenicity, glucose metabolism, target engagement, metabolism/lipolysis, and total energy intake/expenditure. Additionally, Juvena has ongoing preclinical studies expanding PoC related to metabolic cage at thermoneutrality, PK/biodistribution, receptor/interactome proteomic profiling, RNAseq of adipocytes/hepatocytes, Seahorse studies in 3T3L1 adipocytes, incretin combination studies, and endocytosis inhibitor studies.

EXHIBIT 93

Upcoming Obesity Catalysts

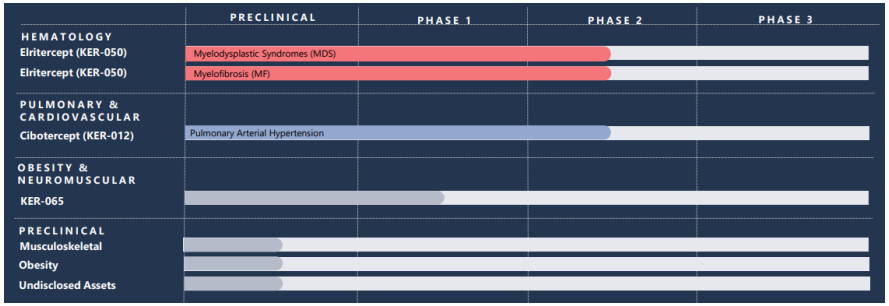
Indication	Drug	Upcoming Catalyst
Obesity/T2D	JUV-112	IND submission in **2026**

Keros Therapeutics (KROS): Catanzaro, OW (Page 1 of 2)

Keros Therapeutics is a clinical-stage company developing differentiated ligand traps that target TGF-β signaling. The company has three clinical-stage assets in its pipeline: (1) Elritercept (KER-050) for the treatment of MDS and MF, (2) Cibotercept (KER-012) for the treatment of PAH, and (3) KER-065 for the treatment of obesity and potentially DMD. KER-065 was designed to bind to and inhibit (i.e., "trap") select TGF-ß ligands, including myostatin and activin A, which are negative regulators of muscle and bone mass. To assess its potential to treat obesity, the asset is currently being evaluated in a Phase I healthy volunteer (HV) trial to determine its safety profile and explore its effects on skeletal muscle, fat, and bone health. While the first clinical data will not be readout until 1Q25, preclinical data support the effectiveness of KER-065 in combination with GLP-1R agonists to synergistically decrease fat mass and favorably increase lean mass. We believe KER-065's design is thoroughly differentiated from competitor molecules based on its ability to inhibit TGF-β ligands most relevant to muscle preservation and fat loss, while sparing inhibition of less-relevant targets that could diminish tolerability and safety.

EXHIBIT 94

KROS's Pipeline



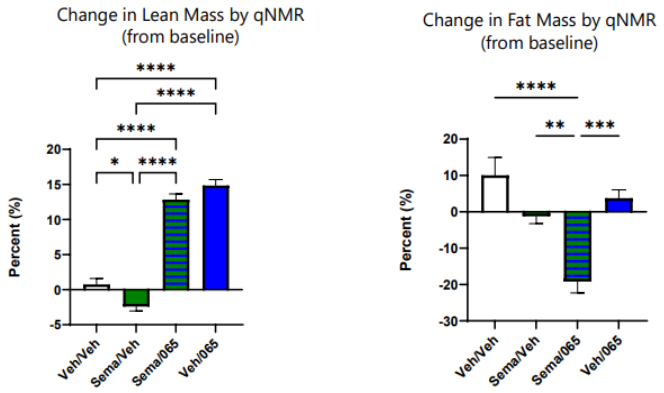
Source: Keros Therapeutics Company Materials. Piper Sandler Research.

How is KER-065 differentiated? GLP-1 agonists, such as semaglutide, are known to cause reductions in both fat and lean (i.e., muscle) mass. KER-065 is part of a differentiated class of assets designed to offset muscle loss induced by GLP-1 agonists and synergistically promote fat loss by targeting the TGF-ß pathway. Mechanistically, KER-065 was engineered to "trap" a selective group of TGF-ß ligands that interact with the Activin Type II receptors A and B (ActRIIA/B). Across different tissues, distinct TGF-ß ligands are expressed and regulated to drive downstream signaling important for diverse functions, including inhibition of muscle repair. Compared to other investigational therapies that inhibit the TGF-ß pathway, we believe KER-065 targets the most-relevant TGF-ß ligands to drive the most impact on lean muscle preservation and fat loss while sparing less relevant targets, which may improve the AE profile. Specifically, KER-065 selectively targets activin A, activin B, myostatin (GDF-8), and BMP-11 (GDF-11). This PD profile may be an improvement over activin A-specific inhibitors, and myostatin-specific inhibitors that target a single ligand and therefore may lack the breadth necessary to sufficiently inhibit ActRII downstream signaling to maximally impact muscle/fat regulation. Moreover, broad ActRIIA/B inhibitors, such as bimagrumab, directly target the ActRIIA/B receptor, interfering with the function of all TGF-ß ligands across off-target tissues, such as the GI tract, which relies on BMP9 signaling for homeostasis. The impact of ActRIIA/B receptor inhibition by bimagrumab potentially explains why a Phase IIa study evaluating bimagrumab reported that 41% of treated subjects experienced diarrhea and muscle spasms, the most common reported AEs. Importantly, KER-065 is 400x less potent against BMP-9, suggesting that KER-065 may have a more favorable safety profile due to its ideal target profile.

Keros Therapeutics (KROS): Catanzaro, OW (Page 2 of 2)

EXHIBIT 95

KER-065 Preserves Lean Mass & Increases Fat Loss in Combo With GLP-1 Agonist



Summary of preclinical data. KROS recently shared preclinical data demonstrating that KER-065 enhances fat loss and preserves lean mass in obese mice when combined with semaglutide treatment compared to semaglutide alone. For two weeks, obese mice were treated with KER-065 (10 mg/kg twice weekly) or semaglutide (0.082 mg/kg twice weekly) either as monotherapy or in combination. As shown in **Exhibit 95**, KER-065 significantly enhanced lean mass and slowed fat mass gains as compared to untreated (vehicle) obese mice, which continued to gain weight and fat mass. In contrast, semaglutide treatment decreased lean mass. Moreover, the combination of semaglutide and KER-065 favorably increased lean mass and synergistically decreased fat mass. These data support KER-065's proposed differentiation and potential synergy with GLP-1 agonists in obese patients.

Source: Keros Therapeutics Company Materials. Piper Sandler Research.

KER-065 Phase I HV readout is expected in 1Q25. The randomized, double-blind Phase I study will enroll ~44 healthy males (ages 18-55) across both SAD and MAD cohorts. The primary objectives are to evaluate KER-065's safety, tolerability, and PK, and the PD effect on muscle, bone, adipose tissue, cardiac tissue, and fibrosis will be explored. In the SAD portion, participants are given a single SC dose of KER-065 at 1-3 mg/kg or placebo with 4 weeks of treatment follow-up and 4 weeks of additional safety follow up. In the MAD portion, participants are given three SC doses 28 days apart at one of three dose levels or placebo. The treatment period is 12 weeks, with an additional 4 weeks of safety follow up. The MAD portion will enroll patients who are overweight/obese to evaluate KER-065's effect on lean mass, fat mass and bone mineral density, plus additional exploratory biomarkers. As of June 2024, the third dose cohort (5 mg/kg) in the SAD portion was initiated, and the first MAD cohort (2 mg/kg Q4W) had begun dosing. Following these data, KROS expects to initiate a PoC Phase II trial in obesity and sees opportunity to explore KER-065 as both a monotherapy and in combination with GLP-1R agonists.

EXHIBIT 96

Upcoming Catalysts

Indication	Drug	Upcoming Catalysts
Obesity	**KER-065**	Announce data from Phase I healthy volunteer trial in **1Q25**
MDS	**KER-050**	Announce additional data from Part 2 of Phase II in **4Q24**
MF	**KER-050**	Announce additional data from Phase II in **4Q24**
PAH	**KER-012**	Topline data from Phase II TROPOS trial in **2Q25**

Lexicon Pharmaceuticals (LXRX): Rahimi, OW (Page 1 of 2)

Digging into Lexicon's LX9851, a novel MoA/formulation for obesity/weight management. LXRX is developing LX9851 as an oral Acyl CoA Synthetase 5 (ACSL5) inhibitor for chronic weight management. LXRX identified ACSL5 as a compelling target in metabolic disease, which is highly expressed in the GI (jejunum) and liver and acts as the first step in the lipid biochemical cascade. Specifically, ACSL5 inhibition redirects free fatty acids to the intestine, which activates the ileal brake mechanism leading to satiety and improvement across metabolic parameters without initiating hepatic steatosis. As a result, through potent and highly selective ACSL5 inhibition, there is potential for a small molecule to reduce weight, improve body composition (reduce body fat without affecting lean mass), lower cholesterol and triglycerides, improve insulin sensitivity, improve metabolism, and reduce liver fat.

EXHIBIT 97
LXRX's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Heart Failure	INPEFA® (Sotagliflozin)				Approved
Type 1 Diabetes	ZYNQUISTA™ (Sotagliflozin)				Resubmitted
HCM	Sotagliflozin				
Diabetic Peripheral Neuropathic Pain (DPNP)	LX9211				
Obesity/weight management	LX9851				

Source: Lexicon Pharmaceuticals Company Materials. Piper Sandler Research.

This could allow LX9851 to address key indications such as chronic weight management, metabolic syndrome, and MASH. Currently, LXRX is conducting IND enabling studies with LX9851, with the intent to complete and file by mid-2025 and directly launch into a PoC PhI study (mid-2025).

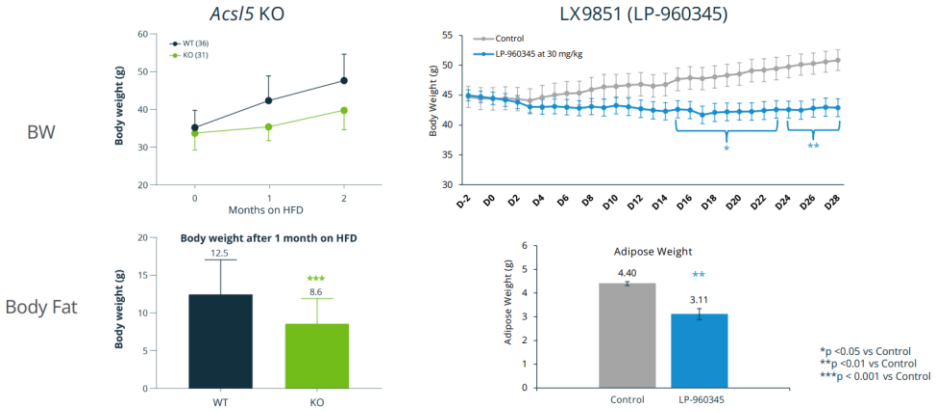
How does it differ from incretins? Firstly, to LXRX's knowledge, no other company has worked on this MoA yet as a promising target in obesity. Thus, as a novel MoA in the space, LX9851 is differentiated vs. the incretin class. Importantly, LXRX has described that this compound has opportunities beyond initial weight loss with a GLP-1 agonist, including sparing lean body mass during weight loss, an overall improved metabolic profile (cholesterol and triglyceride reduction, improved insulin sensitivity), and potential to expand into related indications such as metabolic syndrome and MASH. Furthermore, LXRX's preclinical work has shown that there is incremental benefit of LX9851 on top of GLP-1s as well as unique observations such as change in choice of foods (i.e., a healthy, low fat diet). Taken together, considering that in the real world there are many patients that don't tolerate or don't achieve maximal weight loss with a GLP-1 agent, LXRX's compound could offer a unique position to be additive/complementary to, or take the place of, an incretin.

Summary of preclinical data. Thus far, LXRX has tested LX9851 in a ACSL5 KO mouse model, which has been shown to have substantially less body fat with no difference in lean body mass while on a high fat diet (suggesting that this MoA has the potential for differentiated preservation of lean mass). When LXRX treated these mice with LX9851, they showed similar decreases in body weight and body fat when fed a high fat diet (HFD) (**Exhibit 98**).

Lexicon Pharmaceuticals (LXRX): Rahimi, OW (Page 2 of 2)

EXHIBIT 98

ACSL5 KO Mice & WT Show Similar Decreases in Body Weight & Fat on HFD with LX9851



There were stat sig differences from Days 15 to 23 ($p<0.05$) and Days 24 to 28 ($p<0.01$) in body weight change vs. control, and body fat composition in the KO group was significantly lower ($p<0.001$) after 1 month on High Fat Diet (HFD) vs. WT. Moreover, adipose weight was significantly lower ($p<0.01$) at 3.11 g with LX9851 vs 4.40 g in control. KO mice that were switched from chow to a HFD and HFD-fed WT mice treated with LX9851 showed a decrease in food consumption over the 28 day span. Specifically, the food consumption AUC was 79.01 in control vs. 62.76 in LX9851-treated mice ($p<0.001$). Lastly, inhibiting ACSL5 influences preference for low fat diet (LFD) over HFD, where interestingly, WT mice that received ACSL5 inhibitors preferred a LFD over a HFD. Treatment with LX9851 also delayed gastric emptying, improved glucose tolerance with less insulin, lowered cholesterol and triglycerides, and decreased liver fat after 5 months on 45% HFD.

Source: Lexicon Pharmaceuticals Company Materials. Piper Sandler Research.

Combination with semaglutide demonstrates greater weight reduction.

Importantly, combination of LX9851 and semaglutide showed greater weight reduction in HFD-fed DIO mice that was stat sig out to Day 30 ($p<0.001$). After semaglutide was discontinued after Day 14, LX9851 helped to maintain weight loss in HFD-fed DIO mice after the initial weight loss (**Exhibit 99**). In addition, combination of LX9851 and semaglutide further reduced food consumption in HFD-fed DIO mice vs control and either compound alone ($p<0.01$). LX9851 is undergoing IND enabling studies with filing and PhI PoC study start in 2025.

EXHIBIT 99

LX9851 Sustains Weight Loss After Semaglutide Discontinuation

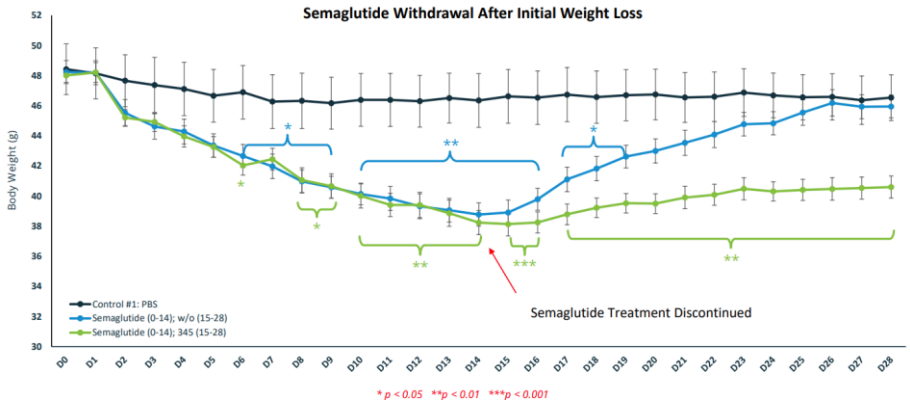


EXHIBIT 100

Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obesity/Metabolic Disease	**LX9851**	IND filing and PhI study in **2025**

MBX Biosciences, Inc. (Private)

MBX Biosciences is a clinical-stage biopharmaceutical company developing Precision Endocrine Peptide (PEP) therapies for endocrine and metabolic disorders. MBX is utilizing its expertise in peptide discovery and development to overcome SoC limitations and reduce the severity of endocrine and metabolic diseases. In obesity, MBX is developing MBX 4291 (most advanced candidate) as a potential long-acting GLP-1/GIP receptor co-agonist that: (1) helps patients lose weight and improve overall health; (2) simplifies dosing scheme; (3) minimizes frequency of administration; and (4) improves GI tolerability. MBX has multiple other programs in lead optimization for obesity and co-morbidities, with undisclosed targets.

MBX 4291 is in IND-enabling studies. MBX 4291 is currently being assessed in IND-enabling studies for the treatment of obesity, with IND filing expected in 2Q25. MBX plans to develop MBX 4291 as a differentiated, long-acting GLP-1/GIP co agonist that minimizes GI side effects, while optimizing weight loss and improving overall patient health.

EXHIBIT 101

MBX Biosciences' Pipeline

	Stage of Development				
Indication	**Program**	**Lead Optim.**	**Preclin.**	**Phase I**	**Phase II**
Hypoparathyroidism	MBX 2109				
Post-Bariatric Hypoglycemia	MBX 1416				
Obesity	MBX 4291				
Obesity/ Co-Morbidities	Undisclosed				

Source: MBX Biosciences. Company Materials. Piper Sandler Research.

How is MBX's technology differentiated from currently-approved incretins? While MBX Biosciences is developing an incretin therapeutic with MBX 4291 (GLP-1/GIP), it is differentiated from current incretins through the use of PEPs. PEPs are specifically designed to have optimal pharmaceutical properties: (1) advanced chemical modifications to promote stability/solubility, increased potency, and multiple MoAs in a single peptide; (2) programmable pro-drug, designed to time chemical conversion to active drug, reducing peak-to-trough ratios; and (3) fatty acylation to provide increased duration of action (simplified dosing) and compatibility with non-injectable formulations. With this, MBX is developing PEPs with potential meaningful benefits of extended half-life, consistent drug delivery and exposure to target tissue, and less-frequent dosing. Importantly, mgmt highlighted MBX 4291 will support monthly dosing in humans due to the prodrug design and clinically-validated platform with MBX 2109. MBX reiterated QW dosing during the titration period leads to drug accumulation in prodrug PK, effectively flattening the curve and potentially leading to greater GI tolerability and higher dosing. Taken together, mgmt emphasized MBX 4291 will likely drive greater compliance via distinct formulation, cleaner safety, and higher dosing, with IND filing expected in 2Q25. For its lead optimization assets, MBX expects to have multiple opportunities to potentially select a second obesity candidate.

Next steps. MBX has guided IND-enabling studies for MBX 4291 are ongoing, with IND filing in 2Q25. MBX is also working on lead optimization for multiple programs across obesity and co-morbidities, and is running a 12-week PhII (NCT06465108) for MBX 2109 (PTH replacement therapy) in 48 patients with hypoparathyroidism, and an up to 45-day PhI (NCT06036784) for MBX 1416 in 84 HVs.

MeiraGTx Holdings plc (MGTX): Raymond, OW (Page 1 of 2)

MeiraGTx is a clinical-stage biotech with end-to-end capabilities in gene therapy. The company boasts a clinical gene therapy pipeline spanning genetic disorders of the salivary gland, neurodegenerative and ocular diseases, as well as 2 commercial-scale GMP facilities for gene therapy manufacturing. MeiraGTx also utilizes its next generation vector optimization capabilities and a novel synthetic riboswitch program to foster a new generation of genetic medicines. The company's wholly owned lead asset is AAV-AQP1, a gene therapy for xerostomia and Sjögren's syndrome, currently in a pivotal Phase II study. MeiraGTx is also partnered with **JNJ (not covered)** on botaretigene sparoparvovec (BotaVec), a gene therapy for X-linked retinitis pigmentosa (pivotal data expected YE24). The company is working on two approaches to obesity: BDNF-MC4R, a gene therapy for genetically-derived obesity, and GLP-1/GIP/myokine riboswitch combinations as a possible new approach to tackling obesity. For this report, we will focus on the latter program.

EXHIBIT 102

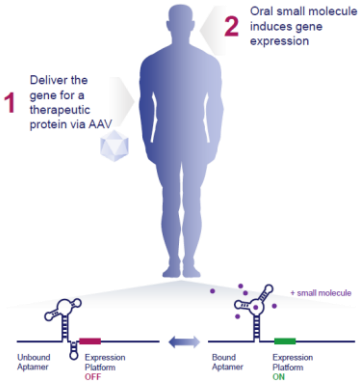
MeiraGTx's Pipeline

Product	Indication	Discovery / Preclinical	Phase 1/2	Phase 2	Phase 3
Salivary Gland					
AAV-AQP1	Xerostomia	Orphan Drug		Pivotal	
	Sjögren's Syndrome				
Neurodegenerative Disease					
AAV-GAD	Parkinson's Disease				
AAV-UPF1	ALS				
BDNF for Genetic Obesity – MC4R					
BDNF- MC4R	Metabolic				
Riboswitch Inducible Expression Programs					
GLP-1-GIP Myokine combinations	Metabolic				
Ribo-CAR-T	Oncology				
Other prevalent indications	Undisclosed				
X-Linked RP					
Botaretigene sparoparvovec[1]	X-linked RP	PRIME, Fast Track, Orphan Drug			
Inherited Retinal Diseases					
AAV-RPE65	RPE65-Associated Retinal Dystrophy	RPDD, Orphan Drug			
AAV-CNGB3	Achromatopsia	RPDD, PRIME, Fast Track, Orphan Drug			
AAV-CNGA3	Achromatopsia	RPDD, Fast Track, Orphan Drug			
AAV-AIPL1	LCA4	Compassionate use under MHRA Specials License			
A007, A008	RDH12, Stargardt, KCNV2, GUCY2D				
Degenerative Ocular Diseases (non-inherited)					
	Wet & Dry AMD, Glaucoma, Uveitis				

Source: MeiraGTx Company Materials. Piper Sandler Research.

EXHIBIT 103

Description of Riboswitch-powered Gene Therapy



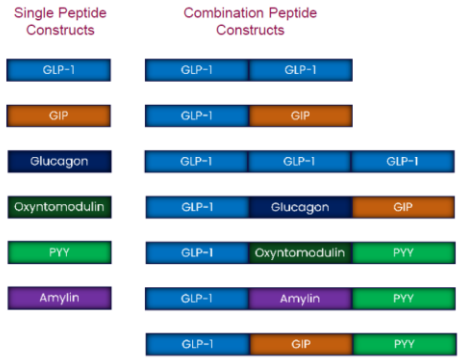
Transcriptional regulators and riboswitch technology for superior gene regulation. The gene therapy field is limited by the safety and efficacy risks of lacking control over the timing, location, and level of gene expression from a gene therapy cassette. MeiraGTx's multiple innovations seek address this problem. First, it has developed a series of transcriptional regulators, including promoters and enhancers, to allow spatial control over gene expression (enabling tissue specificity) and to control expression levels. The company has also adapted mammalian riboswitches into the gene therapy construct to provide promoter-independent, orally-inducible control over gene expression. These riboswitches stay in the off-state preventing gene expression unless activated by a small molecule, which can be tunable and dose-dependent. Pairing superior transcriptional regulation with the tunability of riboswitches has enabled MeiraGTx to apply a gene therapy approach to new indications which have not been targeted with genetic medicine before.

MeiraGTx Holdings plc (MGTX): Raymond, OW (Page 2 of 2)

Riboswitch technology opens up opportunity for an obesity gene therapy. Currently-marketed anti-obesity products and those in development largely work by delivering medicines which mimic natural gut peptides, like GLP-1, GIP, and glucagon. A gene therapy approach would obviate the need for continual dosing and could provide durable weight loss results while utilizing the natural form of the peptide instead of the synthetic approaches used today. However, gut peptides have been difficult to express via gene therapy, and tight control over gene expression is needed to maximize activity and ensure safety. MeiraGTx's riboswitch platform has allowed it to achieve strong, tightly-controlled expression of natural gut peptides preclinically, alone or in combination. In one preclinical experiment with DIO mice, mice treated with a GLP-1/GIP-expressing riboswitch gene therapy + inducer achieved improved glucose tolerance over control mice and mice receiving the gene therapy but no inducer (**Exhibit 105**, above right).

EXHIBIT 104

Possible Constructs For Cardiometabolic Gene Therapy



Source: MeiraGTx Company Materials. Piper Sandler Research.

EXHIBIT 105

Improved Glucose Tolerance in Gene Therapy-treated DIO Mice

Steady preclinical progress. So far, MeiraGTx's obesity gene therapy program is in early preclinical stages, and it is unclear when a development candidate might reach the clinic. However, the company notes that it has successfully delivered multiple combinations of gut peptides, including incretins as well as novel myokine and adipokine peptides that drive muscle metabolism and fat storage, which could enable multiple MoAs in one therapy. The riboswitch platform enables daily dosing of the oral inducer to drive peptide production at physiologically-relevant levels and timing. Importantly, MeiraGTx and **Sanofi (SNY, not covered)** entered into a strategic investment agreement where Sanofi has a right of first negotiation for obesity gene therapy candidates, as well as other riboswitch programs.

NodThera Ltd. (Private): (Page 1 of 2)

NodThera is a clinical-stage biotech company developing brain-penetrant NLRP3 inflammasome inhibitors to treat chronic inflammatory diseases. NodThera is focused on unlocking the potential of NLRP3 inflammasome inhibition to deliver medicines to patients suffering from chronic inflammatory diseases with clear unmet need. Its lead molecule, NT-0796 (NLRP3 inflammasome inhibitor), is designed to directly target specific immune cells that drive inflammatory disease, with potential applications in peripheral and neuroinflammatory diseases.

NT-0796 is in Phase II development in obesity. NodThera recently completed the 28-day PhIb/IIa (NCT06129409) assessing BID oral NT-0796 in 67 obese patients at risk of CVD, with primary endpoint of change in hsCRP levels and secondary measures of change in BW and body composition. Preparations are underway for a PhII study in obesity and other PhII studies across cardiometabolic diseases and Parkinson's disease.

EXHIBIT 106

NodThera's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Parkinson's Disease/Obesity	NT-0796				
Inflammatory Disease	NT-0249				
Neuroinflammatory Disease	NT-0150				
Undefined	Additional Candidates				

Source: NodThera Company Materials. Piper Sandler Research.

How is NT-0796 differentiated from incretins? NT-0796 is a novel chemotype specifically designed as an orally-available, brain-penetrant NLRP3 inhibitor optimized for potency, tissue distribution, and brain parenchyma penetration. Recall, the NLRP3 inflammasome is an upstream activator of IL-1β and IL-18, and is a validated therapeutic target for chronic inflammatory diseases. NodThera designs small molecules with the potential to penetrate multiple tissue types and cross the blood-brain barrier. NT-0796 is a small molecule optimized to prevent activation of NLRP3 and inflammasome assembly, minimizing the immune response and directly addressing conditions driven by IL-1β and IL-18 and other danger signals induced by pyroptosis (HMGB1). Management detailed NT-0796 aims to alleviate hypothalamus-driven inflammation and normalize metabolic function in obesity. It was also noted that NT-0796 is being assessed in combination with GLP-1 (preclinical), with an additive effect driving either: (1) reduction in GLP-1 agonist dose; or (2) potential switch therapy if a patient wants to transition from GLP-1.

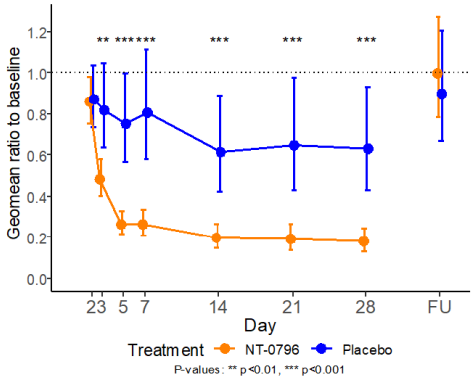
Summary of clinical data. NodThera recently announced NT-0796 met the primary endpoint of inflammation reversal (change in hsCRP levels) in the 28-day PhIb/IIa trial in obese subjects with CV risk (see our note). At topline, NodThera detailed the trial enrolled obese patients with elevated baseline C-reactive protein (CRP; sig marker of chronic inflammatory disease) and 1+ CV risk factors (ex. metabolic syndrome, prediabetes, diabetes, hyperlipidemia, or hypertension). A highly stat sig and rapid CRP reduction was observed vs. placebo ($p<0.001$ Day 5-28; **Exhibit 107**). >75% of patients treated with NT-0796 achieved a CRP reduction to ≤2 mg/L (meaningful threshold to reduce CV risk) vs. <25% of placebo patients on Day 28. Additionally, NT-0796 reduced pro-inflammatory and cardiometabolic biomarkers further

NodThera Ltd. (Private): (Page 2 of 2)

supporting the NLRP3 inhibitor MoA in obesity. Regarding weight loss, all subjects lost weight due to calorie restriction incorporated into the protocol (2000 kCal/day), with high-risk subgroups treated with NT-0796 experiencing more pronounced placebo-adjusted weight loss. NT-0796 was also shown to be relatively safe and well-tolerated in obese patients. Specifically, most AEs were mild and transient with no observed SAEs. The PhIb/IIa data aligned with positive PhI data where NT-0796 demonstrated blood-brain barrier penetration and clear reduction of inflammatory biomarkers (ex. CRP). Management believes the recent PhIb/IIa obesity readout in tandem with the PhI data continues to support NT-0796 development in obesity, with clear potential for additional longer-term reductions in weight.

EXHIBIT 107

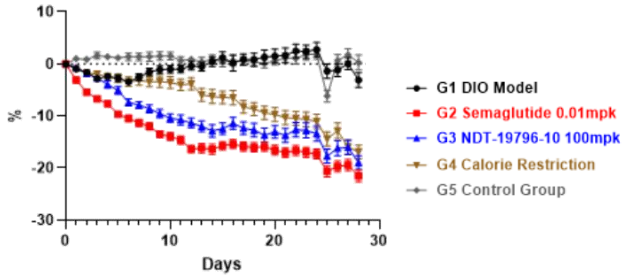
NT-0796 Reduced CRP in Inflamed Obese Patients



Summary of NT-0796 preclinical obesity data. NodThera published preclinical data that showed NT-0796 induced comparable weight loss to semaglutide (note). Specifically, hCES1 DIO mice were treated with oral NT-0796 and achieved -19.0% weight loss in 28-days ($p<0.01$), compared to semaglutide-treated DIO mice that showed -21.5% weight loss ($p<0.01$) (vs. -16.9% in caloric restricted group; **Exhibit 108**). Additionally, the preclinical study showed body fat reductions of -31.8% with NT-0796 and -37.8% with semaglutide across perirenal, inguinal, and epididymal fat mass.

EXHIBIT 108

NT-0796 Decreased Body Weight in Obese Mice



Upcoming catalysts. Given its positive NT-0796 PhIb/IIa trial in obese patients, NodThera noted it plans to present more data at a scientific conference and in a publication in 1H25. Further, the company guided that preparations are underway for a PhII obesity trial, and additional PhII trials in cardiometabolic diseases and PD.

EXHIBIT 109

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**NT-0796**	PhIIb monotherapy initiation in **1H25**
Obesity	**NT-0796/GLP-1R**	PhIIa combination planning **underway**

Source: NodThera Company Materials. Thornton et al. *J Pharmacol Exp Ther*. 2024;388:813. Piper Sandler Research.

OrsoBio (Private): (Page 1 of 2)

OrsoBio's portfolio of molecules are designed to restore energy homeostasis. OrsoBio is a clinical-stage biopharmaceutical company developing therapeutics focused on targeting fundamental pathways of energy metabolism in high prevalence metabolic disorders where there is clear path to approval, such as diabetes, severe dyslipidemia, obesity, and MASH. OrsoBio has a portfolio of >400 molecules, and is currently developing TLC-6740, a potent liver-targeted mitochondrial protonophore, with potential to address T2D, obesity, and MASH. OrsoBio believes its approach of developing first-in-class compounds to modulate energy expenditure has not only potential for monotherapies, but may also be suited to combo therapies that include GLP-1s, given the complementary MoAs.

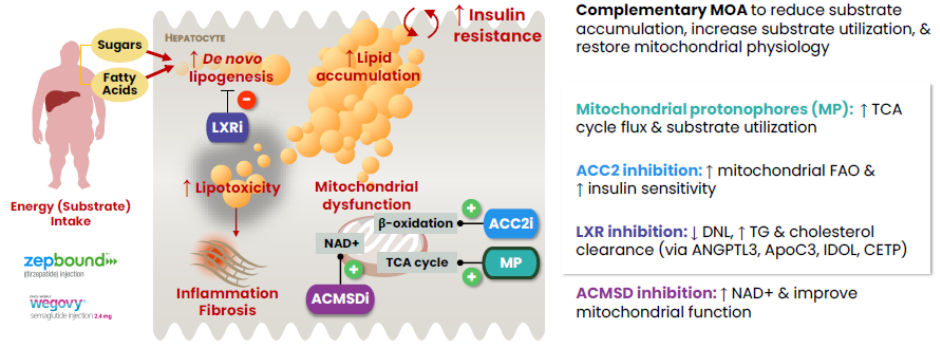
EXHIBIT 110
OrsoBio's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
T2D	TLC-3595 (ACC2i)				
MASH	TLC-2716 (LXR inverse agonist)				
T2D/Obesity	TLC-6740 (mitochondrial protonophore)				
Obesity	TLC-1235 (mitochondrial protonophore)				
Organ Failure	ACSMDi				

Source: OrsoBio Company Materials, Piper Sandler Research.

How does the approach differ from incretins? Considering different categories of treatments for obesity, while incretins reduce oral intake of food and total calorie consumption, OrsoBio is taking a liver-targeted approach with TLC-6740 to increase energy expenditure. Given that patients on incretins have lower energy expenditure over time due to metabolic adaptation, TLC-6740's clinically validated MoA of uncoupling oxidative phosphorylation and ATP synthesis to increase energy expenditure might have utility, given that this could mitigate the effects of physiologic metabolic adaptation. This MoA may also offer other metabolic benefits, such as AMPK activation, DNL inhibition, and increased fatty acid oxidation, along with TCA cycle flux. In particular, TLC-6740 has been developed as a liver-targeted protonophore, which enhances the safety profile of the molecule by reducing excessive systemic uncoupling, while simultaneously maintaining positive metabolic effects and increasing whole body energy expenditure.

EXHIBIT 111
OrsoBio's Therapeutic Assets are Complementary with Existing MoAs



OrsoBio (Private): (Page 2 of 2)

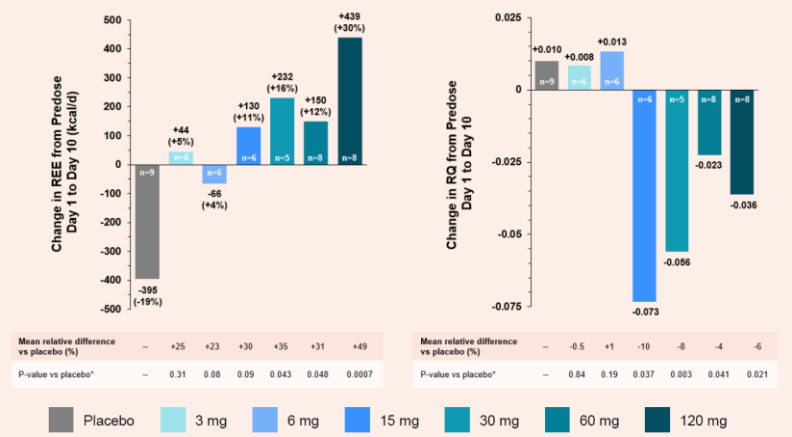
TLC-6740's PhI FIH study is complete. OrsoBio has completed its 10-day Ph1 SAD/MAD (NCT05822544) study in healthy subjects, where the objective was to evaluate the safety, tolerability, PK, and PD effects of single and multiple ascending doses of TLC-6740. We note that the mean half-life ranged from 19-47 hours (SAD) and 18-33 hours (MAD), with no food effect, supporting QD dosing.

TC-6740 leads to dose-dependent, stat sig improvements in energy expenditure and lipids. As shown below in **Exhibit 112**, OrsoBio reported a dose-dependent increase in energy expenditure of up to ~440 kcal/day in the highest dose group (120 mg), whereas in placebo there was mean reduction in energy expenditure of -400 kcal/day. OrsoBio is confident in advancing TLC-6740 into late stage obesity development, where a longer trial duration could reveal meaningful weight loss reductions. When looking at the *quality* of weight loss, OrsoBio also evaluated fuel preference for oxidation based on the respiratory quotient (RQ). Digging into the details, changes in RQ were stat sig across doses 15-120 mg (**Exhibit 112**), which demonstrated a strong preference for fat oxidation while being lean mass neutral. This could be a key differentiator for TLC-6740's product profile, given that weight loss reductions with incretins are typically composed of ~40% lean mass. Lastly, TLC-6740 showed sig dose-dependent reductions in metabolic parameters such as serum total cholesterol (~1.4-17.6% reduction) and LDL-C (~1.5-25.4% reduction), as well as stat sig improvements in glucose and HOMA-IR by Day 10.

Clean safety with high therapeutic margin. With regards to safety, across doses: (1) there were no SAEs; (2) no symptoms of thermogenesis, increases in body temperature, flushing, or palpitations; (3) no GI side effects; and (4) the majority of TEAEs were Grade 1. TLC-6740's clean safety presents an opportunity for OrsoBio to explore even higher dosing and potential efficacy.

EXHIBIT 112

TLC-6740 Results in Dose-Dependent Increases in REE and RQ



Source: OrsoBio Company Materials, Piper Sandler Research.

EXHIBIT 113

Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**TLC-6740**	PhIb topline data in **4Q24**
Obesity/T2D ± GLP1RA	**TLC-6740**	Kick off 12-week PhIIa study in **4Q24**
Obesity ± T2D; maintenance; GLP-1 combos	**TLC-6740**	Complete chronic tox package in **2Q25**, and initiate 24-52-week PhIIb study in **2025**

PegBio Co., Ltd. (Private)

PegBio is a biotech company discovering and developing innovative therapies for chronic diseases (metabolic disorders). PegBio has a diverse pipeline of six product candidates spanning T2D, obesity, metabolic dysfunction-associated steatohepatitis (MASH), opioid-induced constipation (OIC), and congenital hyperinsulinemia. At ADA 2024, PegBio presented data for PB-718 (GLP-1R/GCGR dual agonist), a fixed-dose combination of PB-119 (GLP-1) and PB-722 (GCGR), in subjects with obesity and plans to further develop assets in obesity and MASH.

PB-718 is in Phase Ib/IIa development in obesity. PegBio recently presented topline PB-718 data (see our note) from the up to 18-week PhIb/IIa (NCT06147544) in n=36 obese patients, testing SC QW doses of PB-718 (PB-119/PB-722) at 600/1560 µg, 900/2340 µg or 1600/4160 µg vs. placebo (randomized 3:1, drug:placebo) to assess the primary endpoints of TEAEs. PegBio also ran an up to 11-week PhI SAD/MAD (NCT05021666) trial in 82 healthy patients with primary endpoint of safety.

EXHIBIT 114
PegBio's Metabolic Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity/T2D	Visepegenatide				
Obesity/MASH	PB-718				
Obesity/T2D/MASH	PB-2301				
Obesity/T2D/MASH	PB-2309				

Source: PegBio Company Materials. Piper Sandler Research.

How is PB-718 differentiated from incretins? PB-718 is differentiated from currently-approved incretins as it was developed as a long-acting GLP-1/GCG dual receptor agonist. As such, through dual activation of both the GLP-1 and Glucagon receptors PB-718 is specifically designed to demonstrate synergy that exceeds either MoA alone. Additionally, PB-718 has already shown a consistent safety profile in PhI SAD/MAD and topline from the PhIb/IIa obesity trial.

Summary of clinical data. In the up to 18-week PhIb/IIa trial PB-718 showed: (1) 4-6% dose-dependent weight loss at week 12; (2) decreases across FPG, HbA1c, lipids, insulin levels, and HOMA-IR; (3) significant reductions in LFC and visceral fat, with more fat loss relative to lean mass; (4) decreases in serum uric acid; (5) linear PK parameters (AUC0-last and Cmax) with dose response; and (6) the most common AEs were GI-related and all events were Grade 1 in severity. Together, PB-718 was found to be safe with a predictable PK profile and to produce significant reductions across BW, HbA1c, blood lipids, uric acid, liver fat content, and visceral fat mass.

Upcoming catalysts. Given its positive topline data for the PhIb/IIa trial, PegBio has guided continued development of PB-718 in both obesity and MASH, with initiation of a PhIIb obesity trial in China and a PhII MASH trial in China (pending IND clearance).

EXHIBIT 115
Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**PB-718**	PhIIb initiation following NMPA communication
MASH	**PB-718**	PhII initiation in mid-2024

Regeneron Pharmaceuticals (REGN): Raymond, OW (Page 1 of 2)

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REGN: A diversified pipeline with a franchise of commercial blockbusters. REGN's pipeline targets a broad range of conditions, including retinal diseases, oncology, allergic and inflammatory diseases, neurology, cardiovascular, and metabolic diseases. The cardiometabolic franchise is headlined by marketed products Praluent for lowering LDL-C in CV disease and Evkeeza for HoFH. Investigational medicines include REGN5381 for heart failure, mibavademab for generalized lipodystrophy, and trevogrumab and garetosmab for muscle loss prevention in obesity. REGN also has a collaboration with **Intellia Therapeutics (NTLA, not covered)** on an investigational gene editing therapy NTLA-2001 in ATTR-CM.

EXHIBIT 116

Regeneron's Early-stage Cardiometabolic Pipeline

Phase 1

MOLECULE NAME	THERAPEUTIC AREA(S)	MODALITY	INDICATION	TARGET
REGN13335	Cardiovascular/ Metabolic	Monoclonal antibodies	Healthy volunteers	PDGF-B
REGN5381/ REGN9035	Cardiovascular/ Metabolic	Monoclonal antibodies	Reversal agent in healthy volunteers	NPR1/REGN5381
REGN7544	Cardiovascular/ Metabolic	Monoclonal antibodies	Healthy volunteers	NPR1

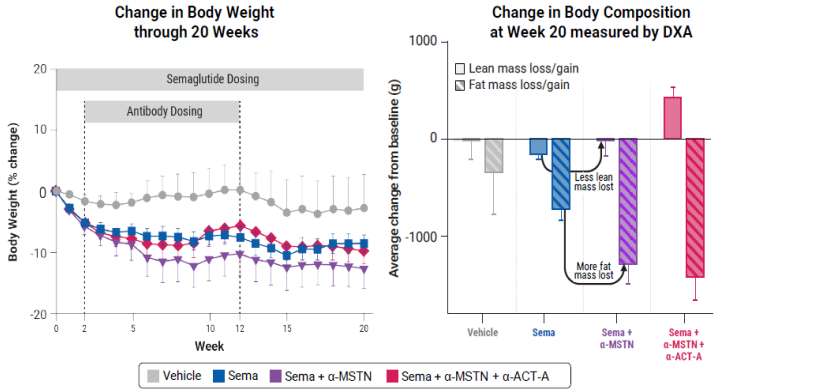
Phase 2

MOLECULE NAME	THERAPEUTIC AREA(S)	MODALITY	INDICATION	TARGET
MIBAVADEMAB	Cardiovascular/ Metabolic, Rare Disease	Monoclonal antibodies	Generalized lipodystrophy	Leptin receptor (LEPR)
ODRONEXTAMAB	Cardiovascular/ Metabolic, Oncology, Hematology	Bispecific antibodies	B-cell non-Hodgkin lymphoma (B-NHL) (pivotal study)	CD20 and CD3
REGN5381	Cardiovascular/ Metabolic	Monoclonal antibodies	Heart failure	NPR1
TREVOGRUMAB (REGN1033)	Cardiovascular/ Metabolic	Monoclonal antibodies	Healthy volunteers	Myostatin (GDF8)

Source: Regeneron Company Materials. Piper Sandler Research.

EXHIBIT 117

Preclinical Data in Non-Human Primates Show Decreased Fat Mass & Increased Lean Mass in Combination With Semaglutide



Trevogrumab and garetosmab for muscle loss prevention. Like other companies, REGN is targeting the myostatin/activin pathway as a means to prevent muscle loss during GLP-1-induced weight loss. Because the risk/benefit of targeting the pathway is still being explored, REGN is giving optionality by assessing two antibodies separately and in combination:

- **Trevogrumab (REGN1033)** is an anti-myostatin antibody originally developed in partnership with **SNY** for inclusion body myositis, myositis ossificans progressiva, and sarcopenia. It targets the mature, active form of myostatin.
- **Garetosmab (REGN2477)** is an anti-activin A antibody that has been assessed in fibrodysplasia ossificans progressive (FOP).

Regeneron Pharmaceuticals (REGN): Raymond, OW (Page 2 of 2)

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Phase I trial showed enhanced fat mass decreases, but no change to overall weight. Based on promising preclinical and early clinical data, REGN assessed the effects of administering trevogrumab alone and in combo with garetosmab on body composition in healthy volunteers (N=48). In this randomized, controlled trial, patients received either single or multiple doses of trevogrumab alone, garetosmab alone, or both in various combinations or placebo (see **Exhibit 118**). The primary endpoint was safety, and key secondary endpoints were changes in thigh muscle volume (TMV) and body composition. In the multiple dose groups, treatment with the combo led to only transient increases in TMV but an enhanced reduction in fat mass versus placebo. The treatment was generally well-tolerated.

Phase II trial will assess enhanced body composition during GLP-1 weight loss. REGN is currently enrolling the COURAGE Phase II trial of trevogrumab ± garetosmab in combination with GLP-1 semaglutide (N=624). In this randomized, double-blind, placebo-controlled study, patients with obesity will receive either semaglutide alone, semaglutide with trevogrumab and garetosmab, or semaglutide with trevogrumab only. In some cohorts, patients will start on semaglutide + placebo and switch to trevogrumab and in other cohorts, patients will start on semaglutide + trevogrumab and then switch to placebo. The primary endpoint is percent weight loss and percent fat mass loss after 26 weeks of treatment. **The current estimated primary completion date is June 2026.**

EXHIBIT 118

Phase I Cohorts

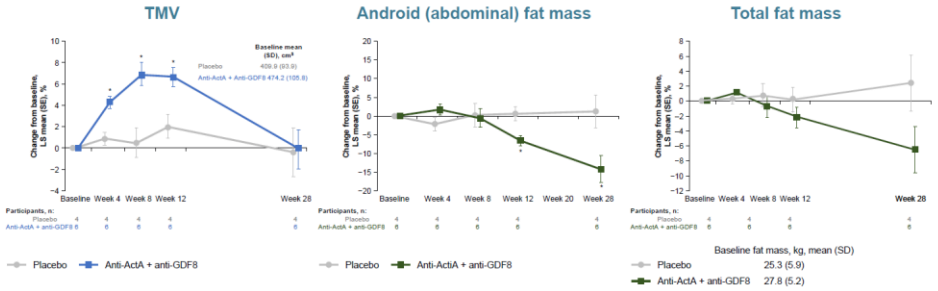
Single dose, females
- Placebo (n=12)
- Anti-activin A 10 mg/kg (n=6)
- Anti-GDF8 6 mg/kg (n=6)
- Anti-GDF8 6 mg/kg + anti-activin A 1 mg/kg (n=6)
- Anti-GDF8 6 mg/kg + anti-activin A 3 mg/kg (n=6)
- Anti-GDF8 6 mg/kg + anti-activin A 10 mg/kg (n=12)

Multiple dose, females
- Placebo Q4W x 4 doses (n=2)
- Anti-activin A 10 mg/kg Q4W x 4 doses (n=6)
- Anti-GDF8 6 mg/kg + anti-activin A 10 mg/kg Q2W x 3 doses (n=6)
- Placebo Q2W x 3 doses (n=4)

Multiple dose, males (safety analysis only)
- Placebo Q4W x 2 doses (n=8)
- Anti-activin A 10 mg/kg Q4W x 2 doses (n=8)

EXHIBIT 119

Phase I Data of Trevogrumab/Garetosmab in Post-Menopausal Women Demonstrating Increase in Muscle Mass

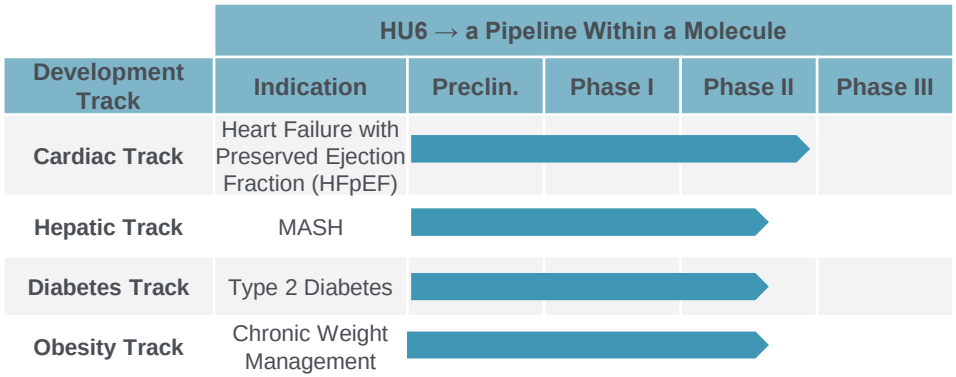


Source: Regeneron Company Materials. Piper Sandler Research.

Rivus Pharmaceuticals (Private): (Page 1 of 2)

Rivus Pharmaceuticals is a clinical-stage company developing a portfolio of oral small molecules designed to reduce excess fat, preserve lean muscle, and drive cardiometabolic benefits. Rivus is pioneering a new group of investigational medicines called **controlled metabolic accelerators (CMAs)**, which can safely and effectively leverage the natural process of mitochondrial uncoupling, activate fat-specific weight loss through reduction in liver, visceral, and subcutaneous fat, improve glycemic control and reduce oxidative stress and inflammation. By increasing the resting metabolic rate, CMAs can drive reduction in fat deposits throughout the body, which has wider implications across metabolic diseases associated with obesity. Rivus' lead program HU6 is an oral small molecule in clinical trials for multiple large market indications. HU6 is differentiated from other uncouplers in development through: (1) Rivus is controlling for over-exposure to uncouplers by having low Cmax and high AUC to mitigate increased body temperature side effects by having sustained release PK and mean CMD (primary metabolite) exposures consistent throughout the day and within a safe therapeutic range; and (2) fully hitting the target to show both oxidation and burning of fat as well as shutdown of reactive oxygen species and free radicals at the cell level to stop the inflammatory cascade.

EXHIBIT 120
Rivus' HU6 Pipeline



Source: Rivus Pharmaceuticals Company Materials. Piper Sandler Research.

PhIIa HuMAIN hit stat sig on the primary endpoint and the MASH M-ACCEL is ongoing. Recall Rivus tested HU6 in PhIIa HuMAIN (n=~65 obesity-related HFpEF patients), to assess the primary endpoint of weight loss and key secondaries of cardiac metabolic improvements. Management provided a bare-boned topline and noted a late-breaker abstract accepted for HFSA (September 27-30). Rivus is also conducting 6-month, two-dose level, PhII M-ACCEL (n=204 MASH patients) with primary endpoint of MRI-PDFF at 6 months. In this trial, Rivus will be looking at significant reductions in liver fat and inflammatory markers, potential to impact insulin resistance, and significant and consistent fat selective weight loss. As we discussed in our recent Obesity Day note (here), data is expected around April 2025 (1H25).

How does the approach differ from incretins? Firstly, recognize that CMAs are working on the opposite side of the energy balance equation compared to incretins (which work on energy intake). CMAs act by raising the resting metabolic rate through natural processes (energy expenditure). In this way, Rivus believes it is able to address the many challenges associated with the incretin class, including weight loss plateauing and rebounding, tolerability, and loss of muscle mass (which decreases a patient's metabolic rate and causes more downstream issues). In addition, when compared to incretin therapies, CMAs have other benefits, such as once-daily oral administration, are well-tolerated (does not reduce GI motility), offer fat-selective weight loss and retained or even enhanced muscle mass strength, increased

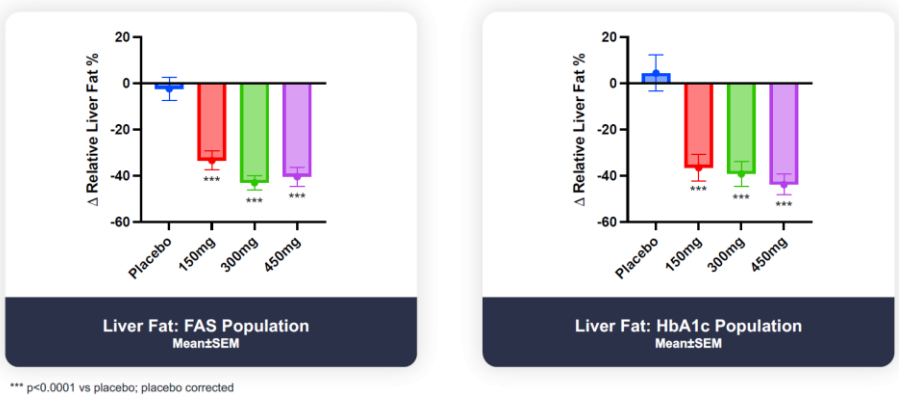
Rivus Pharmaceuticals (Private): (Page 2 of 2)

metabolic rate for sustained weight loss (i.e., no rapid rebound), greater efficacy in patients with insulin resistance, and no increases in heart rate with clean tolerability.

Summary of additional clinical data. Note, Rivus only qualitatively shared that PhIIa HuMAIN hit stat sig on the weight loss primary endpoint and key efficacy secondaries and PD endpoints. That said, recall HU6 was also tested in obese patients with elevated liver fat over an 8-week double-blind treatment period across 3 doses (150 mg, 300 mg, and 450 mg). HU6 produced significant liver fat reduction in both the full analysis set and HbA1c population (stratified by HbA1c > 5.7%). There were stat sig differences (p<0.0001) across all doses tested, and there was also a high responder rate across all doses tested (>30% RR liver fat). In addition, treatment with

EXHIBIT 121

HU6 Causes Significant Liver Fat Reduction

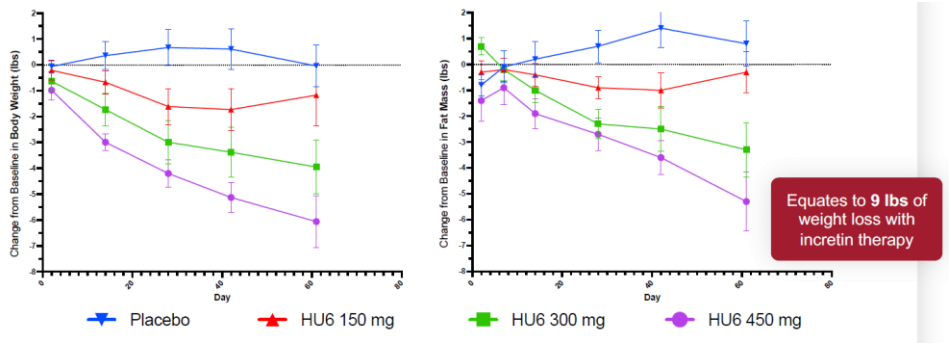


*** p<0.0001 vs placebo; placebo corrected

Source: Rivus Pharmaceuticals Company Materials. Piper Sandler Research.

EXHIBIT 122

HU6 Rapid and Sustained Weight Loss



HU6 showed significant fat-selective weight loss in change from baseline out to day 60 (with no plateauing of the curves), as shown in **Exhibit 122**. No behavioral modification was required, since HU6 preserved lean muscle mass volume and quality. Furthermore, these studies showed that weight and fat loss was amplified with high baseline HbA1c, and body fat loss occurred across all fat compartments (liver, visceral, and SubQ). Lastly, HU6 also showed a clear and significant effect on lowering systemic inflammation, with high levels of reduction in hs-CRP.

EXHIBIT 123

Upcoming Catalysts

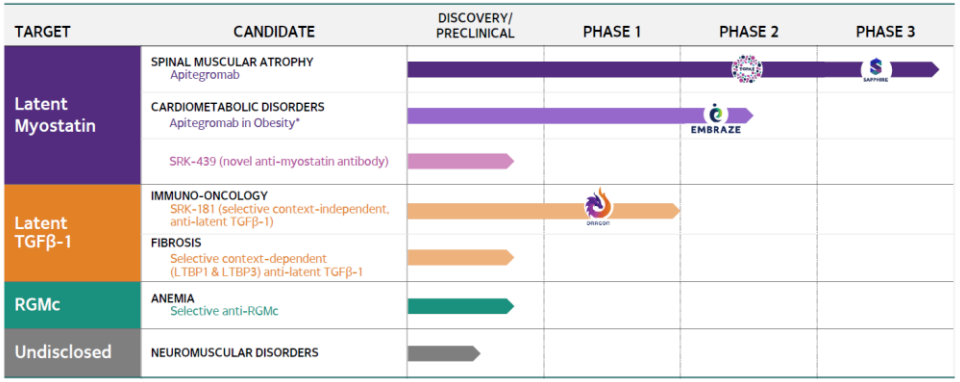
Indication	Drug	Upcoming Catalyst
HFpEF	HU6	Phase IIa HuMAIN data at **HFSA (September 27-30)** Initiate a PhIII in **2025**
MASH	HU6	M-ACCEL Study readout **1H25**

Scholar Rock (SRRK): Bratzel, OW (Page 1 of 2)

Scholar Rock is a clinical-stage company focused on developing targeted inhibitors for growth factors involved in muscular and cardiometabolic disorders and other severe diseases. SRRK specializes on targeting the inactive, latent forms of these growth factors to increase drug specificity and prevent unwanted action in off-target tissues. SRRK's lead candidate is apitegromab, a selective anti-myostatin antibody currently in late-stage development for SMA. On the obesity side, SRRK is running a Phase II PoC trial of apitegromab to show muscle loss prevention during GLP-1-induced weight loss, while at the same time advancing SRK-439, a second generation anti-myostatin antibody with drug properties more suited for treating obesity. Additional programs include anti-TGFβ-1 antibody SRK-181 for immuno-oncology, a preclinical anti-TGFβ-1 antibody for fibrosis, and a preclinical anti-RGMc antibody for anemia.

EXHIBIT 124

Scholar Rock's Pipeline



Source: Scholar Rock Company Materials. Piper Sandler Research.

EXHIBIT 125

Upcoming Catalysts for Apitegromab and SRK-439

Indication	Upcoming Catalyst	Timing
SMA	Initial Phase III SAPPHIRE data	4Q24
	Potential launch in SMA	4Q25
Obesity	Topline data from Phase II EMBRAZE trial with apitegromab + semaglutide	Mid-2025
	IND filing for SRK-439	2025
	Initiate clinical program for SRK-439 *(PSC est.)*	2025

Selective myostatin inhibition for superior weight loss quality. Similar to other companies profiled like **REGN (Raymond, OW)** and **BHVN (Raymond, OW)**, Scholar Rock is targeting the myostatin pathway to improve muscle mass during GLP-1-induced weight loss. However, since targeting this pathway is known to carry safety concerns, Scholar Rock uniquely targets two inactive forms of myostatin, pro- and latent, in an effort to improve safety:

- Targeting pro- and latent myostatin creates maximal selectivity for myostatin over other signaling components, compared to targeting mature myostatin.
- Minimizing interference with other signaling components should preserve normal function outside of myostatin and thus reduce off-target AEs.
- However, this safety benefit may come with a tradeoff, as solely targeting myostatin may lead to lesser efficacy compared to approaches that modulate activin A or target the downstream receptor.

Scholar Rock (SRRK): Bratzel, OW (Page 2 of 2)

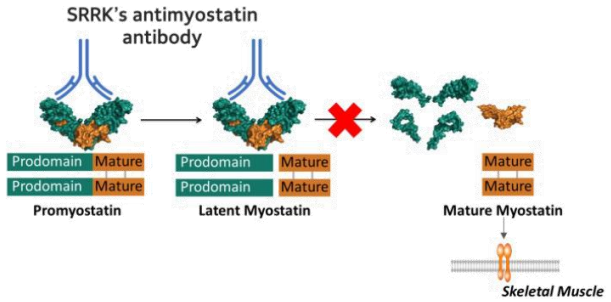
Preclinical data for SRK-439 show promising body composition results.

Scholar Rock is currently advancing apitegromab, its anti-myostatin antibody for SMA, into a Phase II PoC trial in combo with GLP-1 therapy. SRK-439, a similar pro- and latent myostatin-targeting antibody, will be the go-forward asset in obesity (IND clearance expected in 2025). SRK-439 was designed specifically for cardiometabolic indications, and importantly allows for SC dosing. Preclinical data for SRK-439 in DIO mice show:

- In combination with semaglutide, SRK-439 led to approx. -15% reduction in body weight, minimal change in lean mass at the highest dose, and approx. -46% decrease in fat mass.
- In separate experiments, after receiving 4 weeks of semaglutide treatment and then 4 weeks of withdrawal from semaglutide, mice receiving SRK-439 maintained higher relative lean mass and lower relative fat mass than mice receiving placebo.

EXHIBIT 126

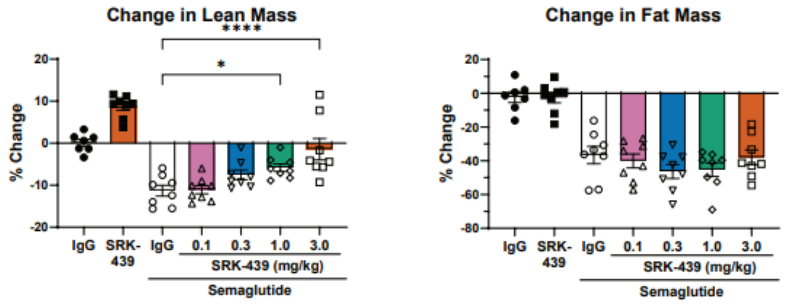
Apitegromab/SRK-439's Mechanism of Action



Source: Scholar Rock Company Materials. Piper Sandler Research.

EXHIBIT 127

Preclinical Lean and Fat Mass Loss With SRK-439 + Semaglutide in DIO Mice



Phase II EMBRAZE trial could provide rapid proof-of-concept. Before SRK-439 reaches the clinic in 2025, Scholar Rock plans on generating compelling PoC data for the selective anti-latent myostatin approach by running the Phase II EMBRAZE trial in obese patients with apitegromab (N=100). The randomized, double-blind, placebo-controlled trial is enrolling patients who are overweight or obese to receive apitegromab Q4W + semaglutide or tirzepatide QW or matching placebo + semaglutide or tirzepatide for 24 weeks. The primary endpoint is change in lean mass at week 24, and key secondary endpoints include additional weight loss measures, safety and tolerability, and PK/PD. **Initial data from the trial are currently expected in mid-2025.** If the trial is successful at showing preservation of lean mass with SK-439, it will also bolster the underlying rationale for targeting the myostatin pathway for lean mass preservation.

Sciwind Biosciences Co., Ltd. (Private): (Page 1 of 2)

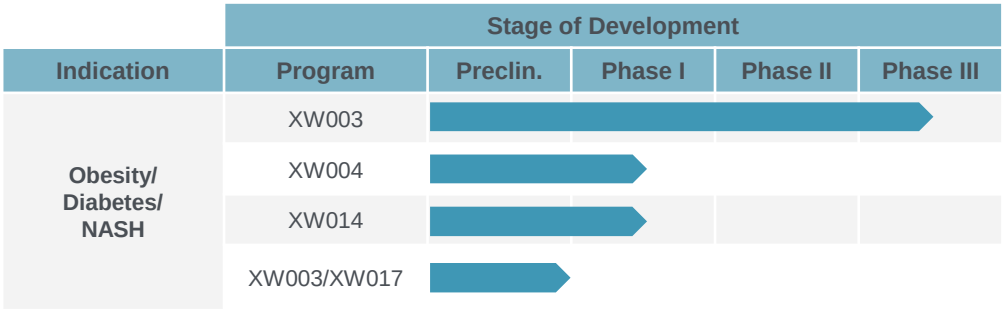
Sciwind Biosciences is a clinical-stage biopharmaceutical company developing novel therapies to treat metabolic diseases. Sciwind aims to develop therapeutics for metabolic conditions including obesity, T2D, non-alcoholic fatty liver disease (NAFLD), and non-alcoholic steatohepatitis (NASH) due to their high prevalence and global morbidity and mortality. Sciwind's development pipeline includes: (1) XW003 (ecnoglutide; SC GLP-1 peptide) in PhIII; (2) XW004 (oral GLP-1 peptide) in PhI; (3) XW014 (oral GLP-1R agonist small molecule) in PhI; and (4) XW003/XW017 (SC GLP-1/GIP peptide).

Ecnoglutide (XW003) is in Phase III development for obesity. Ecnoglutide (SC) is currently being assessed in the 48-week PhIII SLIMMER (NCT05813795) in 664 adults with overweight or obesity and primary endpoint of % change in BW and % of subjects with weight loss ≥5%. Ecnoglutide was shown to be safe and effective in a 26-week PhII (NCT05111912) in 206 obese adults with primary endpoint of % change in BW and an up to 71-day PhI (NCT04389775) trial. Further, at ADA 2024, Sciwind presented data from its placebo-controlled PhI (NCT05184322) assessing XW004 (oral ecnoglutide) in HV and healthy obese patients, with endpoints of safety and % change in BW.

How is ecnoglutide differentiated from incretins? Sciwind is taking a differentiated approach to developing novel incretin therapies via a diversified drug development pipeline. The company is developing both SC and oral peptide GLP-1 therapies (XW003 and XW004), as well as an oral small molecule GLP-1R agonist (XW014), and combination SC peptide GLP-1/GIP (XW003/XW017). SC ecnoglutide (XW003) is a novel, long-lasting GLP-1 peptide analog optimized to improve biological activity, with cost-effective manufacturing and QW dosing. Oral ecnoglutide (XW004) was developed to enable oral bioavailability and the peptide is co-formulated with an oral absorption enhancer to prevent drug deactivation and allow for QD dosing. Sciwind is also developing a small molecule GLP-1R agonist (XW014) to be easy to manufacture and with the potential to be co-formulated with other oral drugs. Lastly, Sciwind is developing XW017 as a novel, long-acting GIP peptide analog optimized for biological activity and with potential for co-formulation with GLP-1 analogs. Taken together, SC ecnoglutide is Sciwind's most advanced asset in development, with the company focused on developing oral and SC drugs across multiple MoAs.

EXHIBIT 128

Sciwind's Obesity Pipeline



Source: Sciwind Biosciences Company Materials. Piper Sandler Research.

Sciwind Biosciences Co., Ltd. (Private): (Page 2 of 2)

Summary of SC ecnoglutide (XW003) clinical data. Sciwind ran a 26-week PhII (NCT05111912) assessing QW SC ecnoglutide (XW003) in 206 obese adults with primary endpoint of % change in BW. At 26-weeks 2.4 mg ecnoglutide showed a -14.7% change in BW (vs. -8.8% liraglutide; p<0.001), 1.8 mg showed a -11.2% change in BW, and 1.2 mg showed a -11.5% change in BW. Additionally, ecnoglutide showed reductions in BMI (-5.1 kg/m^2 2.4 mg vs. -3.1 kg/m^2 liraglutide), waist circumference (-12.7 cm 2.4 mg vs. -4.4 cm liraglutide), and hip circumference (-11.5 cm 2.4 mg vs. -6.3 cm liraglutide). Importantly, weight loss for QW 2.4 mg SC ecnoglutide at 26-weeks (-14.7%) was comparable to 2.4 mg semaglutide at week 28 (~-12%) and 15 mg tirzepatide at week 24 (~-14%). Lastly, ecnoglutide's overall safety profile was consistent with other GLP-1 therapies and aligned with the previously-completed, up to 71-day PhI (NCT04389775) trial.

Summary of oral ecnoglutide (XW004) clinical data. At ADA 2024, Sciwind presented positive results from the 6-week PhI (NCT05184322) in 58 HVs and healthy obese patients with primary endpoint of safety. as detailed in our previous note, QD 30 mg oral ecnoglutide (XW004) showed a mean BW reduction of -6.8% vs. -0.9% placebo at 6-weeks, and was safe and well-tolerated. Further, Sciwind noted that to enable better oral bioavailability the peptide is co-formulated with an enhancer agent that prevents drug deactivation in the intestinal tract and increases intestinal absorption. Specifically, Sciwind assessed 7 mg, 15 mg, or 30 mg QD for two weeks in Cohort 1-3 and 30 mg QD for 6-weeks in Cohort 4. Notably, treatment was found to be dose dependent with -3.63% 7 mg, -3.38% 15 mg, and -6.55% 30 mg vs -0.85% placebo at week 2. Oral ecnoglutide was found to be generally safe and well tolerated with only 2 patients experiencing TEAEs leading to drug withdrawal in Cohort 3 (30 mg HV arm). Moreover, the most common AEs reported were nausea, constipation, vomiting, abdominal pain, and diarrhea (higher incidence in Cohort 3 attributed to higher 7 mg starting dose).

Upcoming catalysts. Sciwind is developing SC ecnoglutide (XW003) in PhIII across obesity and T2D (NCT05813795 and NCT05680155), oral ecnoglutide (XW004) in a PhI trial in HVs and healthy obese patients (NCT05184322), and XW014 (oral small molecule GLP-1R agonist) in HVs and T2D (NCT05579314). Sciwind has not provided formal guidance on when more data will be presented.

EXHIBIT 129

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity/T2D	XW003	PhIII trials **ongoing**
Obesity/T2D	XW004	PhI trial **ongoing**
T2D	XW014	PhI trial **ongoing**

Source: Sciwind Biosciences Company Materials. Wilding et al. *N Engl J Med*. 2021;384:989. Jastreboff et al. *N Engl J Med*. 2022;387:205. Piper Sandler Research.

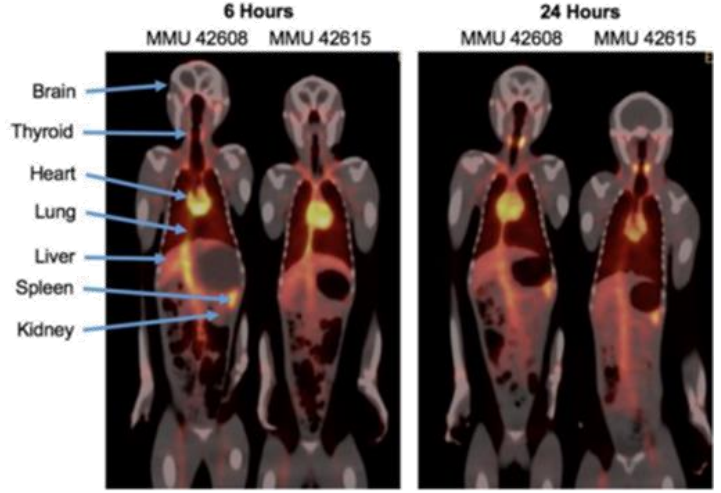
Skye Bioscience (SKYE): Tenthoff, OW (Page 1 of 2)

Skye is developing anti-CB1 antibody nimacimab for obesity. Nimacimab is peripherally-restricted to prevent psychiatric AEs and achieves weight loss by restoring leptin sensitivity and increasing fat metabolism. In a Phase I study, nimacimab demonstrated clean safety and decreased triglyceride levels in non-alcoholic fatty liver disease (NAFLD) patients. Skye recently initiated the Phase II *CBeyond* study of nimacimab +/- *Wegovy* (semaglutide) in 120 obese patients with initial data in 2Q25 and final data in 4Q25. The Phase II study is 80% powered to show 8% placebo-adjusted weight loss at 26 weeks. Importantly, the study is also designed to show additive (10%+) weight loss in the combo arm, as well as the effect of monotherapy nimacimab vs. Wegovy. Secondary endpoints include changes in body composition and may demonstrate that nimacimab spares muscle loss due to its fat "browning" mechanism. We view Skye's approach of developing an antibody with muscle-sparing weight loss and no psychiatric AEs as having blockbuster potential.

CB1 inhibition validated for weight loss, de-risking nimacimab. Rimonabant is a CB1 inverse agonist that acted centrally and peripherally. In clinical trials, rimonabant consistently induced weight loss of 4-8kg over 6-12 months vs. placebo, with improvements in metabolic control and hyperlipidemia. *Accomplia* (rimonabant) was approved in Europe in 2006 to treat obesity. However, subsequent analyses showed that rimonabant increased the risk of serious psychiatric AEs including anxiety, depression and suicidal ideation. In the CRESCENDO study, rimonabant significantly increased the % of patients reporting serious psychiatric side effects from 1.3% to 2.5%. Rimonabant was subsequently withdrawn from the market in 2008.

Nimacimab is peripherally-restricted. Rimonabant accumulated in the brain, where the concentration of CB1 is high, and mediated the adverse psychiatric effects. As an antibody, nimacimab is a large molecule that is peripherally restricted at an order of magnitude greater than next-gen small molecule CB1 antagonists. Nimacimab showed a brain:plasma concentration ratio of 0.8% at 48 hours in rhesus monkeys, and did not accumulate over time (**Exhibit 130**, below). 4-week tox studies of weekly intravenous doses of up to 75 mg/kg nimacimab revealed no neurologic AEs. The Phase I MAD study evaluated 4 weekly intravenous doses of up to 2.5 mg/kg weekly in 82 NAFLD patients with no signs of psychological AEs. Based on these data, it is likely that nimacimab will have a differentiated neurological AE profile.

EXHIBIT 130
Nimacimab Does Not Accumulate In The Brain



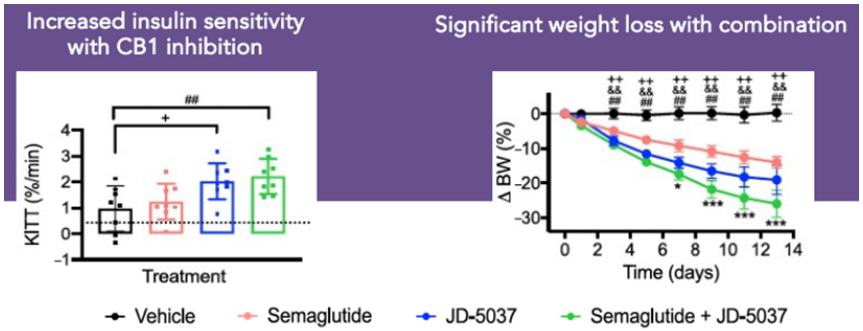
Source: Skye Biosciences Company Materials. Piper Sandler Research.

Skye Bioscience (SKYE): Tenthoff, OW (Page 2 of 2)

Nimacimab could synergize with GLP-1s. GLP-1 agonism is leading a revolution in weight loss with prescriptions of weekly *Wegovy* and *Zepbound* exploding over recent quarters. However, two drawbacks of GLP-1 therapy exist: (1) patients experience a rebound in weight once off therapy, and (2) loss of lean muscle mass. Both of these negative effects may be addressed by nimacimab's MoA. CB1 antagonism achieves weight loss through restoration of leptin and insulin sensitivity and enhancing fat metabolism across tissues. Thus nimacimab may improve the lipogenic/lipolysis profile to "reset" the patient's natural set point, and could thus show extended weight loss benefit even after patients go off therapy. Preclinical models have shown no muscle wasting on nimacimab or other CB1 antagonists. In fact, CB1 antagonism appears to improve running distance and energy intake without weight gain. Importantly, nimacimab's mechanism does not impinge on GLP-1 agonism, allowing for combination therapy. In fact, preclinical evidence suggests that targeting both GLP-1 and CB1 mechanisms causes additive weight loss (**Exhibit 131**).

EXHIBIT 131

CB1 Antagonist (JD-5037) Synergizes With GLP-1 Agonism

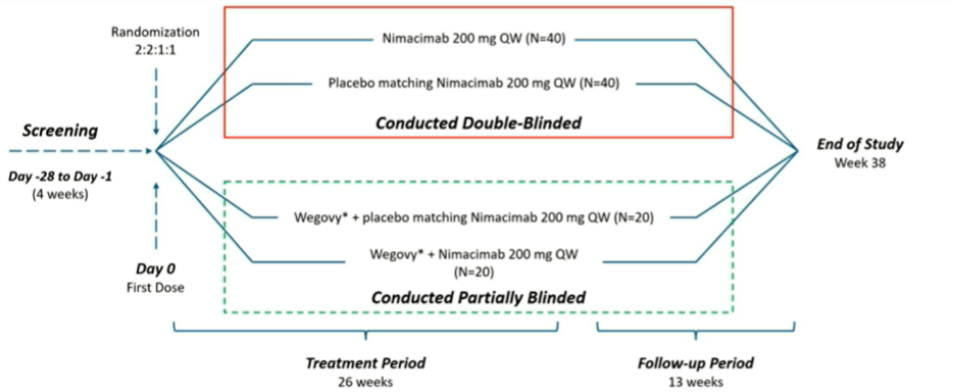


Source: Skye Biosciences Company Materials. Piper Sandler Research.

Skye recently initiated the Phase II CBeyond study of nimacimab +/- Wegovy in obese (BMI≥30) or overweight patients (BMI≥27) with at least one weight-related co-morbidity. The study is not enrolling diabetics or patients with a history of suicide attempt or major depression within 2 years. 80 patients will be randomized (1:1) to 200 mg weekly nimacimab or placebo. An additional 40 patients will receive 2.4 mg weekly Wegovy plus either (1:1) nimacimab or placebo. Patients will be treated for 26 weeks with 13-week follow-up. The study is 80% powered to show an 8% placebo-adjusted weight loss at 26 weeks. The study is also designed to show additive (10%+) weight loss in the combo arm, as well as the effect of monotherapy nimacimab vs. Wegovy. Secondary endpoints include safety, waist circumference, body composition (DEXA), sleep metrics, triglycerides, cholesterol and HbA1c. Skye expects to report interim data in 2Q25 and full data in 4Q25. Skye anticipates initiating Phase IIb studies that could evaluate higher and less-frequent monthly nimacimab dosing.

EXHIBIT 132

CBeyond Phase II Study Design

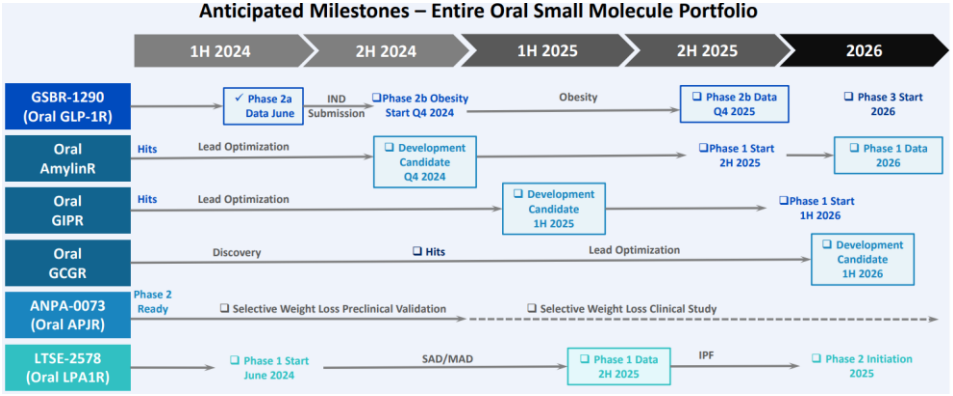


Structure Therapeutics (GPCR): Rahimi, OW (Page 1 of 2)

Structure Therapeutics is developing a differentiated class of oral small molecules. Structure's unique approach to developing best-in-class oral compounds is being applied across a wide breadth of MoAs and targets, including GLP-1R-selective, amylin, GIPR, GCGR, Apelin/APJR, and LPA1R. As either peptides or biologics, these molecules have the potential to unlock multiple market opportunities across obesity that offer a competitive edge through efficacy, safety, and tolerability. GPCR's lead asset GSBR-1290 in Phase IIa studies has shown 6.2-6.9% placebo-adjusted weight loss at 12 weeks, and no liver liabilities with a large therapeutic window (thus having the ability to go higher in dose), low number of AE-related study discontinuations (5-11%), and a clean PK that supports QD dosing with no fasting requirement needed. In addition, GPCR is proactively fine-tuning manufacturing to drive scalability (to serve >120M patients) and low COGS requirement for GMP-ready batches (and at this point they have completed GMP batches for the Phase IIb studies). In addition, GPCR has an oral small molecule portfolio of 5 other assets with distinct MoAs which the company intends to bring forward, with multiple key catalysts throughout the 2024-2026 timeframe. Taken together, through leveraging its next generation structure-based drug discovery platform, GPCR has a rich pipeline of molecules designed to overcome limitations of current biologics and peptide therapies.

EXHIBIT 133

GPCR's Pipeline



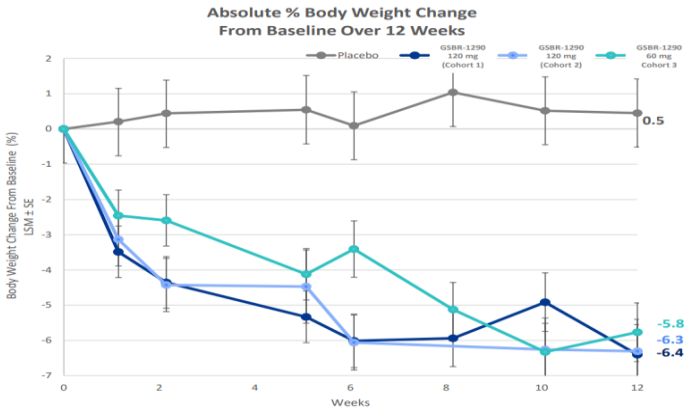
Source: Structure Therapeutics Company Materials. Piper Sandler Research.

GPCR is planning to initiate a 36-week PhIIb obesity study in 4Q24 with GSBR-1290. Following strong 12-week PhIIa study data in obesity (see note here) and capsule to tablet PK study data, the next steps for GPCR is to initiate a PhIIb obesity study (36 weeks) in 4Q24. In addition, GPCR is on track to submit an IND to the FDA in 3Q24 to support a study for chronic weight management.

How does the approach differ from incretins? GPCR is developing a library of novel oral therapeutics with high scalability and low COGS, which differentiates from current injectable medicines which are also inefficient to produce at scale. Furthermore, GPCR shared key data around high tolerability (low 5-11% AE-related study discontinuations) as well as attenuation of GI-related AEs over time. There were no DILI, permanent elevations in liver enzymes, or study discontinuations related to liver function, suggesting the compound is well-tolerated across patients (see more details regarding safety data in our note here). Overall, these oral small molecules offer an alternative to incretins with improved efficacy/safety profile and scalability.

Structure Therapeutics (GPCR): Rahimi, OW (Page 2 of 2)

EXHIBIT 134
Significant Weight Loss Observed with Tablet Formulation



Summary of clinical data. GPCR recently shared Phase IIa data in ~64 obese patients over 12 weeks with GSBR-1290. Notably, there was significant weight loss observed at 12 weeks with 120 mg GSBR-1290 of -6.2% placebo-adjusted body weight ($p<0.0001$). In addition, two-thirds of patients reported at least 6% weight loss over 12 weeks (67%), while 56% lost 8% or more, and 33% lost 10% or more. In contrast, 0% of the patients receiving placebo achieved at least 5% weight loss. Furthermore, in the coinciding capsule to tablet PK study with GSBR-1290 to assess the comparability of capsule and tablet at 60 mg, there was additional significant weight loss observed with tablet formulation (6.2% to 6.9% placebo-adjusted) weight loss after 12 weeks (**Exhibit 134**). This was true across both the 60 mg and 120 mg doses, which highlights the favorability of switching to the tablet formulation. For safety, the incidence of nausea decreased over time with similar attenuation with other GI-AEs. All AEs were mild or moderate, with no serious AEs. Key learnings from the capsule to tablet PK study will help to inform the Phase IIb study design, including the "start low and go slow" methodology.

Source: Structure Therapeutics Company Materials. Piper Sandler Research.

The next few years are catalyst-rich for GPCR. Across the pipeline, GPCR is advancing a wealth of oral assets with a catalyst line-up in the next few years that includes: (1) for GSBR-1290 (oral GLP-1), initiating a PhIIb in obesity in 4Q24 with data 4Q25, IND submission for chronic weight management study in 3Q24; (2) oral amylin program developmental candidate selection 4Q24 with PhI start 2H25; (3) oral GIPR candidate selection in 1H25 and PhI start in 1H26; and (4) oral GCGR developmental candidate selection in 1H26.

EXHIBIT 135
Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**GSBR-1290**	Initiate PhIIb study (36 week) in **4Q24** with data **4Q25** (and PhIII start **2026**)
Chronic weight management	**GSBR-1290**	Submit an IND to FDA to support study in **3Q24**
Obesity	**Oral Amylin**	Developmental candidate selection **4Q24** and PhI start **2H25** (data **2026**)
Obesity	**Oral GIPR**	Developmental candidate **1H25** and PhI start **1H26**
Obesity	**Oral GCGR**	Developmental candidate **1H26**

Terns Pharmaceuticals (TERN): Not Covered (Page 1 of 2)

Terns Pharmaceuticals is a clinical-stage biotech company developing oral small molecules with clinically-validated MoAs in oncology and metabolic disease (obesity). In addition to its Chronic Myeloid Leukemia asset (TERN-701; allosteric BCR-ABL TKI), TERN is developing three key programs in obesity: (1) TERN-601, an oral small molecule GLP-1R agonist currently in PhI development; (2) TERN-501 (THR-β agonist) in combination with a metabolic agent, in preclinical studies; and (3) lead optimization is underway for the TERN-800 series (GIPR modulators). TERN is focused on developing potent oral QD dosing small molecules in obesity that are safe with potential combination or co-formulation with other MoAs.

TERN-601 is in Phase I development in obesity. TERN is currently running a 28-day PhI MAD trial assessing QD TERN-601 in 72 healthy obese or overweight adults, with primary endpoint of safety and tolerability and secondary endpoints of PK and change in BW over 28-days.

EXHIBIT 136

TERN's Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Chronic Myeloid Leukemia	TERN-701				
Obesity	TERN-601				
Obesity	TERN-501 + Metabolic Agent				
Obesity	TERN-800 Series				

Source: Terns Pharmaceuticals Company Materials. Piper Sandler Research.

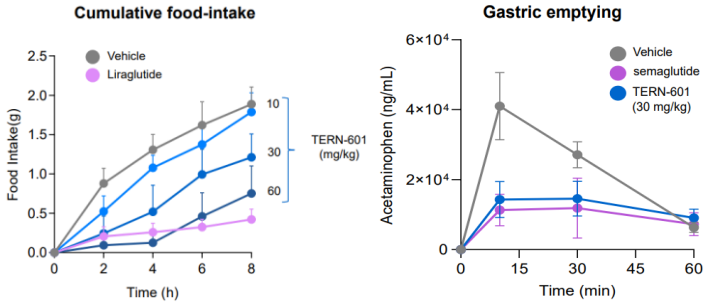
How is TERN-601 differentiated from currently-approved incretins? TERN believes TERN-601 has a differentiated profile when compared to injectable peptide-based GLP-1s and could offer improved convenience, tolerability, and cost. TERN-601 was designed using a proprietary 3D QSAR quantitative SAR model of the GLP-1R, which allows for improved prediction of GLP-1R molecular activity with greater accuracy than conventional physics-based approaches. As such, >20,000 molecular permutations were screened to identify an optimal small molecule scaffold with potential superiority to current GLP-1s. TERN-601 is a potent GLP-1R agonist that is: (1) biased toward cAMP generation, which may preserve target expression; (2) is optimal for combination and co-formulation studies; (3) may be applicable in related indications, such as MASH; and (4) shares a danuglipron **(PFE, not covered)** backbone that was optimized for QD dosing and easy manufacturing. In regard to the TERN-800 series (oral GIPR modulators), TERN combined internal chemistry expertise with external synthesis teams to develop an initial set of compounds and virtually screened 9B compounds *in silico* to identify additional GIPR modulators (focus on combination with GLP-1). At ADA 2024, TERN presented preclinical data for TERN-501 (THR-β agonist) in combination with semaglutide and demonstrated additive weight loss, lean mass preservation, and clear metabolic benefits (see note). TERN is well positioned to develop an oral GLP-1/THR-β combination therapy, given it has two in-house oral assets in development (TERN-501, TERN-601) with potential for liver fat reduction and additive metabolic benefits on top of those of each therapy alone. TERN believes it is developing differentiated oral therapeutics for obesity, with the potential of QD TERN-601 to drive better tolerability, lower COGS, fewer supply constraints, and more favorable pricing/reimbursement dynamics.

Terns Pharmaceuticals (TERN): Not Covered (Page 2 of 2)

Summary of TERN-601 preclinical data. Recall, at ADA 2023 (note) TERN presented preclinical TERN-601 data with meaningful effects that include: (1) high potency; (2) glycemic control; (3) decreased food consumption; and (4) reduced appetite. To begin, TERN-601 achieved high potency with significant intracellular cAMP generation (EC50 = 2.9 ± 0.81 nM) in CHO-K1 cells expressing human GLP-1R. Further, TERN-601 showed stat sig increases in glucose-stimulated insulin secretion (GSIS) in human pancreatic islet microtissues. Additionally, an intraperitoneal glucose tolerance test (IPGTT) was done in fasting hGLP-1R mice that were given a single oral dose of TERN-601 (0.3, 1, or 3 mg/kg) before IP glucose injection. Across all doses, TERN-601 achieved stat sig ($p<0.0001$) reductions in blood glucose area under the curve (AUC) when compared to vehicle (comparable efficacy to liraglutide). TERN-601 (single-dose 10, 30, or 60 mg/kg) meaningfully suppressed cumulative food intake in a dose-dependent manner in transgenic C57BL/6J mice expressing hGLP-1R, and meaningfully slowed gastric emptying (acetaminophen plasma levels reduced) in fasted hGLP-1R mice **(Exhibit 137)**.

EXHIBIT 137

TERN-601 Reduced Food Intake and Slowed Gastric Emptying



Source: Terns Pharmaceuticals Company Materials. Piper Sandler Research.

Taken together, these preclinical data demonstrate TERN-601's potent and effective profile, with improvement of key indicators prior to weight loss. In regard to the ongoing 28-day PhI PoC, TERN has guided that the SAD portion of the trial is complete with no safety concerns and no observations of liver enzyme elevations or drug-induced liver injury.

Summary of TERN-501 preclinical data. At ADA 2024, TERN presented preclinical data assessing TERN-501 (THR-β agonist) in combination with a GLP-1R agonist in obese mice. TERN-501 demonstrated a distinct additive effect with semaglutide, with potential to attenuate metabolic adaptation, effectively enhancing weight loss. For an in-depth review of this poster, please see our Virtual Obesity Day takeaway note.

Upcoming catalysts. TERN has guided topline data in September 2024 for the 28-day PhI MAD trial assessing QD TERN-601 in 72 healthy obese or overweight adults. TERN detailed the importance of the 14-day non-titrated cohort to allow for faster movement to higher doses during the 28-day dose titration period (≥3 cohorts) and optimization of the best starting dose. Additionally, TERN guided continued preclinical activities for TERN-501 combination and lead optimization is underway for TERN-800.

EXHIBIT 138

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**TERN-601**	Topline 28-day PhI data in **September 2024**
Obesity	**TERN-501 + Metabolic Agent**	Preclinical activities underway
Obesity	**TERN-800 Series**	GIPR antagonist lead optimization underway

Ventyx Biosciences Inc (VTYX): Rahimi, OW (Page 1 of 2)

Ventyx Biosciences is a clinical-stage biopharmaceutical company developing oral medicines in autoimmune and inflammatory disorders. VTYX has a pipeline spanning Parkinson's disease, obesity, CVD, ulcerative colitis, and Crohn's disease. VTYX is developing VTX3232 as an oral, selective, CNS-penetrant NLRP3 inhibitor across a range of neuroinflammatory and neurodegenerative conditions, including obesity. VTX3232 was designed to achieve disease-modifying CNS exposure with high potency and selectivity and a favorable safety profile.

VTX3232 is in Phase IIa development in obesity. VTYX guided initiation of a randomized, placebo-controlled 28-day PhIIa trial of VTX3232 in ~70 obese patients with elevated CV risk. Primary endpoint is change from baseline in CRP and secondary endpoints are inflammatory biomarkers and change from baseline in weight and body composition. Further, VTYX detailed inclusion of adult participants with obesity, elevated CRP, and at lease one additional risk factor of atherosclerotic CVD. Following the 28-day trial VTYX is planning to initiate a 3-month PhIIa trial in obese patients with elevated CV risk and primary endpoint of weight loss and other secondaries of inflammation and cardiometabolic biomarkers. As such, the longer trial will help to better understand VTX3232's durability and potential use as a complementary MoA to GLP-1s. Moreover, VTYX is still considering whether to add combination therapy with a GLP-1 in this trial as an additional arm, or a standalone separate study. VTYX is also assessing VTX3232 in Parkinson's disease with a 28-day PhIIa trial (n=~48), with primary endpoint of disease and NLRP3-related biomarkers in the plasma and CSF (more details in our note here).

EXHIBIT 139

VTYX's Pipeline

		Stage of Development			
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Parkinson's Disease/Obesity	VTX3232				
CVD	VTX2735				
Ulcerative Colitis	VTX002				

How is VTX3232 differentiated from incretins? VTX3232 is a novel, CNS-penetrant NLRP3 inflammasome inhibitor with potential as both a monotherapy and in combination with other therapies, such as incretins. Consequently, it is important to recognize the role NLRP3 plays in mediating the release of pro-inflammatory cytokines (IL-1β and IL-18) and driving a form of cell death called pyroptosis. NLRP3 dysregulation has been linked to a number of neuroinflammatory and neurodegenerative diseases with sig unmet need (ex. Parkinson's disease, multiple sclerosis, Alzheimer's disease, obesity). The sulfonylurea class of NLRP3 inhibitors has poor blood-brain barrier permeability and requires high systemic doses for CNS efficacy. Thus, VTYX rationally-designed VTX3232 for CNS efficacy without high peripheral exposures and rapid equilibration to reach microglial target cells. The completed VTX3232 oral tablet formulation study showed ~100% relative bioavailability (vs. injected solution in PhI SAD/MAD) and no food effect, positioning it for significant market uptake in obesity.

Source: Ventyx Biosciences Company Materials. Piper Sandler Research.

Ventyx Biosciences Inc (VTYX): Rahimi, OW (Page 2 of 2)

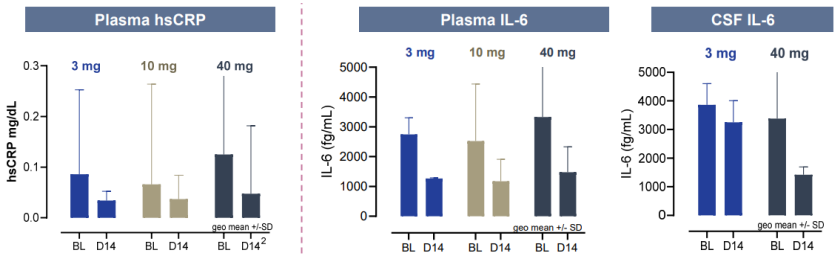
Summary of VTX3232 clinical data. At its R&D Day, VTYX presented VTX3232 data from the PhI SAD and 14-day PhI MAD trial in healthy volunteers (see note). Importantly, the PhI data provide confidence for PoS translation into a PhIIa obesity trial with key findings that include: (1) clean safety profile with all TEAEs considered mild or moderate, no DLTs, no lab abnormalities, and no trends in recurring AEs; (2) robust target engagement at IC50 and IC90 to enable QD dosing with matched plasma and CSF exposures from the MAD portion; and (3) dose-dependent reductions in inflammatory biomarkers with up to 55% lowering in plasma hsCRP and 46% reduction in plasma IL-6, with clear differentiation from canakinumab (anti-IL-1β; **NVS, not covered**) which showed only 35-40% hsCRP and IL-6 reductions. VTYX has noted that internal modeling suggests repeat doses of QD 12 mg may be able to achieve 90% target inhibition in the plasma and CSF, while maintaining a 12x safety margin (based on NOAEL non-GLP tox). Importantly, VTX3232's clean safety profile is crucial for continued development in obesity, given that the incretin class has already shown robust weight loss, and for NLRP3 inhibition to become part of a patient's weight loss regimen safety is critical. VTYX has emphasized in the 14-day PhI trial patients were dosed up to QD 40 mg, which is sig higher than required IC90 exposures to block IL-1β by a wide margin, where 10-15 mg is sufficient for IC90 coverage. As such, VTX3232 has a large therapeutic window to conduct a broad dose-ranging study to identify the optimal dose as a monotherapy and in combination.

Summary of VTX3232 preclinical obesity data. Recently, VTYX shared data across 2 preclinical mouse studies (see note), where VTX3232 showed a stat sig 9% weight loss vs. vehicle through Day 28 as a monotherapy, with reductions in plasma IL-1β, IL-6, and fibrinogen. VTX3232 in combination with semaglutide showed an additive effect, with weight loss of 22% over 28-days vs. vehicle. VTYX believes the preclinical data supports VTX3232 development as a monotherapy and combination therapy, with stat sig improvements in relevant biomarkers vs semaglutide monotherapy.

Upcoming catalysts. VTYX guided initiation in 2H24 of the 28-day PhIIa PoC trial assessing QD 40 mg VTX3232 vs placebo in ~70 obese patients, with endpoints including inflammatory biomarkers (hsCRP, IL-1β, IL-18, IL-6, SAA) and cardiometabolic readouts (lipids, glycemic measurements), with topline guided for 1H25. Further, upon completion of long-term tox work in the summer, VTYX guided initiation of a second, larger 3-month PhII study in obese patients, with primary endpoint of weight loss in 1H25.

EXHIBIT 140

VTX3232 Reduced Inflammatory Biomarkers hsCRP and IL-6



Source: Ventyx Biosciences Company Materials. Piper Sandler Research.

EXHIBIT 141

Upcoming Obesity Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	**VTX3232**	12-week PhIIa initiation in **2H24**

Viking Therapeutics Inc (VKTX): Not Covered (Page 1 of 2)

VKTX is a clinical-stage biopharma developing SC and oral VK2735 (dual GLP-1R/GIPR agonist) for obesity. VKTX's lead program VK2735 (dual GLP-1R/GIPR agonist) is currently in development for obesity with both SC and oral formulations. Topline PhII VENTURE data with the SC formulation was unveiled in Feb'24 showing -13.1% placebo-adjusted weight loss at 13 weeks (p<0.0001) and hitting stat sig across key secondary endpoints with clean safety. Following Type-C meeting with the FDA in 2Q24, VKTX announced plans to advance SC VK2735 directly to Phase III (update on timing expected after the EOP2 meeting in 4Q24). VKTX also announced plans to explore once-monthly dosing intervals for SC VK2735. The once-daily oral formulation of VK2735 is being evaluated in an ongoing Phase I dose-escalation study, which has thus far shown -3.3% placebo-adjusted weight loss at 4 weeks (p=0.0006) with 40 mg. Dose escalation is ongoing, with dosing in the 100 mg cohort ongoing. While safety data beyond the 40 mg cohort has not been unveiled, escalation to the 100 mg cohort implies good safety and tolerability with the 60 mg and 80 mg cohorts. VKTX has plans to initiate a 13-week Phase II study in 4Q24 with the oral formulation of VK2735.

EXHIBIT 142

VKTX's Obesity Pipeline

	Stage of Development				
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity	VK2735 (GLP-1R/GIPR agonist)				
Obesity	Oral VK2735 (GLP-1R/GIPR agonist)				
Obesity	DARCA (Amylin / Calcitonin agonist)				

Source: Viking Therapeutics Company Materials. Piper Sandler Research.

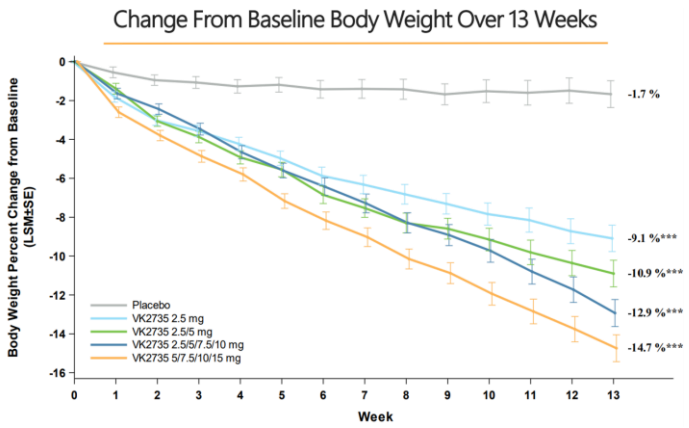
How does VK2735 differ from other incretins? VK2735 is a dual GLP-1R/GIPR agonist with optimized properties to drive a differentiated drug profile, with potent binding (<500 nM) across both human GLP-1 and GIP receptors. There is mechanistic evidence showing the additive benefit of GIP agonist activity on top of GLP-1 agonism alone, with broader improvements across body weight, blood glucose, plasma triglycerides (p<0.005 for all), and numerically higher insulin reductions (vs. GLP-1 mono-agonism at the same dose level) seen in preclinical rodent data.

In PhII VENTURE, SC VK2735 drove rapid and sustained weight loss of -13.1% placebo-adjusted at 13 weeks. Specifically, -13.1% placebo-adjusted weight loss (-14.7% vs. -1.7% placebo; p<0.0001) was achieved at the highest SC QW dose (5/7.5/10/15 mg) at 13 weeks. There was a consistent dose-response (stat sig for all doses), with no sign of weight loss plateau at week 13 (see **Exhibit 143**, on the following page). VENTURE also achieved stat sig on all doses on key secondary endpoint of percent of patients with ≥10% weight loss at week 13, with a dose-responsive delta of 35.6% to 84.3% (39.3-88.0% vs. 3.7% placebo; p<0.005 for all), from the lowest to highest dose cohorts. As for safety/tolerability, dropouts were balanced (13% combined across all cohorts vs. 14% placebo), with only 3% (n=1) drug-related TEAE leading to discontinuation in the highest dose cohort. GI TEAEs were most common (95% were mild-to-moderate), and included: nausea (43% vs. 20% placebo), vomiting (18% vs. 0% placebo), constipation (26% vs. 11% placebo), diarrhea (20% vs. 9% placebo), GERD (12% vs. 3% placebo), and abdominal pain (4% vs. 3% placebo).

Viking Therapeutics Inc (VKTX): Not Covered (Page 2 of 2)

EXHIBIT 143

PhII VENTURE: SC VK2735 Achieved Stat Sig Weight Loss at 13-Wks

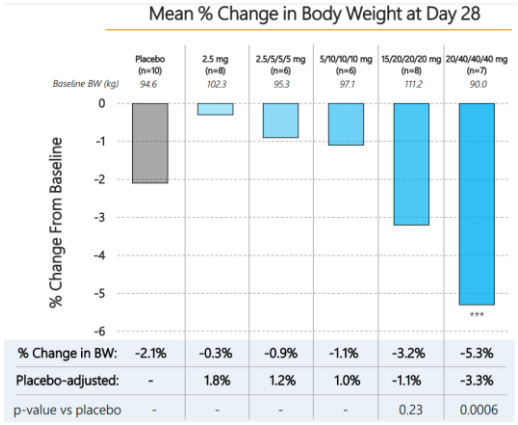


Oral VK2735 PhI MAD data shows -3.3% placebo-adj weight loss at Day 28. Dose responsive weight loss was observed at Day 28, with the top dose (20/40/40/40 mg) achieving a stat sig delta vs. placebo (-5.3% vs. -2.1% placebo; p=0.0006; **Exhibit 144**, right). At Day 34 (6 days post-final dose), there was sustained weight loss and a deeper placebo-adj treatment delta of -3.6% (-5.2% vs. -1.6% placebo; p=0.0003). Thus far, safety data has been impressive with the oral formulation, enabling ongoing dose escalation (currently in the 100 mg cohort, which implies good safety/tolerability for the 60 and 80 mg cohorts). Safety data from the first 5 cohorts (2.5 to 40 mg) had discontinuation rates of 5% vs. 0% placebo, with all GI TEAEs being mild (79%) or moderate. Most common GI events were nausea (14% vs. 0% placebo), abdominal pain (8% vs. 30% placebo), GERD (3% vs. 20% placebo), and diarrhea (3% vs. 20% placebo).

Source: Viking Therapeutics Company Materials. Piper Sandler Research.

EXHIBIT 144

Oral VK2735 Shows Dose Dependent, Stat Sig Weight Loss at 28 Days



	Placebo	2.5 mg	2.5/5/5/5 mg	5/10/10/10 mg	15/20/20/20 mg	20/40/40/40 mg
% Change in BW:	-2.1%	-0.3%	-0.9%	-1.1%	-3.2%	-5.3%
Placebo-adjusted:	-	1.8%	1.2%	1.0%	-1.1%	-3.3%
p-value vs placebo	-	-	-	-	0.23	0.0006

VKTX is advancing a novel amylin/calcitonin receptor agonist, with IND expected in 2025. At ADA in June 2024, VKTX presented *in vivo* data from mice for a series of internally-developed dual amylin and calcitonin receptor agonists (DACRAs), which showed reduced food intake and -8% body weight loss in lean rats at 72 hours following a single SC dose. In DIO mice treated for 24 days, -10% body weight loss ($p<0.05$ vs. baseline) and -24% reductions in blood glucose ($p<0.05$ vs. baseline and cagrilintide control) were observed. IND filing for this program is expected in 2025.

EXHIBIT 145

Upcoming Catalysts

Drug	Upcoming Catalyst
SC VK2735	End of PhII meeting in 4Q24; Initiate PhIII study YE24/early 2025 (*PSC estimates*)
Oral VK2735	Initiate 13-wk PhII obesity trial in 4Q24
Undisclosed (DACRA)	IND submission in 2025

Zealand Pharma (ZEAL): Not covered (Page 1 of 2)

Zealand Pharma is developing an obesity pipeline with advancement of 3 key clinical programs/targets. ZEAL's obesity pipeline programs span different MoAs and clinical phases, led by: (1) survodutide (GCGR/GLP-1R), which recently had MASH Phase II trial data at EASL (see note here), with further MASH development planned and ongoing enrollment of the Phase III SYNCHRONIZE program in obesity in 2H24; 2) Dapiglutide (GLP-1R/GLP-2R) with PhIIa DREAM clinical trial data in 2Q24 (low doses) and PhIb 13-week dose-titration clinical trial data in 2H24 (high doses); and (3) Petrelintide (amylin analog) PhIb 16-week MAD clinical data shared in June and PhIIb trial initiation planned for 2H24.

How do these compounds differ from other incretins? Firstly, starting with survodutide, which is furthest in development, this program is licensed to **Boehringer Ingelheim (Private)** from Zealand Pharma, where BI is solely responsible for global development and commercialization. As a novel glucagon receptor and GLP-1 dual mechanism, this compound has added benefits of the liver-targeted glucagon MoA on top of the GLP-1 mechanism (7.5 GLP-1:1 Glucagon). The compound has shown best-in-class potential in a MASH PhII trial, in which key EASL data (here) showed improvements in MASH without worsening of fibrosis (stages F1-F3): 83% with survodutide vs. 18.2% with placebo (p<0.0001). Moreover, there were statistically-significant improvements in liver fibrosis with a 24.1-28.8% (p<0.01) response rate in paired biopsies across F1-F3 patients. Since survodutide is being developed for both MASH and obesity, the company is currently enrolling in the Phase III SYNCHRONIZE clinical trial. Prior, ZEAL shared PhII obesity data for mean relative

EXHIBIT 146

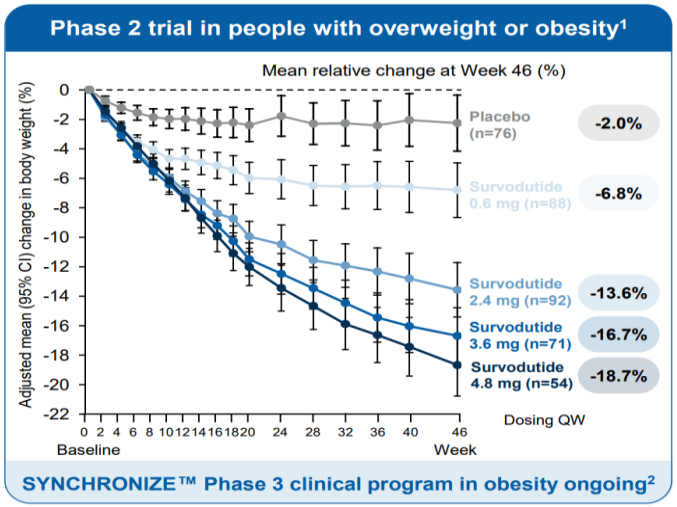
ZEAL's Pipeline

		Stage of Development			
Indication	**Program**	**Preclin.**	**Phase I**	**Phase II**	**Phase III**
Obesity	Dapiglutide (GLP-1/GLP-2 dual agonist)				
Obesity	Petrelintide (amylin analog)				
Obesity	ZP6590 (GIP RA)				
Obesity and MASH	Survodutide (GCGR/GLP-1 dual agonist)				

Source: Zealand Pharma Company Materials. Piper Sandler Research.

EXHIBIT 147

Significant Weight Loss Observed in Phase II with Survodutide

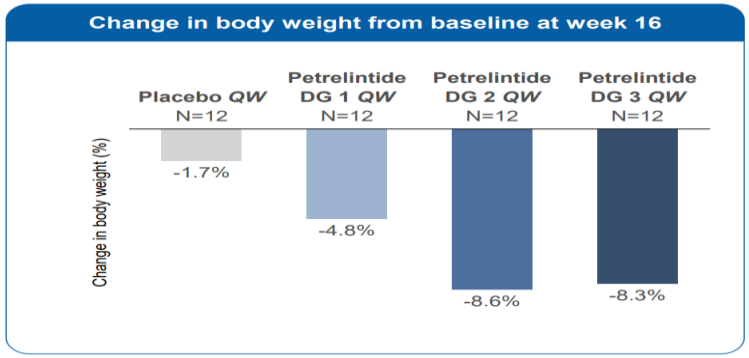


Zealand Pharma (ZEAL): Not covered (Page 2 of 2)

change at week 46 (%), showing a dose-dependent and stat sig change in body weight of -18.7% at survodutide 4.8 mg (n=54), -16.7% at 3.6 mg (n=71), -13.6% at 2.4 mg (n=92), -6.8% at 0.6 mg (n=88), vs. -2% with placebo (n=76) (**Exhibit 147**). Next, Petrelintide is distinct from the GLP-1 class as it is an amylin analog being developed for obesity which is expected to reduce food intake by increasing satiety and restoring leptin sensitivity (as a non-incretin), and significantly improving GI tolerability. In addition, as a long-acting amylin analog (half life of 10 days), it is suitable for once-weekly administration. In June 2024, ZEAL shared the topline data from its 16-week trial (MAD part 2) with Petrelintide, where in Part 1 of the Phase Ib MAD all drug-related GI side effects were mild, and the drug was safe and well-tolerated at all dose levels, with no serious or severe AEs, no ADAs, and only one discontinuation after the third dose after reports of nausea and vomiting. For efficacy, as shown in **Exhibit 148**, substantial weight loss was observed at 16 weeks with Petrelintide: -8.3% with DG 3 QW (n=12), -8.6% with DG 2 QW (n=12), -4.8% with DG 1 QW, and -1.7% with placebo QW (n=12). All participants treated were reported to have lost weight during the trial, and review of the data from individual patients supports separation at the higher doses is possible. Given the positive results, a randomized, double-blind, placebo-controlled PhIIb trial with Petrelintide is initiating in 2H24. Lastly, for Dapiglutide, this drug is unique as an incretin by it being a dual GLP-1 and GLP-2 receptor agonist. ZEAL has noted that there are cardioprotective benefits from GLP-1 agonism and additional anti-inflammatory effects from GLP-2 agonism. At ADA 2024, ZEAL shared data for Dapiglutide noting that in a MAD trial, once-weekly SC injection of Dapiglutide up to 6 mg for 4 weeks was well-tolerated in healthy patients, and showed dose-dependent body weight loss up to a mean 4.3%, as well as dose-dependent reductions in plasma glucose and insulin. These data highlighted that at the cellular level, GLP-1R activation by native GLP-1 induces formation of its major second messenger cAMP and recruitment of ß-arrestin. Topline data from the PhIb 13-week dose titration high doses portion is expected in 2H24.

EXHIBIT 148

Substantial Weight loss at 16 Weeks With Amylin Analog



Source: Zealand Pharma Company Materials. Piper Sandler Research.

EXHIBIT 149

Upcoming Catalysts

Indication	Drug	Upcoming Catalyst
Obesity	Survodutide	Next steps planned in MASH and enrollment ongoing in PhIII SYNCHRONIZE trial
Obesity	Petrelintide	PhIIb initiation in **2H24**
Obesity	Dapiglutide	Topline data from the PhIb 13-week dose titration (high doses) in **2H24**

Risks

Risks associated with all companies described in this report are common to other biotech companies.

Clinical risk. Success in clinical trials will be essential for companies to market their products, but success in the clinic is not guaranteed.

Regulatory risk. The FDA, EMA or other regulatory bodies may have a different view on the benefit-risk balance demonstrated in clinical testing than the company seeking approval. Companies may be required to do additional trials, which may make the development of the candidates more time- and cost-prohibitive.

Commercial risk. Companies may fail to achieve development, regulatory, or commercial objectives. Clinical and/or regulatory success does not guarantee commercial success.

Financing risk. Pipeline development and commercial plans will require capital and time. In addition to cash flow from marketed products and funding from partners, companies may need to raise more money through an equity offering, which may negatively impact the stock price.

Intellectual property risk. Protection of a company's drugs and processes is dependent on issued or pending patents and in-house knowledge. One or more parties often challenge the intellectual property estate of a successful product, claiming priority for other patents or that the patents are invalid or infringe. Significant expense on legal protection could be required in the future, with no guarantee of success.

Source: Piper Sandler Research.

Closing Prices as of September 6, 2024

Company	Ticker	Price
Altimmune	ALT	$6.20
Alnylam Pharmaceuticals	ALNY	$246.78
Amgen	AMGN	$320.56
Arrowhead Pharmaceuticals	ARWR	$22.22
Biohaven	BHVN	$36.90
Crinetics Pharmaceuticals	CRNX	$50.39
Keros Therapeutics	KROS	$52.51
Lexicon Pharmaceuticals	LXRX	$1.61
Madrigal Pharmaceuticals	MDGL	$243.89
MeiraGTx Holdings	MGTX	$3.88
Omega Therapeutics	OMGA	$1.22
Regeneron Pharmaceuticals	REGN	$1,131.50
Scholar Rock Holding	SRRK	$8.03
Skye Bioscience	SKYE	$5.84
Structure Therapeutics	GPCR	$36.95
Ventyx Biosciences	VTYX	$2.17

Source: FactSet. Piper Sandler Research.

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			IB Serv./Past 12 Mos.	
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BUY [OW]	526	57.80	118	22.43
HOLD [N]	350	38.46	40	11.43
SELL [UW]	34	3.74	0	0.00

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