BIOPHARMA

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Beyond Incretins: Evaluating Alternative Mechanisms in Obesity

February 11, 2024

Reason for report:
INDUSTRY UPDATE

S&P 500 Health Care Index: **1,678.00**

Companies Highlighted

BHVN, BMY, GPCR, KROS, LLY, MRK, REGN, SAN FP

- **Bottom Line:** Anti-obesity medication (AOM) candidates that exploit pathways beyond the capabilities of incretins and gut hormones (GLP-1, GLP-2, GIP, etc.) are attracting significant investor interest. To set the stage, we remain bullish about incretin drug prospects, including the potential for demonstration of a wide range of health benefits beyond established use in diabetic control and weight loss. But we also recognize shortcomings/risks: **1) tolerability** — esp. gastrointestinal [GI] distress, can impact compliance/persistence, **2) potential sub-optimal alterations in body composition** — muscle atrophy/lean mass loss accompanies fat mass loss, and **3) possible risks when stopping therapy —** there are fears that patients may regain weight with a worse ratio of lean mass / fat than where they started. New, orthogonal/tangential mechanisms that address certain shortcomings or raise the bar for efficacy/tolerability could drive substantial value. We highlight developmental AOMs that could be administered in combination with or in lieu of incretin therapies. For a deep dive on the incretin class, opportunities for indication expansion, and broader impacts, reference our Healthcare Team report "Obesity Revolution: Illuminating The Runways By Healthcare Subsector."
- **Alternative mechanisms are increasingly capturing investor attention.** Given that investors anticipate AOMs to be a huge market (we est. 2032E global sales of $158B — see pgs. 27-30 of report linked above), novel mechanisms which could offer a more optimal ratio of fat/lean mass loss, better tolerability or more permanent weight loss after discontinuation capture the imagination. Select Ph2 or Ph3 programs to watch with obesity readouts in 2024/2025: **1) LLY's (OP, Risinger) bimagrumab (anti-ActRII)**: Ph2 data in combination with semaglutide are anticipated in 3Q24 — it previously showed approx.+6% lean mass in Ph1 in healthy volunteers at day 84. **2) NVO's (Not Rated) CagriSema (amylin/GLP-1)**: Ph3 data in nondiabetic obese patients are expected by YE24, it previously showed 15.6% body weight reduction at 32 weeks in T2D patients **3) ZEAL's (Not Rated) petrelintide (amylin)**: Ph1b 16-week MAD data in mid-24 — it previously showed up to 4.9% pbo-adj. weight loss at week 6**. 4) REGN's (OP, Risinger) trevogrumab (anti-myostatin)/ garetosmab (anti-activin A)** will enter Ph2 in combo with semaglutide in mid-24 with a potential readout in 2H25 — it previously showed a significant increase (approx. 6-7%) in thigh muscle volume and reduction in android fat mass (approx. 15%) in a small n=6 study in postmenopausal women at about week 30.
- **How problematic is the lean mass loss associated with GLP-1s?** Although loss of lean mass and muscle mass is concerning in elderly

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and frail patients, we believe the jury is still out for the masses. We note that the lean-to-fat mass ratio associated with the use of LLY's tirzepatide in obese patients was said to be "*similar to that reported with lifestyle-based and surgical treatments for obesity*," (Jasteboff et. al. NEJM 2022) although semaglutide at its weight loss dose of 2.4 might have a potentially worse lean mass loss ratio. Specifically, in the Ph3 SURMOUNT-1 trial, tirzepatide showed a 3.11-to-1 ratio of fat-to-lean mass loss on a percentage basis (week 72, absolute basis not reported Jasteboff et. al. NEJM 2022). By comparison, in the Ph3 trial STEP-1, semaglutide showed less optimal 1.98-to-1 ratio on a percentage basis (1.50-to-1 on an absolute basis, at week 68 Wilding et. al JES 2021 and Wilding et. al. NEJM 2021). **Refer to details and caveats in section titled "The Lean/Fat Mass Loss Debate and Muscle-Sparing Programs."** Separately, for patients who stop GLP1+ therapies, it is speculated that they may regain more fat than lean mass in the short term, but it is possible that their bodies may adjust closer to normal over the longer term. Unfortunately, patients' body composition after stopping therapy remains poorly characterized, and it is unclear which studies (if any) will evaluate this in the future.

- **Key controversies associated with select alternative mechanisms.** Given the early stages of development of alternative mechanisms to treat obesity, we look forward to future trial results. We are interested in efficacy to assess magnitude (and in some cases composition) of weight loss and safety because novel mechanisms could have their own distinct liabilities. We discuss various considerations, including myostatin/activin historical association with bleeding risk and LLY's bimagrumab tolerability.
- **Novel candidates mentioned in this report.** See Exhibit 1 for a list of programs in alphabetical order by company.

See details within.

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Exhibit 1: Table of Novel Candidates in this Report (Alphabetical by Company)

Company	Rating	Program	Target/Modality	Phase
Aardvark Therapeutics	*Private*	ARD-101	TAS2R (bitter taste receptors) small molecule	2
ALT	Not Rated	pemvidutide (ALT-801)	GLP-1/GCG peptide	2+
Aphaia Pharma	*Private*	APH-012	distal jejunal-release dextrose	2
AZN	OP, Berens	AZD6234	amylin peptide	1
BHVN	OP, Goodman	taldefgrobep alfa (BHV-2000)	myostatin- & ALK4/5-inhibiting adnectin	2
BioAge	*Private*	BGE-105 (azelaprag)	APJ Agonist small molecule	2
BI	*Private*	BI 1820237	NPY2 agonist peptide	1
BI / ZEAL	*Private/* Not Rated	survodutide (BI 456906)	GLP-1/GCG peptide	3
CRBP	Not Rated	CRB-913	peripheral CB1 inverse agonist small molecule	Preclinical
ERX Pharma	*Private*	ERX-1000	leptin sensitizer small molecule	2
GPCR	OP		amylin small molecule	Preclinical
GPCR	OP	ANPA-0073	APJ Agonist small molecule	1
Kallyope	*Private*	K-757 and K-833	nutrient receptor agonists small molecules	2
KROS	OP, Smith	KER-065	ActRII Ligand Trap	1
LLY	OP	LY3841136 (LAARA)	amylin peptide	1
LLY	OP	LY3541105 (DACRA QW II)	amylin/calcitonin peptide	1
LLY	OP	retatrutide (GGG)	GLP-1/GIP/GCG peptide	3
LLY	OP	Mazdutide	GLP-1/GCG peptide	2
LLY	OP	bimagrumab (BYM-338)	anti-ActRIIA/B mAb	2
LLY	OP	nisotirostide (LY3457263)	PYY analogue peptide	1
NVO	Not Rated	CagriSema (cagrilintide + semaglutide)	amylin & GLP-1 peptides	3
NVO	Not Rated	Amycretin (NNC0487-0111)	amylin/GLP-1 peptide	1
NVO	Not Rated	INV-202	peripheral CB1 inverse agonist small molecule	2
NVO	Not Rated	INV-347	peripheral CB1 inverse agonist small molecule	1
Palatin	*Private*	Bremelanotide	FPI-1Q2024 peptide	2
REGN	OP	trevogrumab & garetosmab	anti-myostatin anti-activin A mAbs	2
REGN	OP	GPR75	GPR75 siRNA, small molecule, and mAb	Preclinical
REGN	OP	mibavademab (REGN4461)	leptin receptor agonist mAb	2
Resalis Therapeutics	*Private*	RES-010	miR-22 microRNA	1
Resalis Therapeutics	*Private*	RES-020	miR-22 microRNA	Preclinical
Rivus Pharma	*Private*	HU6	mitochondrial uncoupler	2
SKYE	Not Rated	nimacimab	peripheral CB1 allosteric antagonist mAb	2
SRRK	Not Rated	Apitegromab (SRK-015)	anti-myostatin mAb	2
SRRK	Not Rated	SRK-439	anti-myostatin mAb	Preclinical
ZEAL	Not Rated	petrelintide (ZP8396)	amylin peptide	1b

Source: Leerink Partners; Company Disclosures

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Exhibit 2: Table of Muscle-Sparing Programs

Company	Program	Target/Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
LLY	bimagrumab (BYM-338)	anti-ActRIIA/B mAb	2	Weight loss trial of bimagrumab +/- semaglutide in nondiabetic patients. Primary endpt; weight loss at 48 wks. n=507. NCT05616013	est. PC May 31, 2024	Ph2 monotherapy study in T2D patients showed 48-wk -20% and +4.4% pbo-adj. fat and lean mass chg., respectively.	Bimagrumab admin. IV in Ph2, but more recent Ph1 in heathy volunteers showed comparable changes in fat/lean mass with SC or IV
REGN	trevogrumab (REGN1033) & garetosmab (REGN2477)	anti-myostatin anti-activin A mAbs	2	Evaluating addition of trevogrumab (anti-myostatin) and semaglutide +/- garetosmab (anti-activin A) on weight loss and body composition	Ph2 initiation mid-2024	Ph1 n=6 postmenopausal women study significantly increased thigh muscle volume (+6-7%) and reduced android fat mass (approx. 15%) Preclinical, obese non-human primate combo data + semaglutide showed 20-wk reduced or increased lean mass with greater reduction in fat mass relative to semaglutide alone.	Mgmt. believes targeting of myostatin and activin-A vs. ActRII could maintain beneficial functions of pathway and improve tolerability. Trevogrumab component is admin. SC, but garetosmab is IV
SRRK	Apitegromab (SRK-015)	anti-myostatin mAb	2	Co-administration with GLP-1	Ph2 initiation 2024	Positive Ph2 POC efficacy in patients with spinal muscular atrophy with no TR-SAEs.	Selectively targets latent, promyostatin, which the company believes could improve safety.
BHVN	taldefgrobep alfa (BHV-2000)	myostatin- & ALK4/5-inhibiting adnectin	2	Administration +/- semaglutide. Chg in body composition/weight, metabolic parameters and influence of taldefgrobep on weight regain following discontinuation of semaglutide.	Ph2 initiation 1H24	Ph1 healthy volunteer study demonstrated fat mass reduction with increase in lean mass.	Inhibits both mature, active myostatin and activity of ActRII receptor. Previously a BMY(MP) program (BMS-986089) before outlicensing to RHHBY and then to BHVN.
BioAge	BGE-105 (azelaprag)	APJ Agonist small molecule	2	Co-administration with GLP-1; program goal is 20-25% healthy weight loss			Ph2 "planning in process" per company website
KROS	KER-065	ActRII Ligand Trap	1	Ph1 SAD/MAD trial. Part 1: 3 single doses (1, 3, and 5 mg/kg) of SC KER-065 in healthy volunteers (BMI 18.5-30) over 4-weeks. Part 2: overweight/obese pts, safety, tolerability, PK, and PD (lean/fat mass and bone mineral density) over 12 weeks.	Ph1 data 1Q25	Predecessor program, RKER-034 showed preserved lean muscle mass and increased fat loss in obese mice treated with semaglutide	Reduced binding to BMPs, which the company believes can decrease risk of bleeding
GPCR	ANPA-0073	APJ Agonist small molecule	1	Co-administration with GLP-1	Program Updates in 2024	Ph1 monotherapy SAD/MAD data showed that ANPA-0073 was well-tolerated in healthy volunteers	
REGN	GPR75	GPR75 siRNA, small molecule, and mAb	Preclinical			GPR75 siRNA administration maintained weight with no change in lean mass in diet-induced obese mouse model at 3 weeks	Preclinical data yet to provide evidence that program will drive weight loss. Company notes that GPR75 gene variants associated with reduced obesity risk
SRRK	SRK-439	anti-myostatin mAb	Preclinical	Co-administration with GLP-1	IND in 2025	Dose-dependent preservation of lean mass in combo with semaglutide seen in diet-induced obese mouse model	Selectively targets latent, promyostatin, which the company believes could improve safety

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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The Lean/Fat Mass Loss Debate and Muscle-Sparing Programs

Anti-obesity medication (AOM) candidates intended to spare/preserve or increase muscle while promoting weight loss have attracted significant attention. But it's unclear exactly how problematic this phenomenon with incretin use might actually be for patients. AOMs that preserve lean mass/muscle are being evaluated as monotherapies or in combination with an incretin agent. **We include a table of programs to watch in Exhibit 2 above and provide further details within**. Our conversations with KOLs have been generally split on the importance of maintaining lean mass in conjunction with fat mass loss for treating obese patients with incretins, but they generally agree that utility of them might be limited in older/frail patients in this regard.

Body composition data in obese-patient trials to date could suggest that LLY's tirzepatide might yield a better ratio of fat/lean mass loss than NVO's 2.4 mg semaglutide, although the two have never been studied head-to-head on this measure and the number of patients evaluated for body composition were small relative to the broader trials. In LLY's SURMOUNT-1 trial, tirzepatide demonstrated an approx. 3.11-to-1 ratio of fat-to-lean mass loss at 72 weeks on a percentage basis (pooled 5/10/15 mg QW dose groups, n=160 measured incl. pbo [n for tirzepatide only not disclosed], absolute chg. not reported, Exhibit 3). This was said to be **"***similar to that reported with lifestyle-based and surgical treatments for obesity*," a statement that cited Pownall et. al. Obesity 2016 (Jasteboff et. al. NEJM 2022). In NVO's STEP-1 trial, semaglutide (2.4 mg QW) demonstrated an approx. 1.98-to-1 ratio of fat:lean mass loss at 68 weeks, also on a percentage basis (1.50:1 ratio on an absolute basis, n=140 with n=95 semaglutide and n=45 pbo, Wilding et. al. JES 2021 and Wilding et. al. NEJM 2021, Exhibit 4). Both tirzepatide in SURMOUNT-1 and semaglutide in STEP-1 resulted in an improved overall lean-to-fat mass ratio with treatment, but the final ratio of lean-to-fat mass improved more with tirzepatide in SURMOUNT-1 (baseline 1.08 to 1.42, a +32% chg. at week 72) compared to semaglutide in STEP-1, albeit STEP-1 had a higher baseline (baseline 1.34 to 1.57, +17% at week 68). The STEP-1 publication noted that the subgroup of patients that underwent body composition evaluation was a subgroup with a baseline "BMI of 40 or less," but the SURMOUNT-1 trial publication did not provide similar inclusion/exclusion criteria. Both studies utilized gold-standard dual energy X-ray absorptiometry (DXA) to assess body composition.

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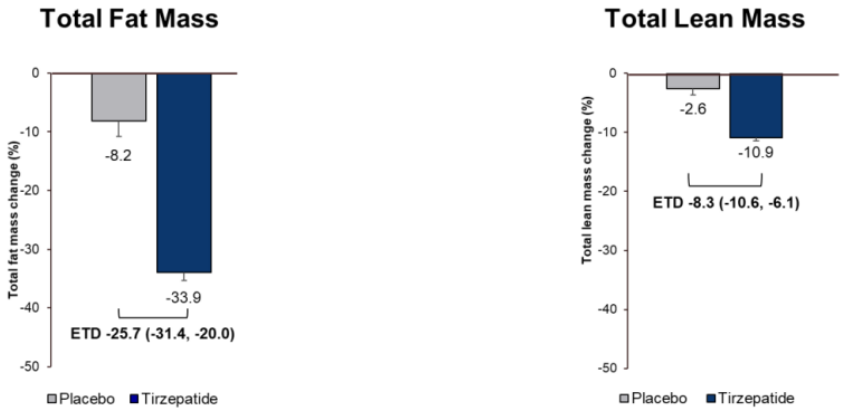
Exhibit 3: Ph3 SURMOUNT-1 tirzepatide change in body composition



Source: Jasteboff et. al. NEJM 2022. Data are least squares means and 95% confidence interval. Data are shown for placebo and pooled tirzepatide 5 mg, 10 mg, and 15 mg groups. Enrolled n=255; completers with both baseline and week 72 DXA n=160. Abbreviations include ETD, estimated treatment difference.

Exhibit 4A: Ph3 STEP-1 semaglutide 2.4 mg change in body composition percentage

total lean body mass proportion: 53.9% vs 52.7%; respectively). Percentage change in body weight from baseline to week 68 was -15.0% with semaglutide vs -3.6% with placebo. This resulted in reductions from baseline with semaglutide in total fat mass (-19.3%) and regional visceral fat mass (-27.4%), leading to 3.5%-point and 2.0%-point reductions in the proportions of total fat mass and visceral fat mass, respectively. Total lean body mass decreased from baseline (-9.7%); however, the proportion

Source: Wilding et. al. JES 2021

Exhibit 4B: Ph3 STEP-1 semaglutide 2.4 mg change in body composition absolute

Supportive secondary endpoints assessed in the DEXA subpopulation

	N=95	N=45	
Body composition change from baseline to week 68 (DEXA)			
Total fat mass			
Kg change	−10.40	−1.17	ETD: −9.23 [−12.72; −5.74]
Percentage-points change in total fat mass proportion§	−4.19	−0.19	ETD: −4.00 [−6.27; −1.73]
Regional visceral fat mass¶			
Kg change	−0.47	−0.03	ETD: −0.45 [−0.60; −0.30]
Percentage-points change in regional visceral fat mass proportion‖	−2.65	0.58	ETD: −3.23 [−5.35; −1.10]
Total lean body mass			
Kg change	−6.92	−1.48	ETD: −5.44 [−7.07; −3.81]
Percentage-points change in total lean body mass proportion§	3.61	0.11	ETD: 3.50 [1.35; 5.64]

Source: Wilding et. al. NEJM 2021

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On LLY's 4Q23 call, CSO/CMO, Dan Skovronsky, validated the importance of body composition and weight loss. On the company's 4Q23 call, we prompted LLY's CSO/CMO, Dan Skovronsky for his take on body composition changes with GLP-1 administration and the differences between tirzepatide and semaglutide, he stated (*sourced from FactSet)*:

"*Maybe just starting with our take on lean vs. fat mass, I think the ratio of lean to fat mass is an important thing to think about. Body composition, not just body weight, matters to patients. For example, in risk of type 2 diabetes or cardiovascular disease, that body ratio seems to be important. The good news is that, for patients on tirzepatide, that ratio appears to improve. As you pointed out, they lose far more fat mass than lean mass. And so in every trial we've done, at the end of the trial if you measure body composition, it's better, a higher ratio of lean-to-fat than at the beginning of the trial.*

So we see this changing body composition as it benefits, potential benefit of tirzepatide to be further explored. Of course, it's also a benefit we want to further extend. You've seen us try to improve the total amount of body weight loss. We're also trying to improve – further improve, I should say, the change in body mass composition, and that's why you saw us acquire Versanis [bimagrumab] and experiment with drugs like domagrozumab. The numbers you quote from the tirzepatide and semaglutide studies, seem right to me. Of course, they're not head-to-head studies, but it does raise a question here about whether there's a potential benefit of GIP-1, GIP agonism here in addition to GLP-1 agonism. That's probably the way I would interpret this data."

Myostatin/Activin and ActRII

Inhibition of myostatin/activin has been thematic in the muscle-sparing, AOM space. One of the most common approaches for maintaining muscle in the treatment of obesity has been inhibiting activity of myostatin/activin and/or its cognate (primary) receptor, ActRII. This pathway plays a key role in modulating muscle growth making it an attractive therapeutic target (Hanson et. al. Nature 2023). Initial studies were in atrophy disorders (i.e., cachexia, sarcopenia, etc.), but now they are being studied for obesity applications, mostly in combination with GLP-1 agents to maintain/promote lean mass.

What about bleeding risk? Of note, inhibition of this pathway has been associated with increased risk of bleeding events. Acceleron's (now a subsidiary of MRK [OP, Graybosch]) ACE-031, a soluble ActRIIB-IgG ligand trap that neutralizes ActRII-associated ligands (including myostatin and activin) was discontinued in Duchenne muscular dystrophy (DMD) due to AEs telangiectasia ("spider veins"), nosebleeds and gingival bleeds (Garber, Nat. Biotech. 2016). Similarly, MRK's sotatercept, an ActRIIA-IgG ligand trap, showed a 21.5% rate of bleeding events (vs. 12.5% pbo) and 10.4% rate of telangiectasia (vs. 3.1% pbo) in its Ph3 trial in patients with pulmonary arterial hypertension (PAH, Hoeper et. al. NEJM 2023). Fibrodysplasia ossificans progressiva (FOP, a rare connective tissue disorder) patients administered REGN's garetosmab (anti-activin A) exhibited epistaxis (nosebleed) 65% of the

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time vs. 37.5% of the time with pbo (Rocco et. al. Nat. Med. 2023), but REGN mgmt. has commented that they believe these bleeding events with garetosmab might not translate to non-FOP patients. **It's hypothesized that these bleeding complications could stem from interfering with BMP9 (separately from myostatin and activin) which also binds ActRII** (Latres et. al. Nat. Com. 2017, Tillet et. al. Front. Genet. 2015, Nolan-Stevaux, O. et al. PLoS ONE 2012). But it's unclear if the role of BMP9 regarding this bleeding risk comes from its activity on ActRII vs. additional receptors, such as BMPRII (Morvan et. al. PNAS 2017). KROS has suggested that its ActRII ligand trap, KER-065, could mitigate bleeding risk by avoiding BMPs in general. We note that LLY's bimagrumab, which blocks ActRII, has not been associated with bleeding events. We await results of additional trials for candidates targeting this pathway to better gauge bleeding risk in obese/overweight, but otherwise healthy individuals.

LLY's bimagrumab (anti-ActRII)

LLY's bimagrumab (acquired with Versanis) is the most advanced muscle-sparing program; Ph2 data in combination with semaglutide could be disclosed in 3Q24. Recall that in Jul. 2023, LLY acquired bimagrumab with its purchase of Versanis Bio for potential future payments totaling $1.925B; the up-front payment was not disclosed. Bimagrumab is a mAb targeting ActRII currently being evaluated in a Ph2 trial as a combination therapy with semaglutide in nondiabetic obese patients to drive substantial fat loss coupled with muscle preservation/gain. The trial is testing multiple different intravenous (IV) doses of bimagrumab, but we note that since the start of this trial, it has been successfully formulated for subcutaneous (SC) administration (see below). The trial enrolled n=507 patients and has primary endpoint of %change in body weight at week 48. But we note that there are several secondary endpoints aimed at assessing body composition. The est. primary completion is May 31, 2024 (NCT05616013). We think that a potential venue for data presentation is the European Association for the Study of Diabetes (EASD) conference from Sept. 9-13. ***Notably, we currently exclude potential sales from our LLY model because we are uncertain about its potential value in the treatment paradigm of obesity.***

Ph2 monotherapy study in T2D patients verified proof of mechanism with increase in lean mass/ loss in fat mass. Bimagrumab monotherapy was evaluated in a 48-week Ph2 study in n=75 patients with type 2 diabetes (T2D) and obesity. Baseline BMI ranged from 28-40 (mean of 32.9) and baseline HbA1c ranged from 6.4-10.2% (mean of 7.8%). Bimagrumab was administered IV Q4W for 12 total doses with dose of 10 mg/kg up to 1,200 mg maximum. The results showed a 21% reduction in body fat mass with bimagrumab vs. 0.5% placebo (Exhibit 5). Lean mass was +3.6% with bimagrumab vs. -0.8% placebo. Change in HbA1c was -0.76% with bimagrumab vs. +0.04% placebo. Overall body weight was −6.5% bimagrumab vs. −0.8% placebo. Most frequent AEs with bimagrumab were diarrhea and muscle spasms (each 41%, Heymsfield et. al. JAMA 2021).

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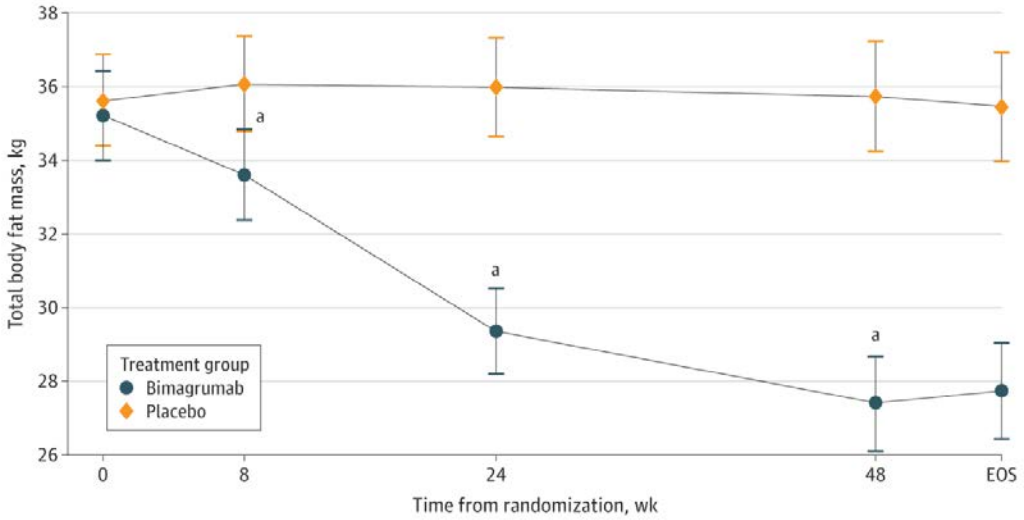
Exhibit 5: Bimagrumab Ph2 effect on total body fat mass in T2D patients



Source: Heymsfield et. al. JAMA 2021

Bimagrumab is being evaluated as IV in Ph2 but has successfully been reformulated for SC administration. Ph1 POC data healthy volunteers continued to verify POC. Data presented at the June 2023 American Diabetes Association (ADA) conference showed that bimagrumab could be formulated for SC administration. In the Ph1 study, n=91 patients were treated with IV or SC bimagrumab or placebo. Treatment was administered monthly for 3 total doses at several different dose strengths: IV 700 mg or 210 mg, SC 1500 mg or 525 mg. The data show similar effects on fat/lean mass regardless of administration route (Exhibit 6). Frequent AEs were muscle spasms (at most 67%, 1500 mg SC cohort) and diarrhea (at most 42%, 1500 mg SC cohort). The presentation also claimed that SC administration improved tolerability, but we note that the highest dose administered SC presented the highest number of AEs of any group (Exhibit 7).

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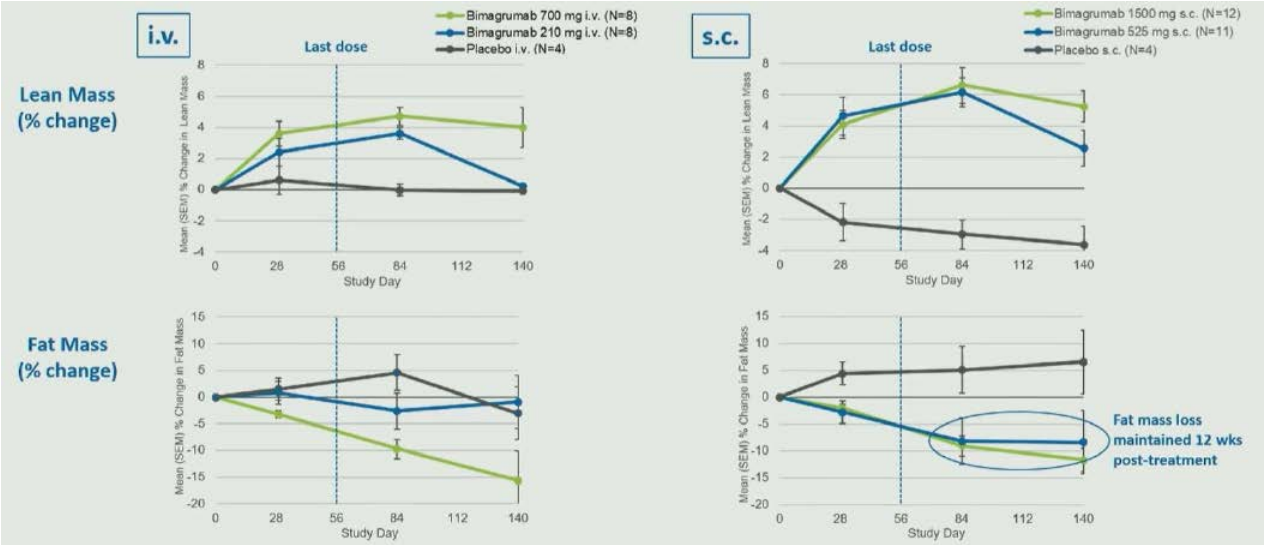
Exhibit 6: Bimagrumab Ph1 bridging study; effect on fat/lean mass with IV or SC administration



Source: Attie et. al. Optimized Weight Loss with Bimagrurmab: Reduced Fat Mass with Increased Muscle Mass by Appetite-Independent Mechanisms. ADA 2023

Exhibit 7: Bimagrumab Ph1 bridging study AEs by administration subgroup

Subjects n (%)	Bimagrumab i.v.			Bimagrumab s.c.		
	700 mg N=8	210 mg N=8	Placebo N=4	1500 mg N=12	525 mg N=12	Placebo N=4
Muscle spasms	5 (62.5)	3 (37.5)	0	8 (66.7)	3 (25.0)	0
Diarrhea	2 (25.0)	2 (25.0)	0	5 (41.7)	1 (8.3)	0
Injection site erythema	0	0	0	4 (33.3)	1 (8.3)	0
Lipase Increased	1 (12.5)	0	0	4 (33.3)	0	0
Urinary tract infection	0	3 (37.5)	0	1 (8,3)	0	0
Erythema	0	2 (25.0)	0	1 (8,3)	0	0
Musculoskeletal pain	0	0	0	2 (16.7)	0	1 (25.0)

Incidence of adverse events occurring in ≥2 participants in any arm

Source: Attie et. al. Optimized Weight Loss with Bimagrurmab: Reduced Fat Mass with Increased Muscle Mass by Appetite-Independent Mechanisms. ADA 2023

Bimagrumab failed to demonstrate efficacy in rare muscle weakness indication. NVS (Not Rated) previously had breakthrough designation for bimagrumab in a rare, muscle weakness indication, sporadic inclusion body myositis (sIBM). But the Ph3 trial failed to hit its primary endpoint as the treatment didn't demonstrate clinical benefit to improve mobility. The 2-year extension study proceeded dosing n=211 patients at 10 mg/kg, 3 mg/kg, 1 mg/kg or matching placebo IV Q4W (same as the parent study). Overall, it continued to see a lack of clinical benefit. The treatment was well-tolerated; the most frequently reported AEs in the

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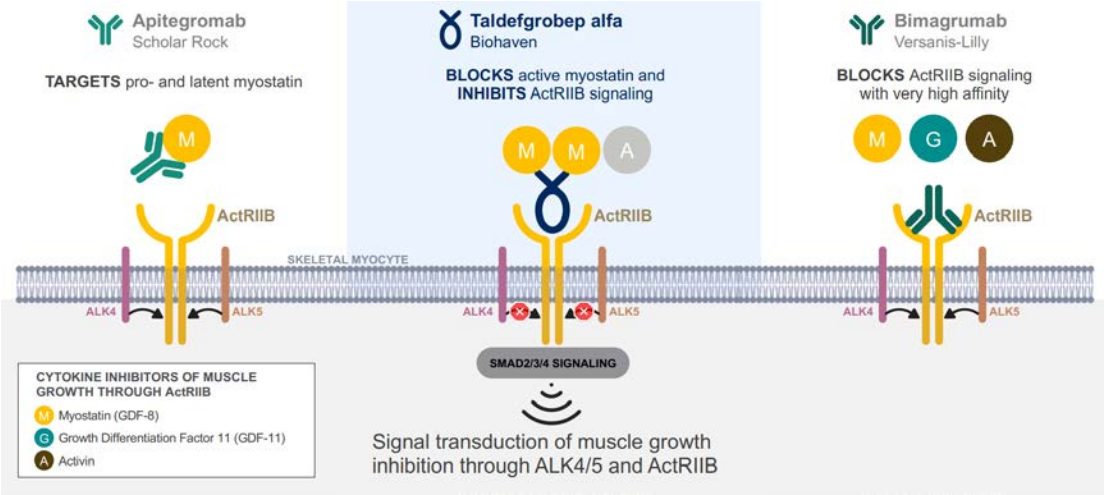
pooled bimagrumab group were diarrhea 14.7% (n=23), involuntary muscle contractions 9.6% (n=15), and rash 5.1% (n=8, Amato et. al. Neurology 2021).

BHVN's (OP, Goodman) taldefgrobep alfa (anti-myostatin adnectin)

Exhibit 8: Therapeutic approach to taldefgrobep alfa vs. other competing programs



Source: BHVN JPM Conference Presentation Jan. 8, 2024

Taldefgrobep alfa appears differentiated from competing anti-myostatins; it blocks myostatin and inhibits activity at the ActRII receptor. Taldefgrobep alfa 45 mg SC Q1W has shown improvement in body composition in a Ph1 healthy volunteer study at 30 days post-dosing with sustained effect beyond the dosing period up to Day 57, and management noted it could potentially extend the dosing intervals. Obesity Ph2 will initiate in 2Q24, topline Ph3 spinal muscular atrophy (SMA) results in 2H24. BHVN's taldefgrobep alfa was developed by BMY (MP, Risinger), previously out licensed to RHHBY (Not Rated) for Duchenne muscular dystrophy (DMD) and more recently BHVN for additional indications. It is an anti-myostatin adnectin that binds mature, active myostatin and inhibits signaling at the ActRII receptor. This combined targeting approach is unique relative to competing programs that either target myostatin or block the receptor (Exhibit 8). Ph1 data of taldefgrobep in healthy volunteers appeared promising, with a significant increase in thigh muscle volume and dose-dependent suppression of myostatin (see details within). In DMD, however, a Ph2/3 trial did not meet its primary endpoint — a pre-specified futility threshold (change from baseline of ≥ 1.5 points on the NSAA total score, Muntoni et. al. Neurol Ther 2024). Importantly, taldefgrobep alfa has been safe and well-tolerated in >350 treated subjects (97 HVs and 209 DMD patients). BHVN will begin a Ph2 in obesity for taldefgrobep with or without semaglutide in 2Q24 (additional details within). A Ph3 study in SMA will also read out in 2H24.

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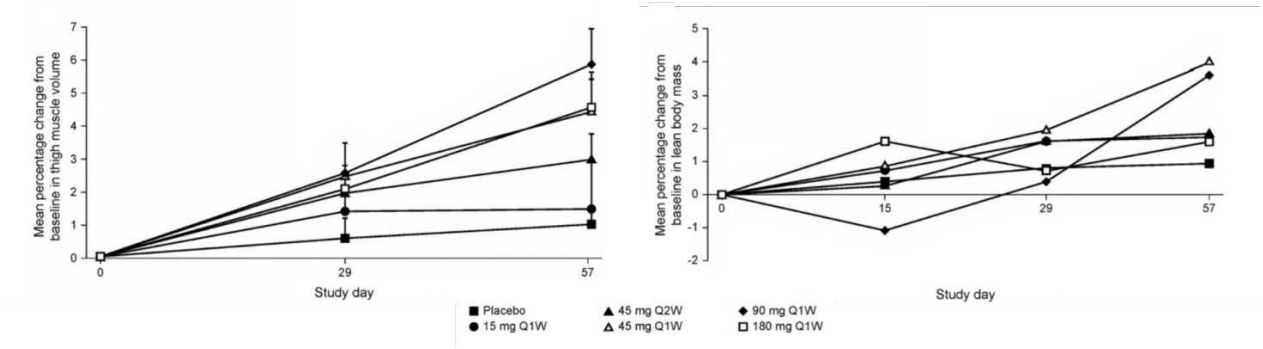
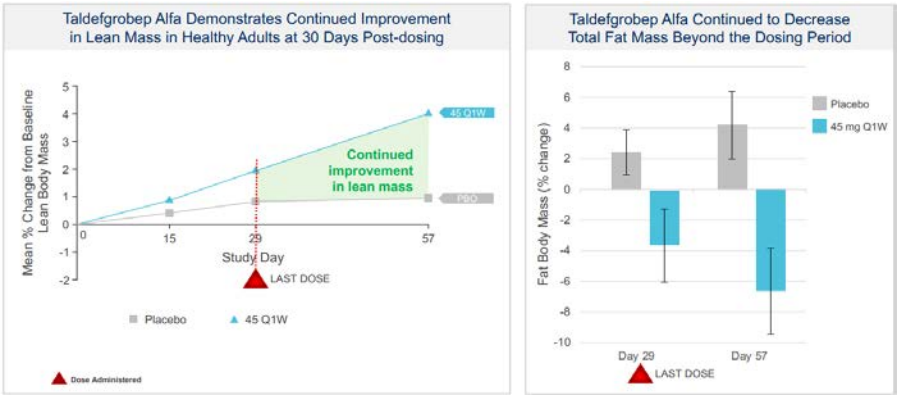
Ph1 healthy volunteer-study recap. Taldefgrobep increased thigh muscle volume and lean body mass but lacked dose-dependency. Administration effectively suppressed myostatin. In the Ph1 healthy volunteer study, taldefgrobep dosed weekly (QW) for 29 days demonstrated a statistically significant increase in thigh muscle volume and lean body mass at 57 days relative to placebo, but we note lack of dose-dependency. Significant increases in mean thigh muscle volume at day 57 vs. placebo were reported in the 45 mg QW (n=11, mean=+3.41%, p=0.0031), 90 mg QW (n=9, mean=+4.75%, p < 0.0001), and 180 mg QW (n=10, mean=+3.52%, p=0.0027) dose groups (Exhibit 9). Significant lean body mass increases vs. placebo were reported in the 45 mg Q1W (n=12, mean=+2.69%, p=0.0154) and the 90 mg Q1W (n=9, mean=+2.43%, p=0.0347) dose groups (Exhibit 9, Muntoni et. al. Neurol Ther 2024). The company's Jan. investor presentation also highlighted reduction in fat mass at days 29 and 57, specifically with the 45 mg QW dose cohort, which could suggest that 45 mg QW might be the go-forward dose (Exhibit 10). Taldefgrobep alfa also efficiently suppressed free myostatin at all doses tested with rebound in plasma concentration after the 29-day treatment period (Exhibit 11).

Exhibit 9: Ph1 healthy volunteers. Taldefgrobep percent change in thigh volume (left) and lean body mass (right)



Source: Muntoni et. al. Neurol Ther 2024

Exhibit 10: Ph1 healthy volunteers. Taldefgrobep percent change in lean body mass and fat mass



Source: BHVN JPM Conference Presentation Jan. 8, 2024

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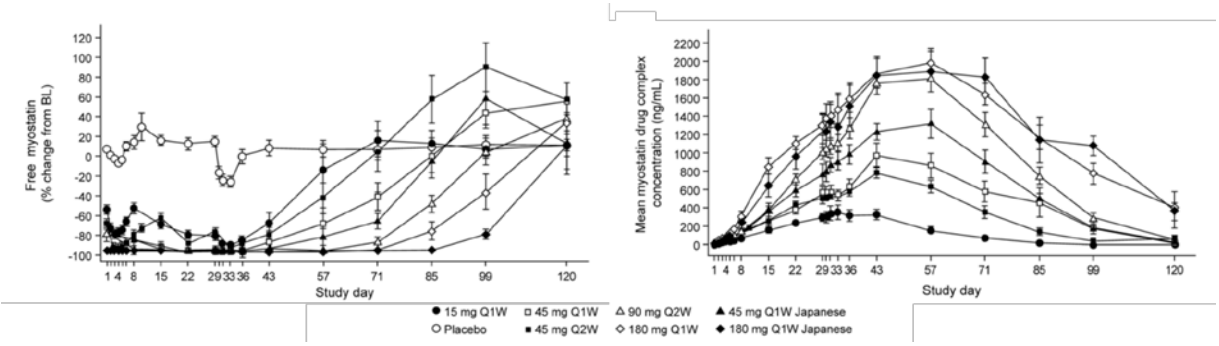
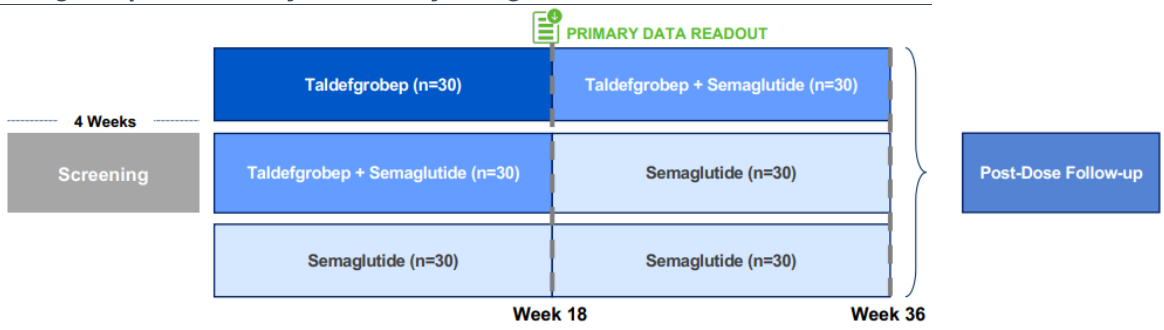
Exhibit 11: Ph1 healthy volunteers. Taldefgrobep change in free myostatin level versus time in the MAD phase (left), myostatin-drug complex concentration (right)



Source: Muntoni et. al. Neurol Ther 2024

Ph2 proof of concept study design will look at taldefgrobep monotherapy and combination with semaglutide. Reference Exhibit 12. The Ph2 obesity study will evaluate taldefgrobep with and without semaglutide and n=90 patients split equally into 3 groups. The trial has an 18-week primary endpoint with 18 weeks of taldefgrobep monotherapy dosing compared to a taldefgrobep + semaglutide group and a semaglutide monotherapy group. Part 2 of the trial is also 18 weeks long and will switch patients from: taldefgrobep monotherapy to taldefgrobep + semaglutide, taldefgrobep + semaglutide to semaglutide monotherapy. The semaglutide monotherapy group will continue the same treatment for the additional 18 weeks. The trial will characterize how taldefgrobep influences changes in body composition, total body weight, metabolic parameters and weight regain after discontinuation of therapy.

Exhibit 12: Taldefgrobep Ph2 obesity POC study design



Innovative study design allows for early insight into a number of key clinical questions

- Impact of Taldefgrobep monotherapy on changes in body composition, total body weight, and metabolic parameters
- Ability of Taldefgrobep to augment fat mass loss when used as adjunct to anti-obesity standard of care (GLP-1 agonist)
- Potential for Taldefgrobep to prevent against GLP-1-induced lean muscle loss
- Influence of Taldefgrobep on weight regain following discontinuation of GLP-1 agonist

Source: BHVN JPM Conference Presentation Jan. 8, 2024

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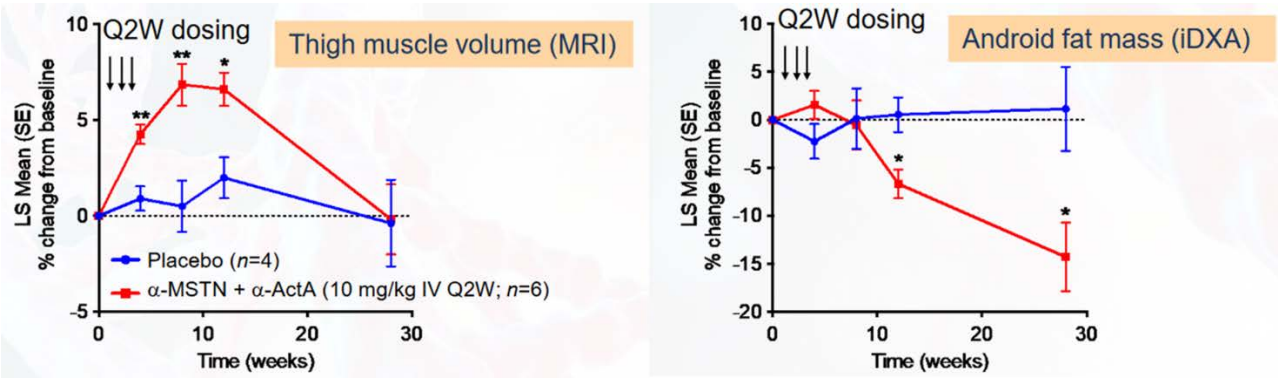
REGN's trevogrumab (anti-myostatin)/garetosmab (anti-activin A)

REGN's lead obesity program, trevogrumab (anti-myostatin) + garetosmab (anti-activin A) increased muscle volume in a Ph1 study in postmenopausal women. Ph2 start in obesity in mid-2024; we estimate topline results could be disclosed in 2H25. REGN's trevogrumab is an anti-myostatin mAb that inhibits mature, active myostatin, garetosmab is an anti-activin A. In a Ph1 trial of n=6 postmenopausal women, the combo administered Q2W led to a significant increase (approx. 7%) in thigh muscle volume and reduction in android fat mass (approx. 15%) relative to placebo at about 30 weeks (Exhibit 13). The combo was reported to be well-tolerated, but led to AEs of muscle spasms, headache, mouth ulcerations/aphthous ulcers, and nausea (none leading to discontinuation, frequency not reported). The company's lead obesity program will administer the combo plus semaglutide. The Ph2 obesity trial is expected to start in mid-2024, pending safety and tolerability assessment of high-dose trevogrumab in healthy volunteers. We estimate that REGN could disclose top-line primary endpoint (26-wk) data in 2H25. ***We do not include any potential sales in our REGN model as we await Ph2 efficacy/safety results.***

Exhibit 13: Ph1 trevogrumab (anti-myostatin) + garetosmab (anti-activin A) in postmenopausal women (red line)



Source: Mastaitis et. al. "Myostatin inhibition synergizes with GLP-1R agonism to accelerate weight loss in male, obese, non-human primates" ADA 2023, June 25, 2023.

Trevogrumab + garetosmab demonstrated compelling preclinical data in non-human primates when combined with semaglutide The combo + semaglutide demonstrated compelling 20-week weight reduction along with maintenance/improvement in lean mass relative to semaglutide alone in a preclinical obesity model with non-human primates (NHPs). Trevogrumab in combo w/semaglutide numerically maintained mean lean mass with additional fat loss relative to semaglutide monotherapy. Trevogrumab + garetosmab in combo w/semaglutide increased mean lean mass and provided even greater numerical fat loss relative to semaglutide +/- trevogrumab. See Exhibit 14. Reference ADA 2023 abstract (Mastaitis et. al. 207-OR ADA 2023).

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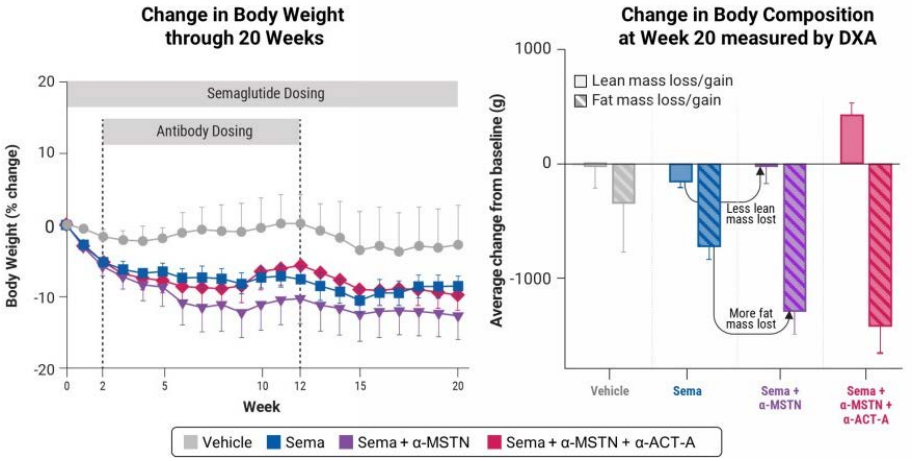
Exhibit 14: Trevogrumab (anti-myostatin)/garetosmab (anti-activin A) in combination with semaglutide shows reduced lean mass loss in NHPs



Source: REGN JPM Presentation Jan 8, 2024

REGN mgmt. believes that there could be a safety benefit to targeting myostatin and activin A vs. inhibiting the entire pathway by blocking the receptor, ActRII, but the Ph1 data in postmenopausal women appeared to have side effects similar to bimagrumab. We note that ActRII is the cognate receptor for a variety of ligands including GDF11, other species of activin and TGF-β (Lach-Trifilieff et. al. Mol Cell Biol 2014). REGN mgmt. believes that there are beneficial functions to these additional ligands, and blocking their activity could impose additional, and potentially unnecessary risk. Their assumption is that myostatin and activin A are the key ligands involved in maintaining lean mass while reducing fat mass so therapies that act against or in place of the receptor, ActRII (i.e., bimagrumab, KER-065 [see below], etc.), could pose additional safety/tolerability concerns. However, the safety benefit appears unclear with the current data. One of the most frequently reported side effects from bimagrumab (which blocks the ActRII receptor) was muscle spasms and this AE also appeared in REGN's small Ph1 data in postmenopausal women (although the frequency was not disclosed). We look forward to future trial results for all programs relevant to this mechanism to gain clarity that could potentially verify REGN's hypothesis.

SRRK's Apitegromab and SRK-439 (anti-promyostatin)

SRRK has two programs that target the pro/latent form of myostatin, and the company believes this could offer an added safety benefit. The first program, apitegromab, will initiate Ph2 in 2024. SRRK antibodies target a more juvenile, pro/latent form of myostatin (promyostatin), and the company believes that this could offer an additional safety benefit vs. targeting late (normal) myostatin (Exhibit 15). The company's first program, apitegromab, has generated positive Ph2 POC efficacy data in patients with types 2 and 3 spinal muscular atrophy (SMA) with no TR-SAEs. In the Ph2 TOPAZ trial, apitegromab administered IV Q4W led to sustained improvements in measures of motor function including a 36-month: mean

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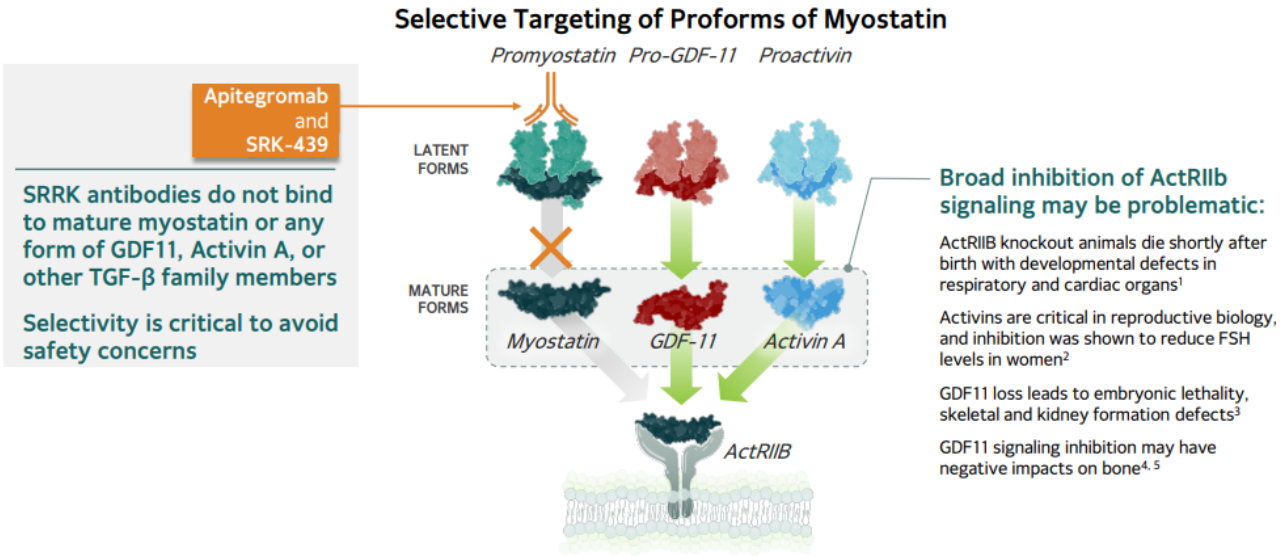
4.0-point improvement in Hammersmith Functional Motor Scale-Expanded (HFMSE) and mean 2.4-point improvement in Revised Upper Limb Module (RULM, PR here, Exhibit 16, (NCT03921528). We also await apitegromab's Ph3 SAPPHIRE results in 4Q24 in a similar, type 2 and 3 SMA patients (NCT05156320, est. primary completion Oct. 2024) to learn more about its efficacy/safety profile. The Ph3 SAPPHIRE trial also has SMA-related endpoints with Q4W administration. **Although SRRK has yet to evaluate apitegromab in otherwise healthy, obese patients, its preclinical, next-gen SRK-439 program has shown positive rodent data with lean mass maintenance and additional fat mass loss in combination with semaglutide.** The company expects to begin a Ph2 trial for apitegromab in combo with an unspecified GLP-1 in obesity in 2024 with a POC data readout in 2025. The second candidate, SRK-439, is expected to file an IND and will also be evaluated in combo with a GLP-1 for obesity in 2025.

Exhibit 15: SRRK antibody program targets a proform of myostatin, which the company believes has a potential safety benefit



Source: SRRK Corporate Presentation Jan. 2024

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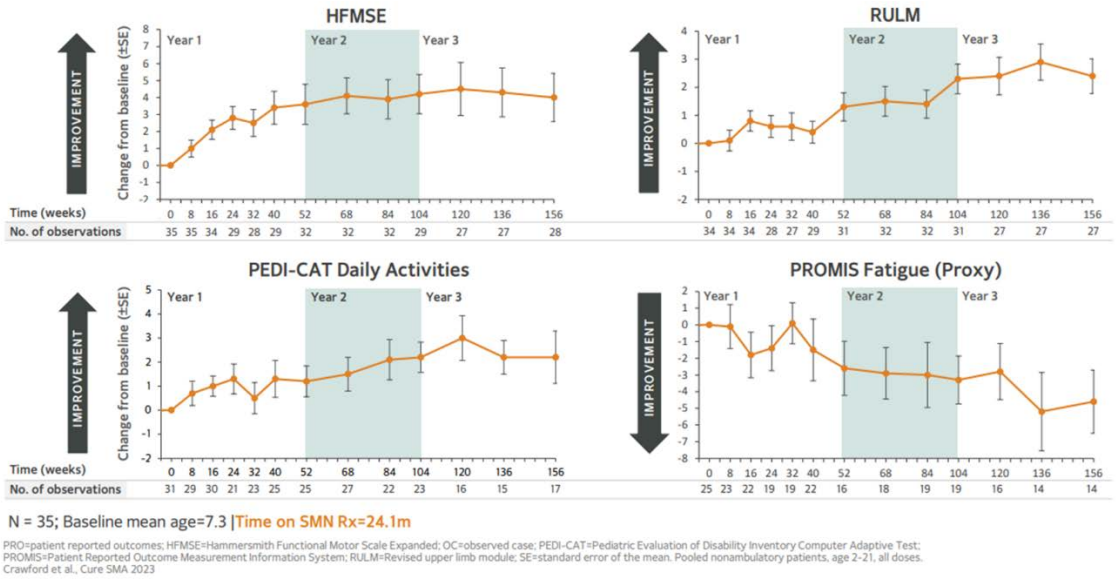
Exhibit 16: SRRK apitegromab Ph2 TOPAZ trial efficacy in types 2/3 SMA patients



Source: SRRK Corporate Presentation Jan. 2024

KROS' (OP, Smith) KER-065 (ActRII Ligand Trap)

KROS is developing ActRIIA/B ligand trap KER-065 that is BMP9 sparing (reduced bleeding risk); Ph1 SAD/MAD data in overweight/obese healthy volunteers expected in 1Q25. KROS' KER-065 is a chimera of the extracellular domains of ActRIIA and ActRIIB fused to a human Fc protein designed to maximally bind select TGF-β ligands, including myostatin and activin A, which are negative regulators of muscle/bone mass and strength, while sparing BMP9 inhibition. The compound was nominated out of KROS' proprietary library of activin receptor type II ligand traps. KROS believes the ligand-trap approach could enable greater signaling inhibition, and BMP9 sparing could provide an improved safety/tolerability profile by reducing bleeding risk. Preclinical studies in diet-induced obesity mouse models showed that RKER-065 (research form of KER-065) and a preclinical asset closely related to RKER-065, RKER-034, led to similar increases in lean muscle mass (see Exhibit 17). Preclinical evidence also suggests that RKER-034 alone or in combination with semaglutide could increase lean muscle mass and reduce fat mass. Specifically, combination treatment with RKER-034 and semaglutide led to reversal of lean mass mediated by semaglutide and enhanced loss of fat mass through increased energy expenditure from increased lean mass (Exhibit 18). Based on these data and the unmet need in obesity, KROS has initiated a placebo-controlled Phase 1 SAD/MAD trial of KER-065. Part 1 will evaluate three single doses (1, 3, and 5 mg/kg) of SC KER-065 in healthy volunteers (BMI of 18.5-30) over 4-week treatment period while Part 2 will include

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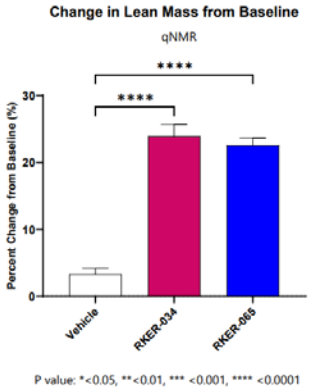
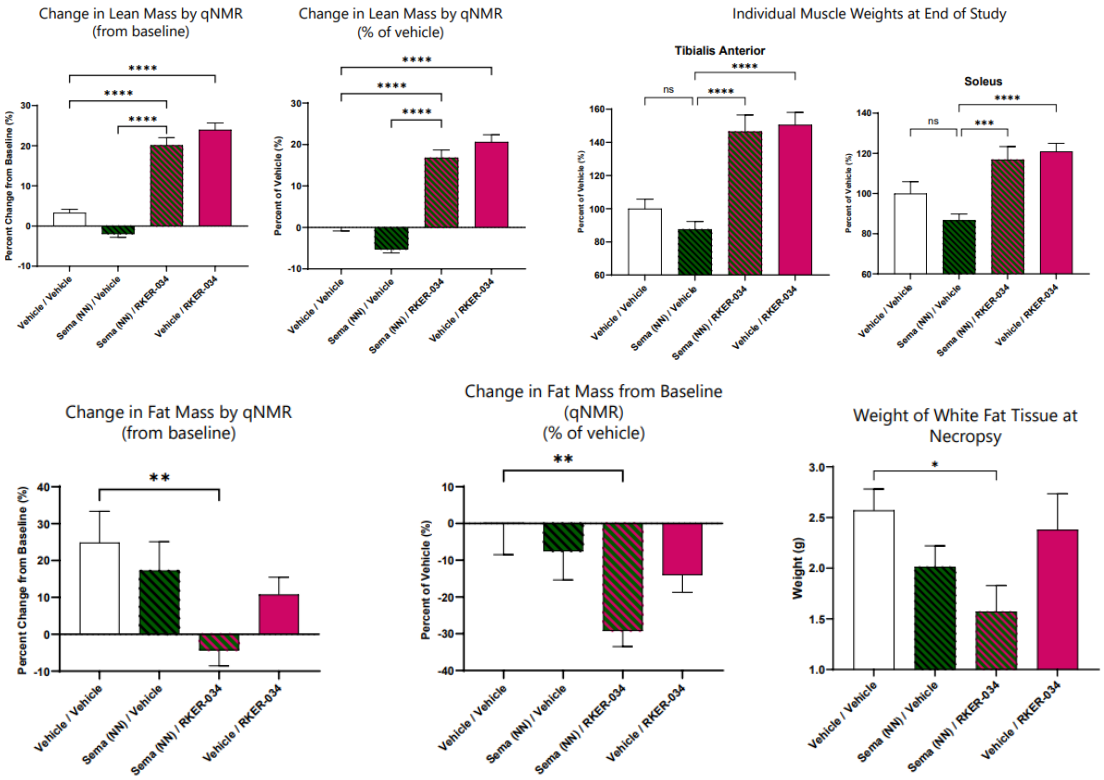
overweight/obesity participants (BMI between 27-33 kg/m^2) to assess safety, tolerability, PK, and PD activities (lean/fat mass and bone mineral density) in a relevant patient population over 12 weeks. KROS previously noted the potential for monthly dosing of KER-065 and expects to announce data from the study in 1Q25.

Exhibit 17: RKER-065 and RKER-034 in obese mice led to similar increases in lean mass



Sources: KROS company presentation

Exhibit 18: RKER-034 alone and in combination with semaglutide increased lean mass and enhanced loss of fat mas in a diet-induced mouse model of obesity



Sources: KROS company presentation

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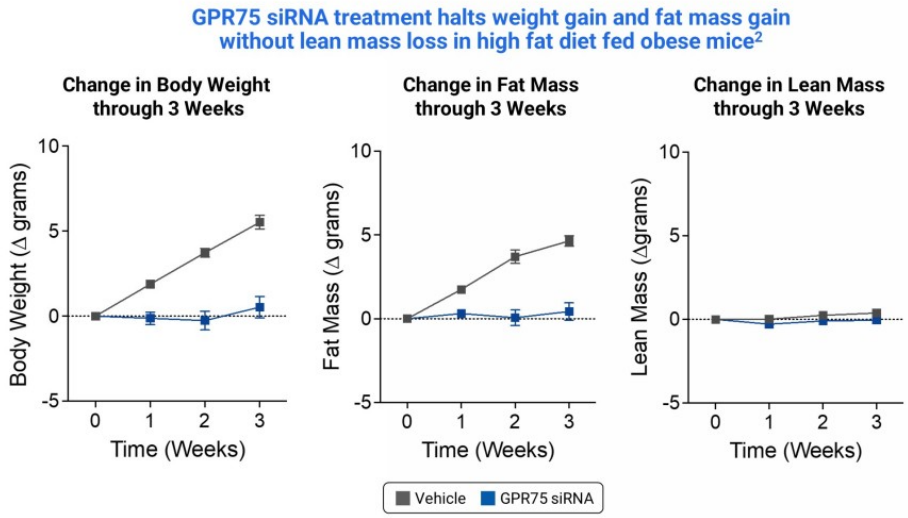
G protein–coupled receptor GPR75

REGN's GPR75 siRNA

REGN is investigating the GPR75 target with multiple modalities; GPR75 gene inactivation is associated with lower BMI. REGN's GPR75 siRNA (collaboration with ALNY [MP, Foroohar]) showed maintenance in body weight in preclinical rodent models of obesity vs. weight gain in untreated controls. The data also show maintenance in lean mass, but it was similar to untreated controls (Exhibit 19) REGN has yet to disclose preclinical data for this program that demonstrates weight loss along with maintenance in lean mass vs. loss in fat mass so we await future updates and timing for the program to enter the clinic. In addition to the siRNA modality, the company is also working on a small molecule approach with AZN (OP, Berens) and an antibody approach. But we understand that GPR75 is very difficult to target with an oral small molecule. REGN and AZN first announced their partnership to evaluate small molecules targeting GPR75 in July 2021 (see PR here) and have not yet been able to advance a candidate to Ph1.

Exhibit 19: siRNA against novel obesity target GPR75 maintains weight in rodent model of obesity



Source: REGN JPM Presentation Jan 8, 2024

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Exhibit 20A: Table of Amylin Programs

Company	Program	Target/Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
NVO	CagriSema (cagrilintide + semaglutide)	**cagrilitintide** - amylin **semaglutide** - GLP-1 combination of peptides	3	REDEFINE 1 in nondiabetic, obese patients. Primary endpoint: chg. in body weight. n=3,400 patients. NCT05567796	Est PC Oct. 2024	In Ph2 in T2D obese patients, CagriSema achieved a 15.6% reduction in body weight at week 32 vs. 5.1% with semaglutide alone or 8.1% with cagrilintide alone on the efficacy estimand In Ph2 in nondiabetic, obese patients, cagrilintide monotherapy achieved a 10.8% reduction in body weight vs. 9.0% liraglutide and 3.0% placebo after 26 weeks	In clinical trials, cagrilintide and semagltuide have been administered as two separate injections. Manufacturing and formulation considerations include commercialization with a dual chamber device to administer both agents simultaneously. Cagrilintide has been associated with injection-site reactons in some of its clinical experience that could bode watching in future readouts
				REDEFINE 2 in obese patients with T2D. Primary endpoint: chg. in body weight. n=1,200 patients. NCT05394519	Est PC Dec. 2024		
				H2H vs. tirzepatide in obese patients with T2D. Primary endpoints: change in body weight and HbA1c. n=1,000. NCT06221969	Est PC Nov. 2025		
				REDEFINE 3 cardiovascular outcomes trial in patients with obesity +/- T2D. Primary outcome: time to first occurance of MACE3. n=7,000. NCT05669755	Est PC Sept. 2027		
ZEAL	petrelintide (ZP8396)	amylin peptide	1b	Ph1b Part 2 ongoing with 16-week endpoint. Healthy volunteer PK/PD trial in obese/overweight patients. Primary endpoint: tolerability. n=68 (total trial Parts 1 and 2). NCT05613387	Est. PC May 2024	Ph1b MAD data showed up to 4.9% pbo-adj. weight loss at week 6 (0.6 mg group; 1.2 mg group slightly less at 4.7% weight loss) Most frequent AE was nausea. No discontinuations Ph1a SAD data showed up to 4.8% pbo-adj. weight loss at week 1 (2.4 mg group). Most frequent AEs were nausea and vomiting. No discontinuations.	Part 2 of the Ph1b testing higher doses with longer duration than Part 1. Part 2 has a dose-escalation scheme with a 16-week endpoint in n=48 patients. Data are expected in 1H24. Ph2 trial initiation expected in 2H24.
LLY	LY3841136 (LAARA)	amylin peptide	1	Healthy and/or nondiabetic obese patients. Primary endpoint safety with PK/PD secondary incl. chg. in body weight at week 28. n=160. NCT05295940	Est. PC Jan. 2024		Wholly owned by Lilly. May decrease body weight primarily through inhibition of food. Peptide intended for QW SC administration that could potentially be co-formulatable with tirzepatide or retatrutide.

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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Exhibit 20B: Table of Amylin Programs

Company	Program	Target/Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
NVO	Amycretin (NNC0487-0111)	amylin/GLP-1 peptide	1	Oral administration. SAD/MAD study in nondiabetic obese patients. Primary outcome safety with PK-related secondary endpoints. n=116. NCT05369390	Completed, Topline Disclosed	Positive Ph1 oral topline data were disclosed on the 4Q23 call limited to "well-tolerated". Company plans to move program forward	Amycretin is a unimolecular peptide that agonizes both amylin receptor and GLP-1 receptor. Given its modality and utilization of NVO's SNAC technology, we expect it to have food interaction considerations with oral administration. Mgmt. said on 3Q23 call that they are pursuing oral and subcutaneous presentations to give patients optionality.
				SC administration. SAD/MAD study in nondiabetic obese patients. Primary outcome safety with PK-related secondary endpoints. n=84. NCT06064006	Est. PC Oct. 2024		
LLY	LY3541105 (DACRA QW II)	amylin/calcitonin peptide	1	Healthy and/or nondiabetic obese patients. Primary endpoint safety with PK/PD secondary incl. chg. in body weight at week 26. n=160. NCT05380323	Est. PC Aug. 2024		Dual, unimolecular amylin-calcitonin receptor agonist (DACRA) peptide developed in collaboration with Key Biosciences (Private). Company believes it could decrease body weight through inhibition of food intake.They also see potential for glucose lowering and beneficial effects on bone. This is an acylated peptide for QW SC administration. LLY IR says it could be co-formulatable with tirzepatide or retatrutide.
AZN	AZD6234	amylin peptide	1	Healthy volunteer PK/PD trial in obese/overwight patients. Primary endpoint: safety with chg. in body weight seconday endpoint. n=68. NCT06132841	Est PC Oct. 2024		
GPCR		amylin small molecule	Preclinical		IND studies to start in late 2024		Mgmt. has stated that they are developing a small molecule amylin receptor agonist that could be combined with it's GLP-1 small molecule, GSBR-1290.

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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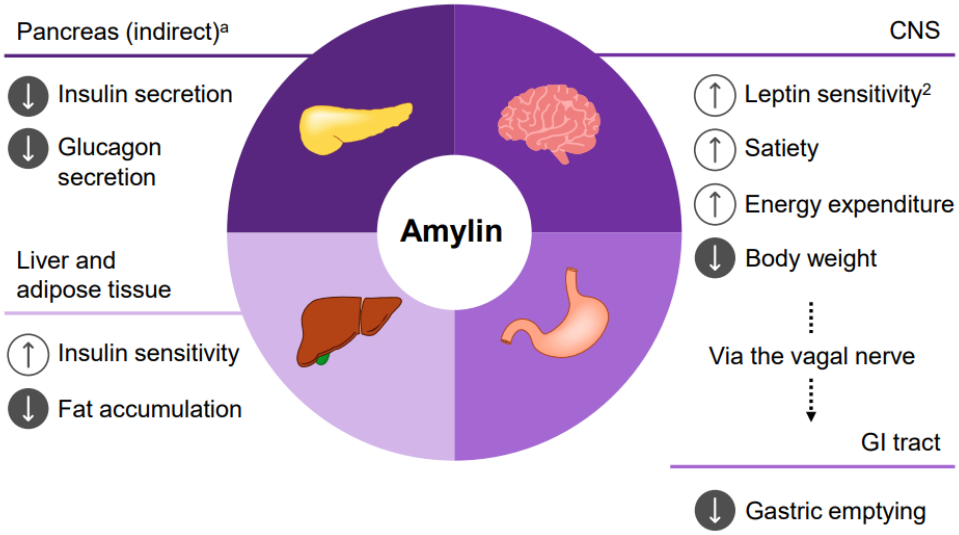
Amylin – Primarily Acts on The Brain

Amylin background. Amylin is a pancreatic β-cell hormone co-synthesized and co-secreted with insulin as a response to nutrient intake. It mostly works as a satiety signal and affects hedonic aspects of eating (reducing the reward feeling associated with food) by acting on a variety of different regions of the brain (Boyle et. al. Mol Met 2018). Amylin slows gastric emptying and suppresses the release of glucagon to control blood sugar (Zakariassen et. al. BCPT 2020). This combination of activities has made amylin analogues an attractive therapeutic approach to treating obesity. See Exhibit 21 for an overview of amylin's physiological effects that could contribute to weight loss.

Exhibit 21: Proposed physiological effects of amylin receptor activation



Source: ZEAL Jan 2024 Corporate Deck; 1. Figure adapted from Mathiesen et al. Eur J Endocrinol 2022;186(6):R93–R111; 2. Roth et al. Proc Natl Acad Sci U S A 2008;105(20):7257–7262. a) Mediated by the effect of amylin on the CNS.

It remains to be seen if amylin analogues (alone or in combination with an incretin therapy) could improve body composition with weight loss (targeting fat loss while preserving lean mass). Reference "Muscle-Sparing Programs" section within. ZEAL (Not Rated) notes in its Jan 2024 corporate deck (pg. 27) that its amylin analogue candidate, petrelintide (ZP8396), showed a significant reduction in body weight while preserving lean mass in a diet-induced obese rodent model (Exhibit 22). See additional details below on ZEAL's program. NVO's amylin analogue, cagrilintide, has been evaluated in multiple clinical trials with and without being combined with semaglutide (CagriSema), but we have yet to see data that evaluates body mass composition with its administration. We'd note that the Ph3 trials have a secondary endpoint of mass composition, and we await disclosure, see

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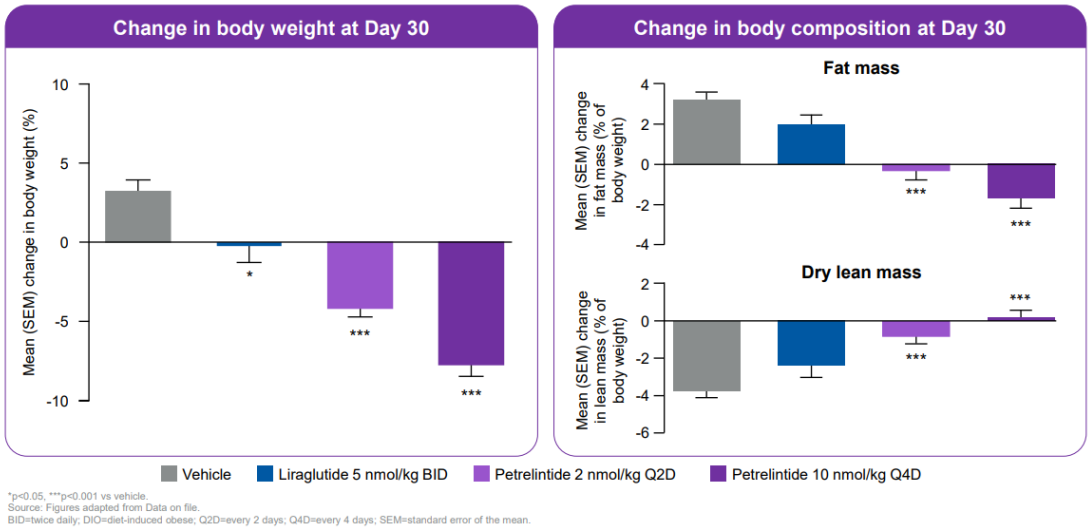
additional details on cagrilintide below. Regardless, lean mass preservation seems to be on the forefront of NVO's eventual strategy. On 3Q23 call when asked about programs that maintain lean mass, NVO's Executive Vice President & Head-Development Martin Holst Lange said (source: FactSet) *"It's also a focus of ours with current treatment, specifically, Wegovy and Saxenda, we actually see a reasonable preservation of lean body mass given the broader weight loss. But it has to be a focus area. And you'll probably see also in our pipeline, without going into details, maybe even quite soon, assets that could lead to preservation of lean mass."*

Exhibit 22: Petrelintide significantly reduced fat mass while preserving lean mass in diet induced obesity rat model



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

Source: ZEAL Jan 2024 Corporate Deck

Symlin (pramlintide) originally developed by Amylin Pharmaceuticals (now a wholly-owned subsidiary of AZN [OP, Berens]) is the only marketed amylin analogue. It was approved in 2005 for patients with type 1 or type 2 diabetes as an adjunct to mealtime insulin for achieving improved glycemic control despite being prescribed an optimal insulin regimen (Symlin FDA Prescribing Information). The adoption of Symlin has been poor, mostly owing to its lack of potency and insufficient pharmacokinetic properties. It has a short, 20–45-minute half-life and poor bioavailability and is administered subcutaneously thrice daily (Soares et. al. Int J Obes 2010). Due to its lack of ideal drug-like properties, several studies of Symlin have shown modest (1-3%) weight loss over 52 weeks in obese/overweight, T2D patients (Youk et. al. Exp. Op Pharm. 2011, Zakariassen et. al. BCPT 2020). However, one study showed up to 43% of patients administered Symlin twice daily achieving ≥10% weight loss after 12 months vs. 12% of patients achieving ≥10% weight loss given placebo (Smith et. al. Diab. Care. 2008).

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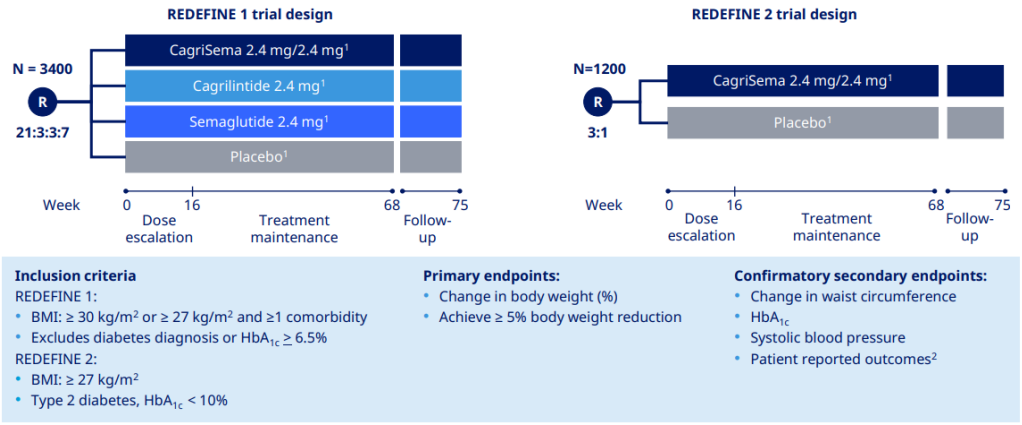
NVO's CagriSema (amylin + GLP-1)

CagriSema is a peptide combination therapy of amylin analogue, cagrilintide and GLP-1 semaglutide that has demonstrated promising data in T2D and nondiabetic obesity, but administration site reactions and commercial manufacturing capacity (given dual chamber device) bear watching. Ph3 data in nondiabetic obese patients are expected by YE24. The Ph3 CagriSema obesity program consists of three primary trials: REDEFINE 1 in nondiabetic, obese patients with est. primary completion in Oct. 2024 and data expected by YE24 (NCT05567796, see trial design in Exhibit 23), REDEFINE 2 in obese patients with T2D with est. primary completion in Dec. 2024 (NCT06221969, see trial design in Exhibit 23) and REDEFINE 3 cardiovascular outcomes trial in patients with obesity +/- T2D with est. primary completion in Sept. 2027 (NCT05669755). The company is also evaluating CagriSema head-to-head (H2H) vs. tirzepatide in obese patients with T2D (NCT06221969, est. primary completion Nov. 2025). **Of note, in clinical trials, cagrilintide and semaglutide have been administered as two separate injections.** NVO mgmt. has described that manufacturing and formulation considerations include commercialization with a dual chamber device to administer both agents simultaneously. **Additionally, administration site reactions have been associated with cagrilintide administration, but not in every trial, see details below.** We await future data disclosure to better understand this potential risk.

Exhibit 23: CagriSema Ph3 REDEFINE 1 and REDEFINE 2 trial design



Source: NVO Company Disclosures

Ph2 data for CagriSema(n=61) in obese/overweight patients with T2D were highly promising with up to 15.6% body weight reduction at 32 weeks. Administration site reactions were infrequent in this small trial. CagriSema achieved a 15.6% reduction in body weight at week 32 vs. 5.1% with semaglutide alone or 8.1% with cagrilintide alone (Exhibit 24). The mean change in HbA1c from baseline to week 32 was -2.2 pp with CagriSema, -1.8 pp with semaglutide and cagrilintide: –0.9 pp. ***Importantly, NVO***

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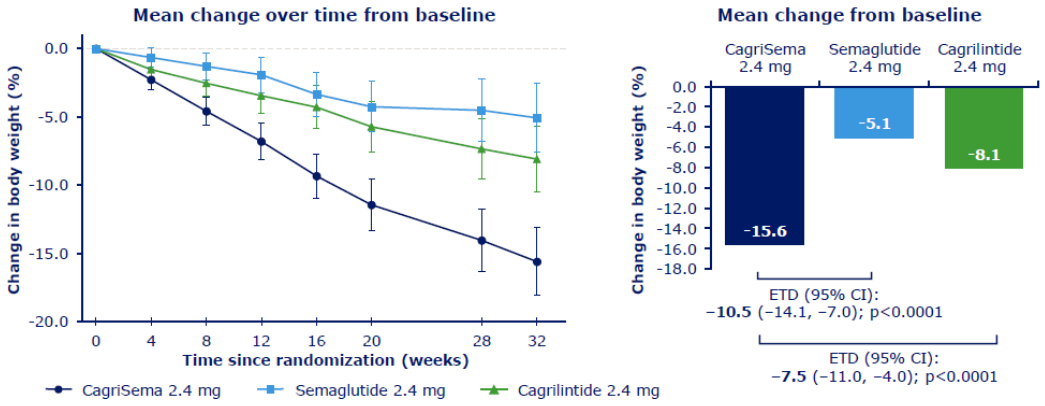
anticipates demonstrating that CagriSema's efficacy is superior to tirzepatide in a head to head trial (n=1000) in T2D patients which should report out in late 2025 or early 2026 (NCT06221969; est. primary completion Nov. 2025). **CagriSema was overall well-tolerated with most AEs mild to moderate and predominately GI-related.** Of note, out of n=31 patients assigned to receive CagriSema, no patients discontinued due to AEs. An injection site reaction only occurred in n=1/31 patients administered CagriSema and 2/30 administered cagrilintide monotherapy vs. 0/31 administered semaglutide monotherapy (Frias et. al. The Lancet 2023).

Exhibit 24: Percentage change in body weight Ph2 CagriSema in obese/overweight patients with T2D



Source: Efficacy and Safety of Co Administered s.c. Semaglutide and s.c. Cagrilintide in Type 2 Diabetes. ADA 2023.

Ph2 cagrilintide monotherapy data in nondiabetic, obese patients were encouraging with up to 10.8% body weight reduction at 26 weeks. Administration site reactions were more frequent in this trial, but they did not lead to frequent discontinuation. A Ph2 trial of cagrilintide monotherapy vs. liraglutide (Saxenda) or placebo was conducted in nondiabetic, obese/overweight patients over 26 weeks. Patients given 4.5 mg QW cagrilintide achieved a 10.8% reduction in body weight vs. 9.0% liraglutide and 3.0% placebo (Exhibit 25). Cagrilintide in this study appeared well-tolerated with at most 6% of patients discontinuing due to AEs (n=6/102 in each of the mid dose groups 1.2 mg QW and 2.4 mg QW). Only 1 patient in the high dose group (4.5 mg QW) discontinued due to AEs (n=1/101, 1%). **Of note, administration site reactions appeared to occur more frequently at higher doses with 17% of patients (n=17/101) administered 4.5 mg QW cagrilintide exhibiting injection-site erythema, and up to 12% of patients (n=12/102) exhibiting generalized injection-site reactions (in the 2.4 mg QW dose group).** The text noted that none of the administration-site reaction events were serious, none were severe with cagrilintide, and few led to treatment discontinuation: 2 patients given cagrilintide 0.6 mg

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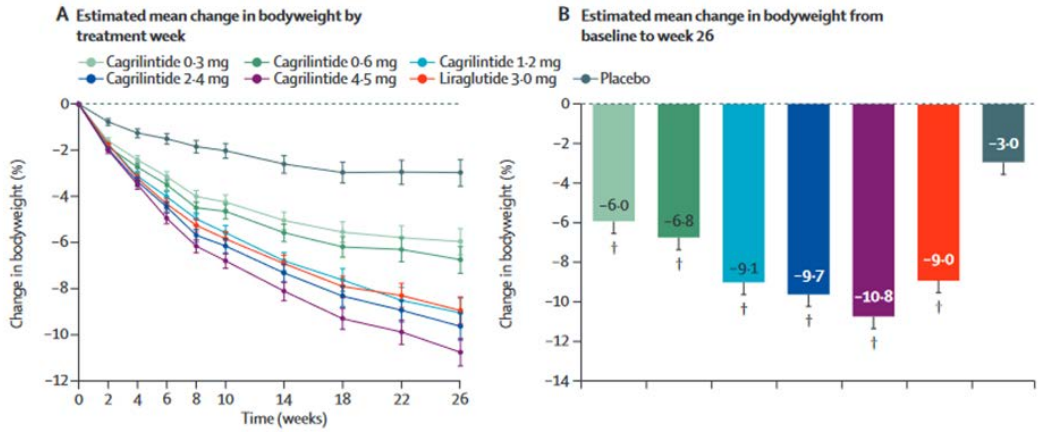
QW, 1 patient given cagrilintide 2.4 mg, and 1 patient given liraglutide 3.0 mg discontinued due to administration site reactions Lau et. al. The Lancet 2021.

In a small Ph1b MAD trial of nondiabetic obese/overweight patients, administration site reactions appeared frequent, with up to half of patients exhibiting them in a 12-patient cohort given weekly doses of 2.4 mg/2.4 mg CagriSema for 20 weeks. The frequency of administration site reactions was not dose-dependent. The text noted that *"All injection-site reactions were mild in severity and most were deemed possibly or probably related to cagrilintide administration, Injection-site reactions were not dose-dependent. The most common injection site-reactions were ecchymosis (34 events in 22 [79%] of 28 participants who reported injection-site reactions) and redness (30 events in nine [32%] participants)."* (Enebo et. al. The Lancet 2021).

Exhibit 25: Percentage change in body weight, Ph2 cagrilintide monotherapy in nondiabetic obese/overweight patients



Source: Lau et. al. The Lancet 2021

NVO's amycretin (amylin/GLP-1)

NVO disclosed positive oral amycretin Ph1 data on its 4Q23 call but didn't share the details. The company plans to move the program into additional Ph1 development with a subcutaneous formulation. Amycretin (NNC0487-0111) is a GLP-1/Amylin unimolecular co-agonist peptide that NVO is studying for oral and subcutaneous administration. On the 4Q23 call, the company disclosed positive Ph1 data for the oral formulation (source FactSet): *"The last highlight for the fourth quarter of 2023 is the successful completion of oral amycretin phase 1.* ***This trial appeared to have a safe and well-tolerated profile for amycretin. We have decided in September of 2023 to also initiate a phase 1 trial with once-weekly subcutaneous amycretin.*** *And further, we expect to advance amycretin into further clinical development."* See trial design in Exhibit X. The company believes this is a differentiated product and they expect that with either oral or

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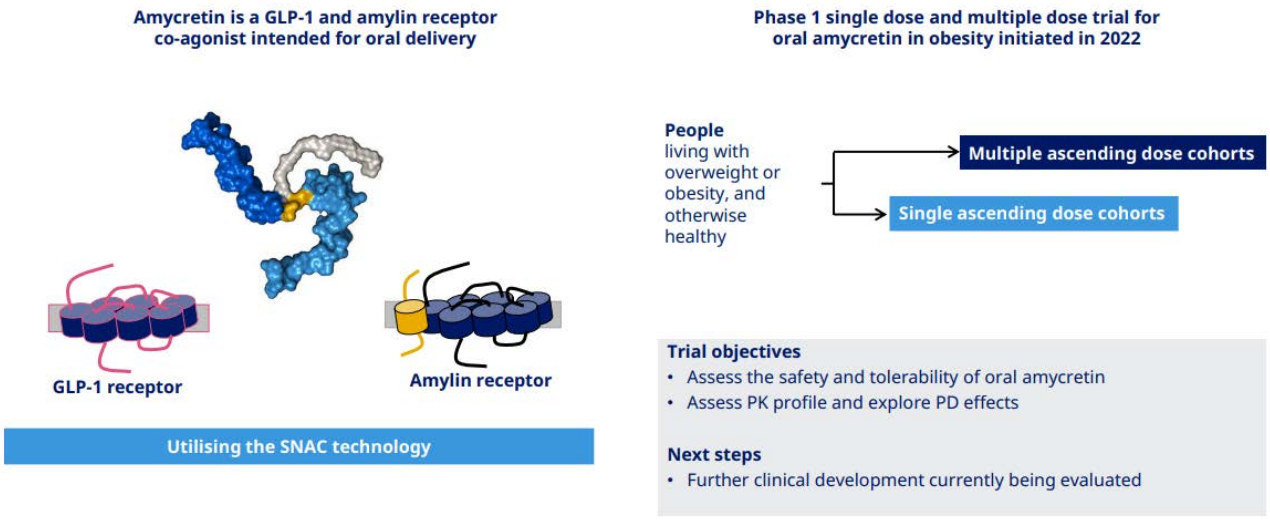
subcutaneous administration, it will have comparable efficacy to CagriSema. The Ph1/2 SAD/MAD subcutaneous study is now recruiting and is evaluating amycretin in nondiabetic obese/overweight patients (NCT06064006; est. primary completion Oct. 31, 2024).

The oral formulation of amycretin utilizes NVO's SNAC technology, the same platform as the company's Rybelsus product, thus we anticipate oral amycretin to also come with food restrictions. Recall that per Rybelsus's label *"Instruct patients to take RYBELSUS at least 30 minutes before the first food, beverage, or other oral medications of the day with no more than 4 ounces of plain water only. Waiting less than 30 minutes, or taking with food, beverages (other than plain water) or other oral medications will lessen the effect of Rybelsus. Waiting more than 30 minutes to eat may increase the absorption of Rybelsus"* (Rybelsus FDA Prescribing Information). Given that amycretin is also a peptide that utilizes this same technology, we expect a similar food effect and await additional company disclosures (Exhibit 26).

Exhibit 26: Oral amycretin platform and Ph1 oral formulation trial design



Source: NVO Company Disclosures

ZEAL's petrelintide (ZP8396)

Petrelintide background. ZEAL's petrelintide is a peptide amylin analog intended for once-weekly administration. **The company notes that petrelintide has properties of "chemical and physical stability" which it claims could enable co-formulation with other peptides in a single solution.**

Petrelintide has shown up to 5.3% weight loss in Part 1 of the Ph1b MAD study in nondiabetic obese/overweight patients after 6 weeks of weekly dosing. Part 2 data

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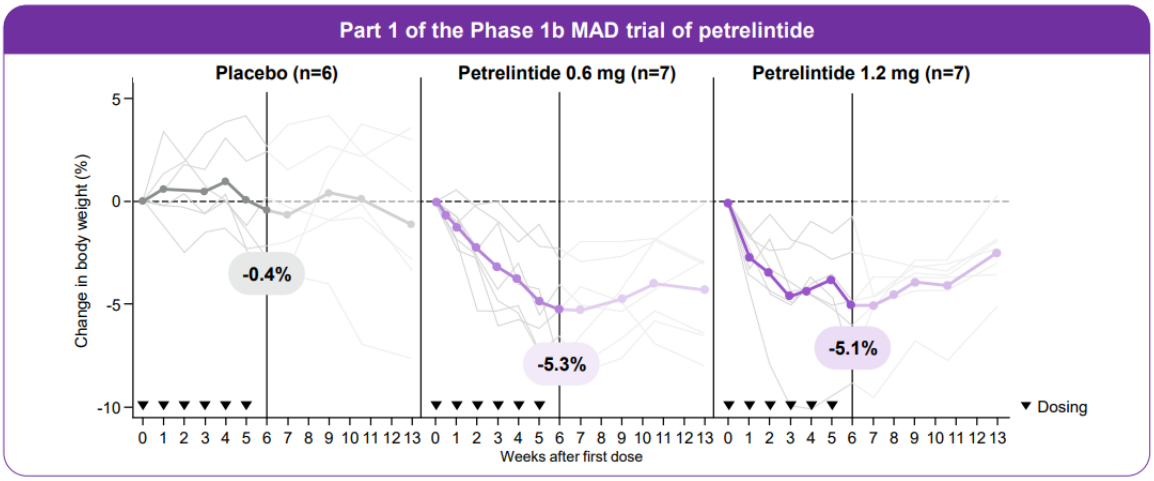
from the Ph1b with higher doses and a 16-week endpoint are expected in 1H24. ZEAL's Ph1 program of petrelintide is assessing weight loss in nondiabetic, obese/overweight patients. In Part 1 out to week 6, patients given petrelintide lost 5.3% mean body weight with 0.6 mg QW (n=7) and 5.1% with 1.2 mg QW (n=7) vs. 0.4% pbo (n=6, Exhibit 27). Petrelintide was well-tolerated during this part of the trial with only mild to moderate AEs and no discontinuations (Exhibit 28). **Of note, no injection site reactions were reported.** Data from Part 2 of the Ph1b with a titration up to higher doses in n=48 patients are expected in 2H24 (NCT05613387, est. primary completion May 2024).

Exhibit 27: Body weight change with petrelintide in Part 1 of Ph1b



Source: Zealand Pharma Obesity R&D Event Dec. 2023

Exhibit 28: AEs reported with petrelintide in Part 1 of Ph1b

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

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

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

Source: Zealand Pharma Obesity R&D Event Dec. 2023

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Exhibit 29A: Table of Glucagon Programs

Company	Program	Target/ Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
LLY	retatrutide (GGG)	GLP-1/GIP/GCG peptide	3	Ph2 trial in patients with CKD and obesity with or without T2D. Primary Outcome Change from Baseline in Glomerular Filtration Rate (GFR) at wk 24. n=120. NCT05936151	Est. PC Nov. 2025	In Ph2, nondiabetic obese/overweight patients lost a mean 24.2% of their body weight at 48 weeks in the highest dose administered (12 mg QW). Discontinuation rate due to adverse events (AEs) was 16% in the 12 mg QW dose group. In Ph2, T2D obese/overweight patients, the highest dose of retatrutide led to an approx. 17% reduction in body weight and 2.2% reduction in HbA1c at 36 weeks. Discontinuation rate due to AEs was 15% in the dose cohort.	Safety requires further validation. Retatrutide's 7% rate of cutaneous hyperesthesia vs. 1% in placebo drew our attention. We spoke with a KOL who speculated that the hyperesthesia could be due to vitamin deficiency due to loss in appetite. But LLY needs to further assess this AE and how to manage it.
				TRIUMPH-3 patients with obesity and cardiovascular (CV) disease. Primary endpoint: chg. in body weight at week 80. n=1,800. NCT05882045	Est. PC Jan. 2026		
				TRIUMPH-4 in obese patients with knee osteoarthritis. Primary endpoint: WOMAC Pain Subscale Score and Weight Loss in nondiabetic obese/overweight patients with osteoarthritis of the knee as a comorbidity. n=405. NCT05931367	Est. PC Feb. 2026		
				TRIUMPH-1. Nondiabetic obese patients. Primary endpoint, Week 80: Weight loss, Change from baseline in AHI for GSA2 subset, Change from baseline in WOMAC pain subscale score for GOA1 subset. n=2,100. NCT05929066	Est. PC Apr. 2026		
				TRIUMPH-2. T2D obese patients. Primary endpoint: Weight loss and Change from baseline in AHI for GSA2 subset. n=1000. NCT05929079	Est. PC May 2026		

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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Exhibit 29B: Table of Glucagon Programs

Company	Program	Target/ Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
BI/ZEAL	survodutide (BI 456906)	GLP-1/GCG peptide	3	SYNCHRONIZE-1 weight loss trial in nondiabetic obese patients. 3.6 mg or 6.0 mg QW vs. pbo. Primary endpoint: chg. in body weight at week 76. n=600. NCT06066515	Est. PC Dec. 2025	In Ph2, nondiabetic obese/overweight patient max dose (4.8 mg QW) survodutide led to 18.7% reduction in body weight vs. -2.0% placebo at 46 weeks. 29% of patients in the 4.8 mg QW cohort discontinued due to AEs.	Data were initially presented at ADA in June 2023, and the presenter noted that the poor tolerability could have been due to the rapid dose titration. It remains unclear from the presentation what the titration schedule was, but we highlight footnotes from the slides: “tolerability was assessed every two weeks, if gastrointestinal adverse events were intolerable, participant remained on the same dose for another week prior to dose escalation.” Thus the trial allowed a bit of titration flexibility, but still forced patients to dose escalate which could have caused the higher discontinuation rate. The presenter was also asked about the composition of body mass (fat vs. lean) lost, but he said that the data were “not available”.
				SYNCHRONIZE-2 weight loss trial in T2D obese patients. 3.6 mg or 6.0 mg QW vs. pbo. Primary endpoint: chg. in body weight at week 76. n=600. NCT06066528	Est. PC Dec. 2025		
				SYNCHRONIZE-CVOT. Cardiocascular (CV) outcomes study in obese/overweight patients with est. CV disease or chronic kidney disease (CKD). 3.6 mg or 6.0 mg QW vs. pbo. Primary endpoint: time to first occurrence of any components of composite endpoint: CV death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (to demonstrate non-inferiority) at week 114. n=4935. NCT06077864	Est. PC Mar. 2026		

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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Exhibit 29C: Table of Glucagon Programs

Company	Program	Target/ Modality	Phase	Trial Details/Info	Timing	Initial POC	Notes
ALT	pemvidutide (ALT-801)	GLP-1/GCG peptide	2+	Ph2 MOMENTUM trial in nondiabetic obese patients completed. Had 48-week weight loss endpoint in n=391 patients given pbo, 1.2 mg, 1.8 mg or 2.4 mg QW. 4-week titration schedule for 2.4 mg QW. Will meet with FDA mid-24 to discuss Ph3 design. Ph3 program design not fully disclosed, but mgmt. said it will include all three Ph2 doses, approx. n=5,000, and a longer duration dose-titration scheme. The company has not yet committed to also studying T2D patients in Ph3.	End of Ph2 FDA Meeting mid-24	Ph2 MOMENTUM trial demonstrated up to 15.6% weight loss at 48 weeks vs. 2.2% weight loss placebo. Treatment-related discontinuations were up to 16.2%.	Company plans to have partner moving into Ph3, with plan to move into Ph3 by mid-24 following FDA meeting.
LLY	Mazdutide	GLP-1/GCG peptide	2	Ph2 weight loss trial in nondiabetic obese/overweight patients. Primary endpoint chg. in body weight at 32 weeks. n=165. NCT06124807	Est. PC Nov. 2024	Topline Ph3 results in Chinese nondiabetic obese/overweight adults reported in Jan. 2024, but details not provided. Ph2 24-week study in Chinese nondiabetic obese/overweight patients showed up to −11.3% weight loss with 6 mg QW (n=61). There was only 1 treatment-related discontinuation and it corresponded to the 4.5 mg QW dose group (1.6%)	Initially developed in China, partnered with Innovent Biologics (Not Rated). LLY is beginning a Ph2 program in the US to complement their incretin portfolio. Filed for regulatory approval in China in Feb. 2024

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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Glucagon – Debatably an Incretin

Glucagon could treat obesity by promoting satiety and increasing energy expenditure. It is a pancreatic peptide hormone secreted in response to low blood glucose and acts on glucagon receptors (GCGR) most abundantly found in the liver (Kleinhart et. al. Int J Mol Sci 2019). While glucagon isn't a classical "incretin" gut hormone, it's often lumped into the same category for its ability to amplify insulin secretin (D'Alessio et. al. Diabetes 2023). Given their effect on liver fat, GCGR-targeted programs could also potentially reach beyond general obesity (i.e., into liver indications such as NAFLD and NASH). On the company's 1Q23 call, LLY's CSO/CMO Dan Skovronsky said (sourced from FactSet): *"In terms of which drug could be best, right now, of course, we have the most confidence around tirzepatide, but there might be some indications where a drug like retatrutide, which adds glucagon and – we call it GGG, could be better.* ***For example, glucagon has profound effects on fat in the liver. So, maybe that plays better for complications of obesity related to liver disease like NASH****."*

LLY's retatrutide (GLP-1/GIP/GCG)

LLY's retatrutide (GGG) is a unimolecular tri-agonist of GLP-1,GIP, and GCG. The company presented highly compelling Ph2 retatrutide data at ADA 2023 in June, exhibiting the greatest weight loss seen for any program to date. Nondiabetic obese/overweight patients lost an average of 24.2% of their body weight at 48 weeks in the highest dose administered (12 mg weekly). This compares favorably to tirzepatide's (Mounjaro's) 22.5% weight loss at week 72 in SURMOUNT-1 (roughly 20% at the same, week 48 timepoint, Jastreboff et. al. NEJM 2022). Retatrutide's results were particularly impressive because the trial enrolled a smaller percentage of females (who typically lose more weight than men) than other trials, and there was room for even more weight loss because the curves didn't plateau by the end of the study at 48 weeks (Exhibit 30). **We model 80% PoS-adj. 2032E retatrutide sales of $12B**. The next readout to watch will be from the Ph2 trial in obese/overweight patients with CKD and with/without T2D with est. primary completion in Nov. 2025 (NCT05936151). The Ph3 TRIUMPH-3 weight loss readout in obese/overweight patients with cardiovascular (CV) disease has est. primary completion in Jan. 2026 (NCT05882045). **See table in Exhibit 29 for the Ph3 retatrutide program.**

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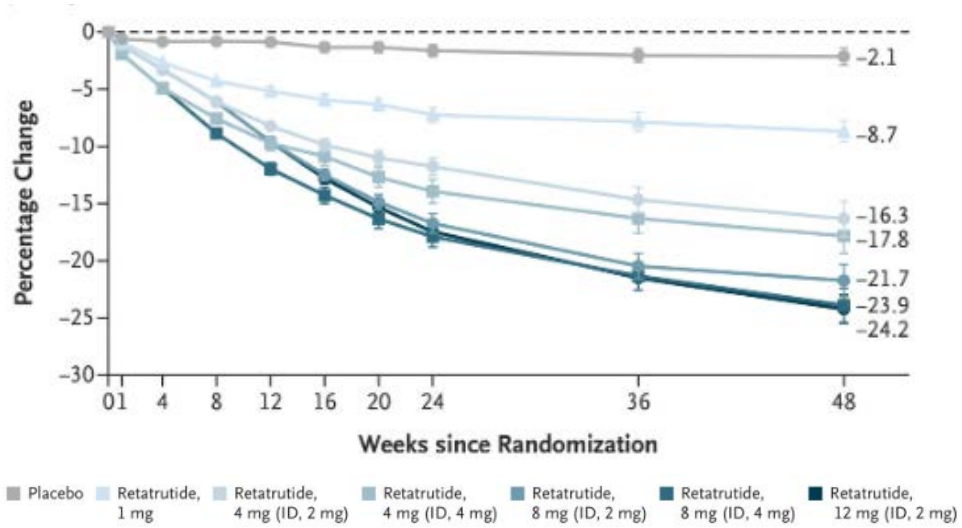
Exhibit 30: Ph2 retatrutide percent change in body weight in nondiabetic obese/overweight patients



Source: Jastebroff et. al. NEJM 2023

Retatrutide appeared tolerable, but safety requires further validation. The discontinuation rate due to adverse events (AEs) was 16% in the highest dose group, which compares unfavorably to tirzepatide's 6% in SURMOUNT-1. But there were only a small number (n=62) of patients in Ph2 retatrutide vs. Ph3 SURMOUNT-1 (n=630 in highest dose group 15 mg, Jastreboff et. al. NEJM 2022), and the dose escalation schedule could change in Ph3 to improve tolerability. Separately, retatrutide's 7% rate of cutaneous hyperesthesia with retatrutide vs. 1% in placebo drew our attention. The published text also noted: *"Reported cardiac arrhythmias were mild to moderate in severity with the exception of one severe adverse event (prolonged QT syndrome) in a participant treated with ondansetron [Zofran]." (Jastebroff et. al. NEJM 2023).* ***We note that Zofran is an anti-nausea medication with an FDA label warning regarding QT prolongation risk.*** We await retatrutide's Ph3 results to better assess retatrutide's safety and tolerability.

BI (Not Rated) and ZEAL's survodutide (GLP-1/GCG)

Survodutide demonstrated solid weight loss in Ph2, but tolerability remains a potential concern. In Ph2, nondiabetic obese/overweight patients given the max dose (4.8 mg QW, n=54 evaluable) of survodutide led to 18.7% reduction in body weight vs.-2.0% placebo (n=76 evaluable) at 46 weeks (Exhibit 31). Notably, 29% (n=22/77) of patients in the 4.8 mg QW cohort vs. 4% (n=3/77) discontinued due to AEs (Exhibit 32). The data were initially presented at ADA in June 2023, and the presenter noted that the poor tolerability could have been due to the rapid dose titration. It remains unclear from the presentation what the titration schedule was, but we highlight footnotes from the slides: "tolerability was assessed every two weeks, if gastrointestinal adverse events were intolerable, participant

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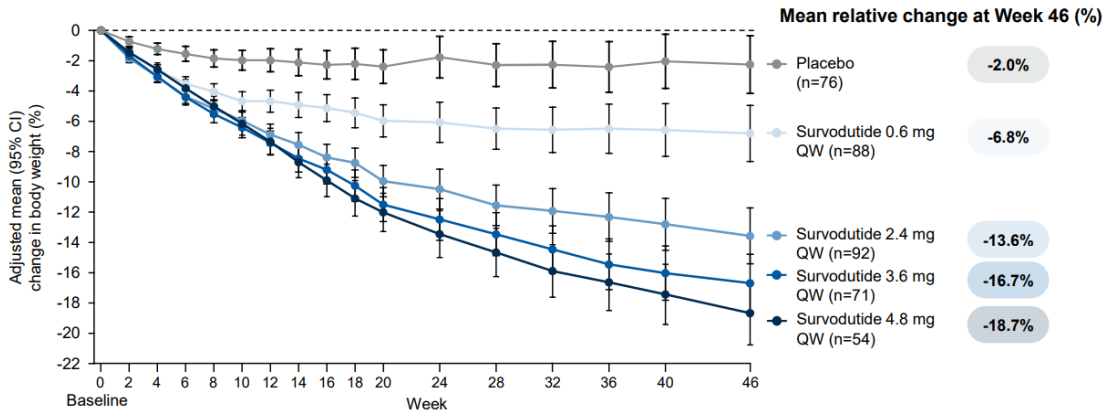
remained on the same dose for another week prior to dose escalation." Thus, the trial allowed a bit of titration flexibility, but still forced patients to dose escalate which could have caused the higher discontinuation rate. The presenter was also asked about the composition of body mass (fat vs. lean) lost, but he said that the data were "not available". The next obesity readout to watch for survodutide will be the Ph3 SYNCHRONIZE-1 weight loss trial in nondiabetic obese patients with est. primary completion in Nov. 2025 (NCT05936151). Survodutide will also have a Ph2 NASH readout in 1H24 (NCT04771273, actual primary completion was Nov. 2023).

Exhibit 31: Ph2 survodutide trial weight loss in obese/overweight nondiabetic patients



Source: Zealand Pharma Obesity R&D Event Dec. 2023

Exhibit 32: Ph2 survodutide trial AEs in obese/overweight nondiabetic patients

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

Source: Zealand Pharma Obesity R&D Event Dec. 2023

ALT's (Not Rated) pemvidutide (GLP-1/GCG)

ALT's pemvidutide is another GLP-1/GCG that had solid Ph2 weight loss in nondiabetic patients and the tolerability appears better than survodutide. The company plans to have a partner moving into Ph3, with plan to move into Ph3 by mid-24 following FDA meeting. Pemvidutide's Ph2 MOMENTUM trial demonstrated p to 15.6%

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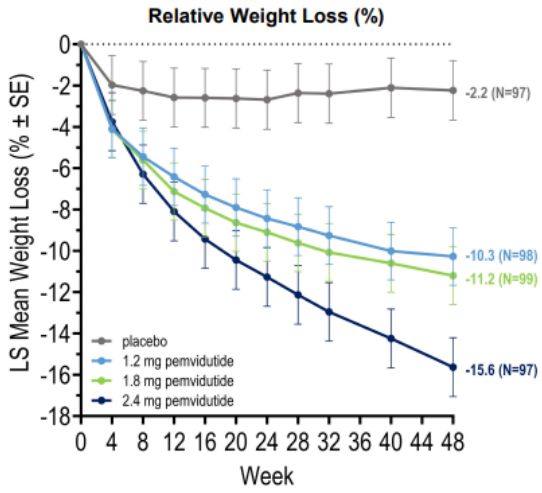
weight loss at 48 weeks with the highest, 2.4 mg dose (n=97 evaluable) vs. 2.2% weight loss placebo (n=97, Exhibit 33). Treatment-related discontinuations were at most 16.2% (Exhibit 34). The next readout to watch will be the Ph2b IMPACT trial in NASH with a readout in 1Q25 (NCT05989711, est. primary completion Feb. 2025). The company is planning to move into Ph3 by mid-2024 following a meeting with the FDA. The Ph3 program design is not yet fully disclosed, but mgmt. said it will include all three Ph2 doses (1.2, 1.8, and 2.8 mg QW), approx. n=5,000, and a longer duration dose-titration scheme. The company has not yet committed to also studying T2D patients in Ph3.

Exhibit 33: Ph2 pemvidutide trial weight loss in obese/overweight nondiabetic patients



Source: ALT Corporate Presentation Dec. 2023

Exhibit 34: Ph2 pemvidutide trial AEs in obese/overweight nondiabetic patients

Characteristic		Treatment			
		Placebo (N=97)	1.2 mg (N=98)	1.8 mg (N=99)	2.4 mg (N=97)
SAEs related to study drug	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
AEs leading to study drug discontinuation					
All AEs leading to discontinuation	N (%)	6 (6.2%)	5 (5.1%)	19 (19.2%)	19 (19.6%)
Drug-related AEs leading to discontinuation	N (%)	2 (2.1%)	4 (4.1%)	16 (16.2%)	15 (15.5%)
Gastrointestinal (GI) AEs—mainly mild to moderate					
Nausea	N (%)	11 (11.3%)	25 (25.5%)	59 (59.6%)	50 (51.5%)
Vomiting	N (%)	3 (3.1%)	6 (6.1%)	27 (27.3%)	27 (27.8%)
Diarrhea	N (%)	5 (5.2%)	8 (8.2%)	10 (10.1%)	18 (18.6%)
Constipation	N (%)	8 (8.2%)	17 (17.3%)	13 (13.1%)	22 (22.7%)
AEs of Special Interest (AESI)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Major Adverse Cardiac Events (MACE)	N (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiac AEs, including arrhythmias	N (%)	4 (4.1%)	3 (3.1%)	4 (4.0%)	3 (3.1%)

Source: ALT Corporate Presentation Dec. 2023

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Exhibit 35: Table of Select Additional Programs of Interest

Company	Program	Target/Modality	Phase	Timing
Leptin				
REGN	mibavademab (REGN4461)	leptin receptor agonist mAb	2	Trial initiation in 2024
ERX Pharmaceuticals	ERX-1000	leptin sensitizer small molecule	2	
Peptide YY (PYY)				
LLY	nisotirostide (LY3457263)	PYY analogue peptide	1	
CB1				
NVO	INV-202	peripheral CB1 inverse agonist small molecule	2	NCT05891834 Est. PC Jul. 2024
NVO	INV-347	peripheral CB1 inverse agonist small molecule	1	
SKYE	nimacimab	peripheral CB1 allosteric antagonist mAb	2	
CRBP	CRB-913	peripheral CB1 inverse agonist small molecule	Preclinical	IND 4Q24
Neuropeptide Y Type 2 (NPY2)				
BI	BI 1820237	NPY2 agonist peptide	1	NCT05751226 Est. PC Jul. 2024
Other				
Kallyope	K-757 and K-833	nutrient receptor agonists small molecules	2	NCT06019559 est. PC Feb. 2024
Aphaia Pharma	APH-012	distal jejunal-release dextrose	2	NCT05385978 est. PC Mar. 2024
Rivus Pharmaceuticals	HU6	controlled metabolic accelerator, mitochondrial uncoupler	2	NCT05284617 est. PC May 2024 (Obese HFpEF study)
Palatin	Bremelanotide	FPI-1Q2024 peptide	2	Data in 2H24
Aardvark Therapeutics	ARD-101	TAS2R (bitter taste receptors) small molecule	2	
Resalis Therapeutics	RES-010	miR-22 microRNA	1	
Resalis Therapeutics	RES-020	miR-22 microRNA	Preclinical	

Source: Leerink Partners; Company Disclosures; clinicaltrials.gov

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Select Additional Programs of Interest

Leptin

Leptin Background. Leptin is a peptide hormone predominantly secreted by adipose tissue, and plays a key role appetite regulation, energy balance, metabolism, endocrine function, and immune responses. Dysregulation of leptin is associated with metabolic disorders including obesity. Early studies on recombinant leptin therapy showed promise in suppressing appetite and increasing energy expenditure in leptin-deficient patients, sparking clinical interest in leveraging leptin to treat generalized obesity (Farooqi et al. NEJM.1999). However, translating these initial successes into effective treatments for the broader obese population has proven challenging. Most obese subjects exhibit central and peripheral leptin resistance, marked by increased serum leptin levels in the absence of physiological effects such as increased satiety. Encouraging, recent evidence has shown that partial reduction of plasma leptin levels restores sensitivity, decreases weight gain and improves insulin sensitivity (Zhao et al. Cell Met. 2019). Alternative leptin receptor agonists could offer opportunity to innovate on prior candidates which were limited by the short serum-half life, bioavailability and immunogenicity (Tao et al. Adv Sci. 2020).

REGN's mibavademab (REGN4461)

REGN mgmt. has discussed co-administration of leptin receptor agonist antibody, mibavademab, with a GLP-1. Ph2 trial could start in 2024. Mibavademab is a first-in-class leptin receptor agonist that has shown some proof of concept in patients with leptin disorders: congenital leptin deficiency (**CLD**) and generalized lipodystrophy (**GLD**). The program appeared to show selective fat loss in CLD (Exhibit 36, Ozsu et. al. J Endocr Soc. 2023). The company will be assessing whether mibavademab can produce incremental weight loss in combination with a GLP-1 agent and/or facilitate weight maintenance in general obesity.

Mibavademab proof of concept studies. A Ph2 trial enrolled n=16 patients with **GLD**, baseline diabetes (mean HbA1c 9.6%) and hypertriglyceridemia (median TGs 669 mg/dL). Publication of the initial data notes that after 8 weeks of "low-dose" mibavademab, clinically meaningful differences were not observed relative to placebo. But in an exploratory pooled analyses after 28 weeks of mibavademab administration, clinically significant reductions from baseline in HbA1c (mean: -1.9) and in TGs (median: -102.1 mg/dL) were observed (Olenchock et. al. J Endocr Soc. 2023). Separately, in a case report of an obese child with **CLD** and baseline bodyweight of 89.9 kg, administration of mibavademab led to rapid weight loss at an initial rate of 7.1 kg/month until Month 7. Upon dose adjustment, weight loss velocity decreased to 3.1 kg/month. The child achieved weight stabilization at Month 11 at a weight of 28.9 kg (approx. -68% change) while continuing mibavademab (Exhibit 36, Ozsu et. al. J Endocr Soc. 2023).

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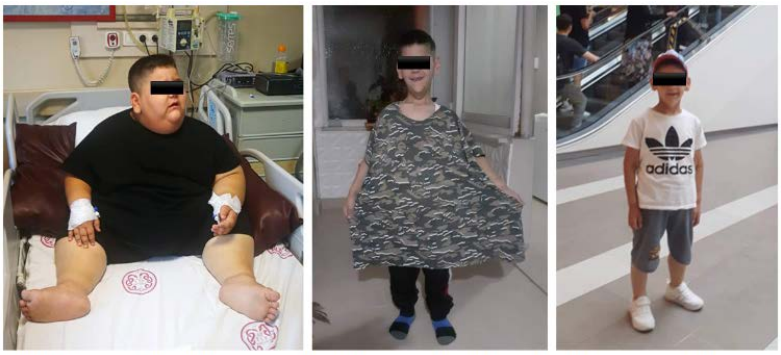
Exhibit 36A: Mibavademab demonstrates weight loss in a child with CLD

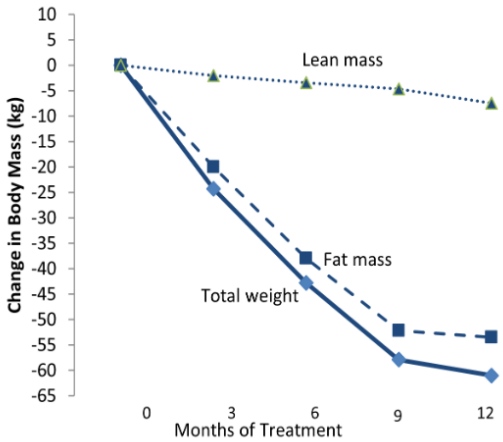


Neutralizing antibody to metreleptin present

Neutralizing antibody to metreleptin present, being treated with mibavademab at 9 months (middle) and 12 months (right) of therapy

Source: REGN Company Disclosures, Ozsu et. al. J Endocr Soc. 2023

Exhibit 36B: Mibavademab demonstrates weight loss in a child with CLD



Source: REGN Company Dislocsures, Ozsu et. al. J Endocr Soc. 2023

Peptide YY (PYY)

Peptide YY is another gut hormone that can control appetite by increasing satiety, but its analogues have had a history of failed development, most recently with NVO's dropped Ph2 program. LLY currently has a Ph1 program. Peptide YY (PYY) has been shown to play a role in regulating appetite and affecting energy expenditure and food-seeking behavior by acting centrally and peripherally (Karra et. al. J Physio 2009). However, analogues of PYY have had difficulty in the clinic primarily owing to lack of efficacy. On NVO's 2Q call, the company stated that it's PYY analogue program, PYY1875, didn't meet the threshold for continued development (*sourced from FactSet)*: "*Within obesity, we completed a Phase 2 proof-of-concept trial with PYY in May. Due to a modest treatment*

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effect, we have decided to terminate the development of this PYY agonist." It remains unclear if NVO will publish the failed dataset.

LLY remains interested in PYY, with its Ph1 analogue program, nisotirostide, (LY3457263). LLY has nisotirostide listed as for diabetes in its pipeline chart, but IR told us it's not meant to indicate diabetes is the only indication the company is evaluating. We thus assume that LLY is considering developing it in nondiabetic obesity as well. Nisotirostide is an acylated peptide PYY analog that selectively activates the NPY-receptor 2 engineered for once-weekly delivery. The company is currently evaluating this nisotirostide both alone and in combination with an incretin in Ph1. There are completed trials for nisotirostide listed on clinicaltrials.gov in diabetic and nondiabetic patients (NCT05582096 actual primary completion Jun. 2023, NCT05377333 actual primary completion Nov. 2023). We hope to see updates on nisotirostide presented at an upcoming medical conference.

Cannabinoid CB1 Receptor

Initial cannabinoid CB1 receptor antagonists that act centrally were withdrawn from the market due to severe mood disorders, but programs that act peripherally could potentially offer promise with reduced liability. SAN FP's (OP, Risinger) Acomplia (rimonabant) was a CB1 antagonist that showed up to 10% weight loss over 1 year. It was originally approved as an AOM in the EU, but its marketing authorization was withdrawn by the EMA in 2009 after it was shown to cause severe psychiatric side effects such as depression (EMEA/537153/2008, EMEA/537153/2008). But Acomplia was known to act centrally which could have been the underlying cause of the psychiatric AEs.

Newer programs, such as NVO's INV-202 & INV-347 plus SKYE's (Not Rated) nimacimab are intended to act peripherally with CNS exclusion to potentially abrogate the possibility of mood-related AEs. But their efficacy in obesity remains to be seen. NVO's subsidiary, Inversago, is developing small molecule, peripherally acting CB1 inverse agonists. Furthest along program is INV-202 that is in Ph2 for nondiabetic obese patients with est. primary completion Jul. 2024 (NCT05891834). Inversago also has a second-gen program, INV-347 in Ph1 per the company website. SKYE is developing nimacimab, an anti-CB1 antagonist antibody. In Ph1, nimacimab demonstrated "trends in reduction of ALT, AST, alkaline phosphatase, GGTP, and ELF score (non-dose dependent) with significant reduction in hyaluronic acid; suggests potential anti-inflammatory and anti-fibrotic effect of nimacimab" per the company's Jan. 2024 corporate presentation. SKYE claims that nimacimab has significantly improved peripheral restriction relative to INV-202. CRBP (Not Rated) also has CRB-913, a peripherally restricted CB1 antagonist in preclinical development that the company expects to file an IND for in 4Q24. We await future updates to see if peripheral CB1 targeting could drive substantial weight loss.

See Exhibit 35 for additional programs.

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Disclosures Appendix

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I, Marc Goodman, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

I, Thomas J. Smith, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

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			IB Serv./Past 12 Mos.	
Rating	**Count**	**Percent**	**Count**	**Percent**
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HOLD [MP]	63	25.1	7	11.1
SELL [UP]	3	1.2	0	0

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

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