



Advancing enobosarm, an oral novel selective androgen receptor modulator (SARM), to avoid muscle loss and augment fat loss when combined with a Glucagon-like peptide-1 receptor agonist (GLP-1 RA) drugs for potentially higher quality weight loss

**Mitchell Steiner, MD
Chairman and CEO
Veru, Inc.
May 16, 2024**



Forward looking statements and safe harbor

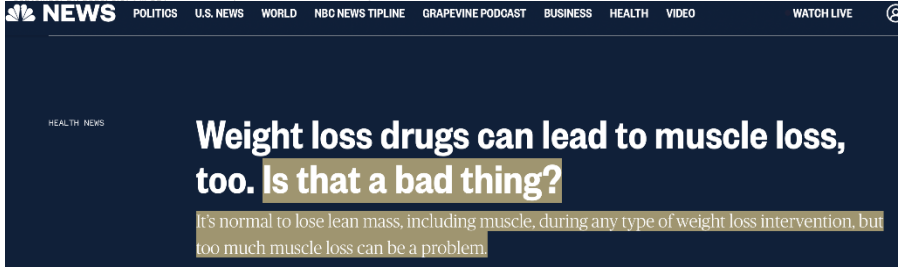
The statements in this document that are not historical facts are “forward-looking statements” as that term is defined in the Private Securities Litigation Reform Act of 1995. Forward-looking statements in this document include statements regarding: the planned design, enrollment, timing, commencement, interim and full data readout timing, scope, regulatory pathways, and results of the Company’s current and planned clinical trials, including the Phase 2b study of enobosarm in combination with a GLP-1 agonist for the treatment of obesity and related muscle wasting, the confirmatory Phase 3 study of sabizabulin for certain COVID-19 patients (if undertaken), the Phase 3 study of sabizabulin in adult hospitalized patients with ARDS (if undertaken), the Phase 2b/3 study of enobosarm in combination with abemaciclib for the 2nd line treatment of AR+ ER+ HER2 metastatic breast cancer, and whether any of such studies will meet any of its primary or secondary endpoints; whether and when the IND for the enobosarm/GLP-1 combination study will be filed with the U.S. FDA, whether the FDA will require any additional studies or any preclinical studies, whether the study, if started, will have the same target patient populations as described in this presentation, and whether and when the planned study will commence enrollment and read out data; whether the historical clinical results showing enobosarm’s effect on preventing muscle wasting, increasing or maintaining muscle mass and bone density or assisting with preferential fat loss will be replicated to any significant degree or at all in the planned Phase 2b study or in any future study and whether, if approved, any such results would be seen in commercial clinical use; whether and when any of the planned interim analyses in the planned Phase 3 confirmatory study of sabizabulin for certain COVID patients or in ARDS patients or in any other trial will occur and what the results of any such interim analyses will be; whether the results of any such interim analyses or any completed Phase 3 study or any other interim data will be sufficient to support an NDA for sabizabulin for any indication; whether and when any potential NDA would be granted; whether and when the Company will meet with BARDA regarding any potential partnering opportunities and whether those efforts will be successful, and when the Company might learn the results of any potential partnering efforts with BARDA; whether and how the Company will fund the planned Phase 3 studies of sabizabulin in COVID-19 and ARDS or any other indication; whether the current and future clinical development efforts of the Company, including all studies of sabizabulin in COVID-19, ARDS, or any other infectious disease indications or enobosarm in obesity or oncology indications, and any of their results will demonstrate sufficient efficacy and safety and potential benefits to secure FDA approval of any of the Company’s drug candidates; whether the drug candidates will be approved for the targeted line of therapy; whether government and private payors will provide sufficient coverage for enobosarm for obesity or any of the Company’s other drugs, if approved in each case; whether the companies that develop and commercialize GLP-1 drugs for obesity will accept the use of enobosarm in combination with their respective products; whether the intellectual property portfolio for enobosarm is sufficient to protect the Company’s interest in enobosarm in obesity, breast cancer or any other indication and whether it will prevent competitors from developing SARMs for the same indication or whether the Company will have the resources or be successful in enforcing its intellectual property rights; whether and how long the relative lack of competition in the obesity market for drugs and drug candidates that might help mitigate muscle wasting will continue and what the effects of any such competition might be on the Company’s prospects in the sector; whether enobosarm will become a treatment, in combination or alone, for obesity or breast cancer, and whether sabizabulin will become a treatment for broad ARDS or COVID-19; whether the Company’s FC2 telemedicine portal sales will grow or replace prior revenue from the U.S. prescription sales of FC2; whether the Company will recover any of the monies owed it by The Pill Club; whether and when the Company will receive the remaining installments from Blue Water in connection with the sale of ENTADFI or will receive any of the potential sales milestones related thereto and whether the Company will ever be able to liquidate the preferred stock that it owns in Blue Water; whether, when and how many shares may be sold under the Lincoln Park Capital Fund equity line; whether the cash raised by any future equity offering will be sufficient for the Company’s planned or expected operations; and whether the Company’s current cash will be sufficient to fund its planned or expected operations. These forward-looking statements are based on the Company’s current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: the development of the Company’s product portfolio and the results of clinical studies possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical studies and the ability to enroll subjects in accordance with planned schedules; the ability to fund planned clinical development as well as other operations of the Company; the timing of any submission to the FDA or any other regulatory authority and any determinations made by the FDA or any other regulatory authority; the Company’s existing product, FC2 and any future products, if approved, possibly not being commercially successful; the ability of the Company to obtain sufficient financing on acceptable terms when needed to fund development and operations; demand for, market acceptance of, and competition against any of the Company’s products or product candidates; new or existing competitors with greater resources and capabilities and new competitive product approvals and/or introductions; changes in regulatory practices or policies or government-driven healthcare reform efforts, including pricing pressures and insurance coverage and reimbursement changes; risks relating to the Company’s development of its own dedicated direct to patient telemedicine and telepharmacy services platform, including the Company’s lack of experience in developing such a platform, potential regulatory complexity, and development costs; the Company’s ability to protect and enforce its intellectual property; the potential that delays in orders or shipments under government tenders or the Company’s U.S. prescription business could cause significant quarter-to-quarter variations in the Company’s operating results and adversely affect its net revenues and gross profit; the Company’s reliance on its international partners and on the level of spending by country governments, global donors and other public health organizations in the global public sector; the concentration of accounts receivable with our largest customers and the collection of those receivables; the Company’s production capacity, efficiency and supply constraints and interruptions, including potential disruption of production at the Company’s and third party manufacturing facilities and/or of the Company’s ability to timely supply product due to labor unrest or strikes, labor shortages, raw material shortages, physical damage to the Company’s and third party facilities, product testing, transportation delays or regulatory actions; costs and other effects of litigation, including product liability claims and securities litigation; the Company’s ability to identify, successfully negotiate and complete suitable acquisitions or other strategic initiatives; the Company’s ability to successfully integrate acquired businesses, technologies or products; and other risks detailed from time to time in the Company’s press releases, shareholder communications and Securities and Exchange Commission filings, including the Company’s Form 10-K for the fiscal year ended September 30, 2023 and subsequent quarterly reports on Form 10-Q. These documents are available on the “SEC Filings” section of our website at www.verupharma.com/investors. The Company disclaims any intent or obligation to update these forward-looking statements.

HEALTH · WEIGHT-LOSS AND DIET CONTROL INDUSTRY

Weight-loss drugs like Ozempic and Wegovy may be risky for older people because they melt away all-important muscles, experts say

BY MADISON MULLER AND BLOOMBERG

September 27, 2023, 3:57 PM EDT



SCIENTIFIC AMERICAN

PHARMACEUTICALS

Ozempic and Other Weight-Loss Drugs Bear Heavy Costs and Questions for Seniors

Limited data on adults age 60 and older raise questions on whether high-priced weight-loss drugs will really help with lowering rates of chronic illness and disability

HEALTH NEWS

✓ Fact Checked

Ozempic Can Cause Major Loss of Muscle Mass and Reduce Bone Density

By [Cathy Cassata](#) on May 2, 2023 — Fact checked by [Jill Seladi-Schulman, Ph.D.](#)



Weight loss medications like Ozempic and Wegovy can help people drop pounds quickly, but they can also cause a rapid loss of muscle mass and bone density unless lifestyle changes are made. anandaBGD/Getty Images

- Rapid weight loss from taking GLP-1 medications like Ozempic and Wegovy can cause a decrease in muscle mass, lessen bone density, and lower your resting metabolic rate, leading to sarcopenia.
- Sarcopenia is the gradual loss of muscle mass, strength, and function and is typically associated with aging.
- Lifestyle changes such as increasing protein intake and incorporating strength and resistance training can help combat muscle and bone density loss while taking GLP-1 medications.

veru | GLP-1 receptor agonist drugs therapy results in significant loss of both fat and muscle in overweight or obese patients

- Weight loss drugs GLP-1 receptor agonists demonstrated a 6.2-17% average total weight loss^{1,2}
- 20-50% of the total weight loss is fro

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 18, 2021 VOL. 384 NO. 11

Once-Weekly Semaglutide in Adults with Overweight or Obesity

John P.H. Wilding, D.M., Rachel L. Batterham, M.B., B.S., Ph.D., Salvatore Calanna, Ph.D., Melanie Davies, M.D., Luc F. Van Gaal, M.D., Ph.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Barbara M. McGowan, M.D., Ph.D., Julio Rosenstock, M.D., Marie T.D. Tran, M.D., Ph.D., Thomas A. Wadden, Ph.D., Sean Wharton, M.D., Pharm.D., Koutaro Yokote, M.D., Ph.D., Niels Zeuthen, M.Sc., and Robert F. Kushner, M.D., for the STEP 1 Study Group*

	Semaglutide 2.4 mg once weekly (N=1306)	Placebo once weekly (N=655)	Treatment comparison for semaglutide vs. placebo [95% CI]
<i>Co-primary endpoint assessed in the overall population</i>			
Body weight change from baseline to week 68 – %	-16.86	-2.44	ETD: -14.42 [-15.29; -13.55]
Body weight reduction ≥5% – proportion of participants (%) at week 68	92.4	33.1	OR: 37.0 [28.0; 49.0]

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]

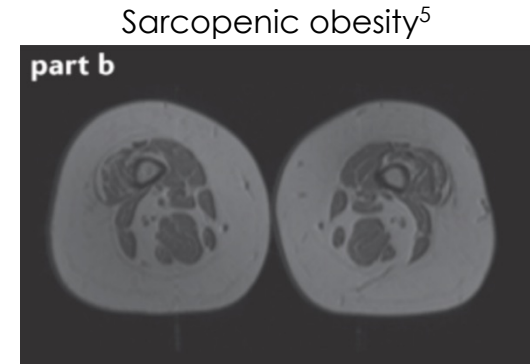
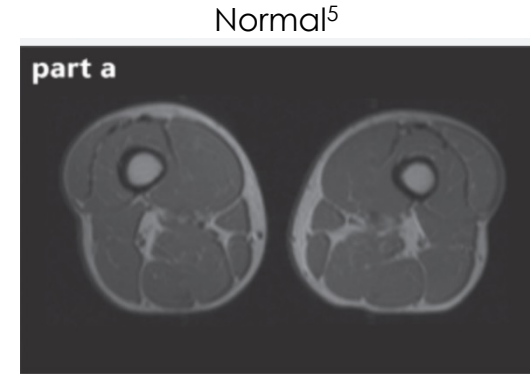


1 pound of muscle for 1 pound of fat

¹ Wilding JPH et al. NEJM 384:989-1002, 2021 | ² Wegovy FDA PI | ³ Sargeant JA et al. Endocrinol Metab 34:247-262, 2019 | ⁴ Ida S et al. Current Diabetes Rev 17:293-303, 2021 | ⁵ McGrimmon RJ et al. Diabetologia 63:473-485, 2020

veru | **GLP-1 RA drugs result in significant loss of both fat and muscle**
The target population is the at risk obese or overweight patients with low muscle reserves

- **Approximately 42% of older adults (>60 yo) have obesity or overweight and could benefit from weight-loss drugs¹**
- **Subpopulation: older obese or overweight patients with low muscle mass/ functional limitations**
 - 30% of people over 60 years old and more than 50% of those over 80 years old have sarcopenia
 - Patients with sarcopenic obesity, high fat mass with very low muscle mass, have the greatest risk to develop **muscle weakness** because of critically low muscle mass with weight-loss drug treatment²⁻⁴
 - Elderly patients with sarcopenia obesity have a higher risk of frailty/**muscle weakness**, which can lead to poor balance, decrease in gait, loss of muscle strength, functional limitations, mobility disability, **falls and fractures**, higher hospitalization rate, and increased mortality²⁻⁴



CT scans

¹ CDC | ² Wennamethee SG et al. Current Diabetes Reports 2023 | ³ Spanoudaki M et al. Life 13:1242, 2023 | ⁴ Roh E et al. Front Endocrinol 11: 2020 | ⁵ Batsis J et al. Nature Reviews Endocrinology 14:513-537, 2018



WEGOVY FDA label now has **hip and pelvic fracture** safety data from SELECT cardiovascular outcomes study

wegovy[®]

semaglutide injection **2.4 mg**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WEGOVY[®] safely and effectively. See full prescribing information for WEGOVY[®].

WEGOVY[®] (semaglutide) injection, for subcutaneous use

Fractures

In the cardiovascular outcomes trial in adults, more fractures of the hip and pelvis were reported on WEGOVY[®] than on placebo in female patients: 1.0% (24/2448) vs. 0.2% (5/2424), and in patients ages 75 years and older: 2.4% (17/703) vs. 0.6% (4/663), respectively.

The Atlantic

HEALTH

The Ozempic Plateau

Everyone hits a weight-loss plateau, but the race is on for next-generation drugs that can help patients lose even more weight.

By Sarah Zhang

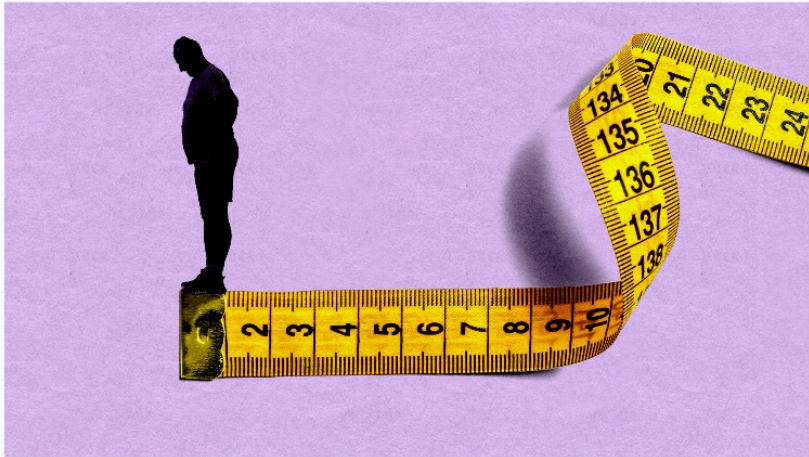


Illustration by The Atlantic. Source: Getty.

JANUARY 17, 2024, 8 AM ET

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Why Do GLP-1 Drugs Stop Working, and What to Do About It?

Marilynn Larkin
January 12, 2024

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There's no question that **glucagon-like peptide 1 (GLP-1)** agonists represent a major advance in the treatment of **obesity** for patients with or without diabetes. In clinical trials, participants lost **15%-20%** of their body weight, depending on the drug.

But studies also have shown that once people stop taking these drugs — either by choice, because of shortage, or lack of access — they **regain most**, if not all, the weight they lost.

Arguably more frustrating is the fact that those who continue on the drug eventually reach a **plateau**, at which point, the body seemingly stubbornly refuses to lose more weight. Essentially, it **stabilizes at its set point**, said Fatima Cody Stanford, MD, MPH, MPA, MBA, an obesity medicine physician at Massachusetts General Hospital and associate professor at Harvard Medical School in Boston.

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2024 Outlook: Can GLP-1 patients stop taking the drug and keep weight off?

By Noah Tong - Dec 28, 2023 7:00am

GLP-1 weight loss semaglutide tirzepatide

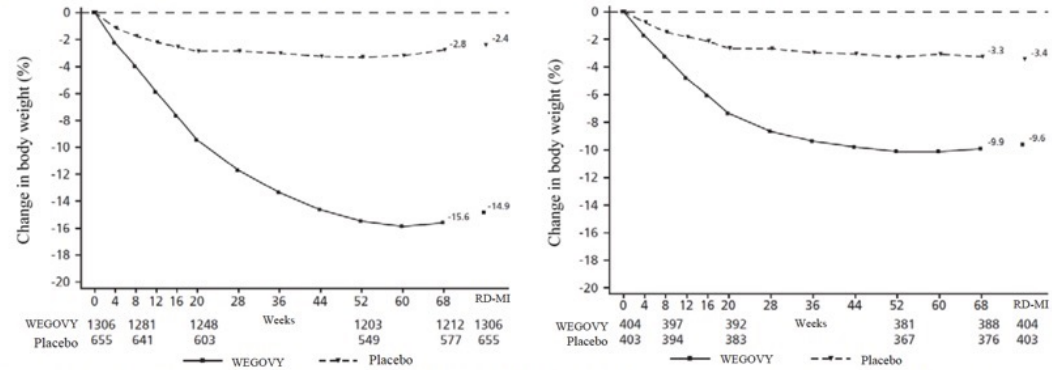


Wegovy approval clinical studies¹: overweight and obese adult patients

Rate of weight loss reaches a plateau

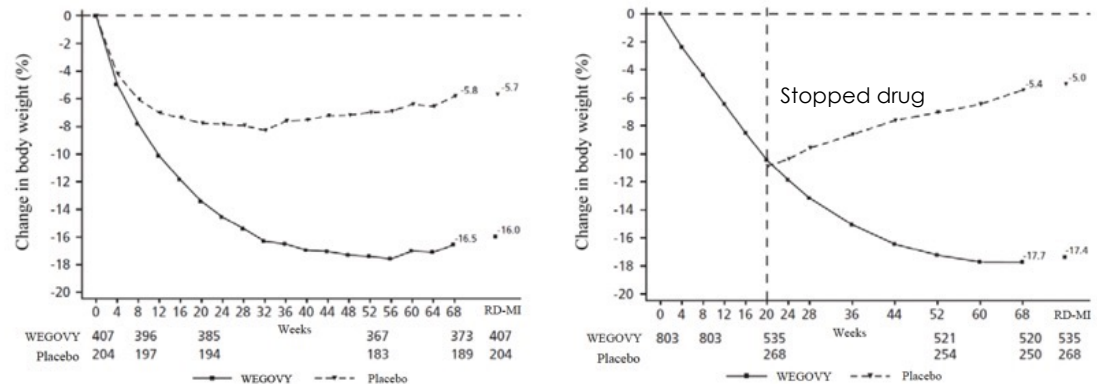
- Greatest amount of absolute total weight loss between weeks 0 and 20
- Patients who discontinued treatment at week 20 had significant weight gain (rebound)
- The reported weight gain was almost entirely fat mass not muscle
- One explanation: deficit in lean body mass (muscle) drives an increase in appetite and fat rebound weight regain^{2,3}

Figure 6. Change from baseline (%) in body weight (Study 1 on left and Study 2 on right)

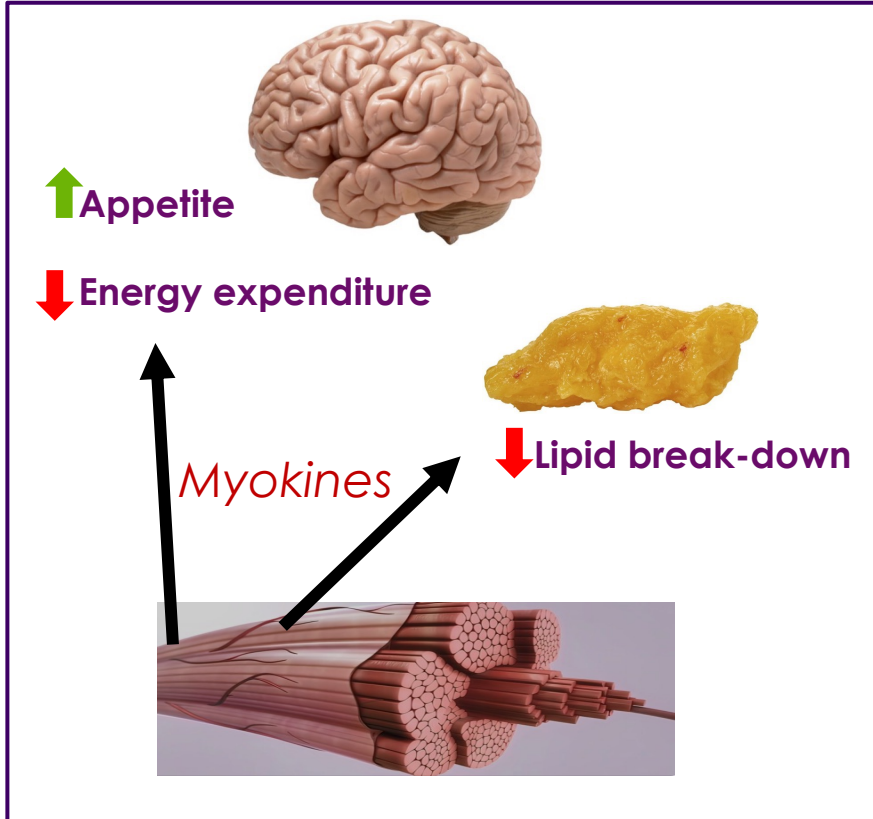


Observed values for patients completing each scheduled visit, and estimates with multiple imputations from retrieved dropouts (RD-MI)

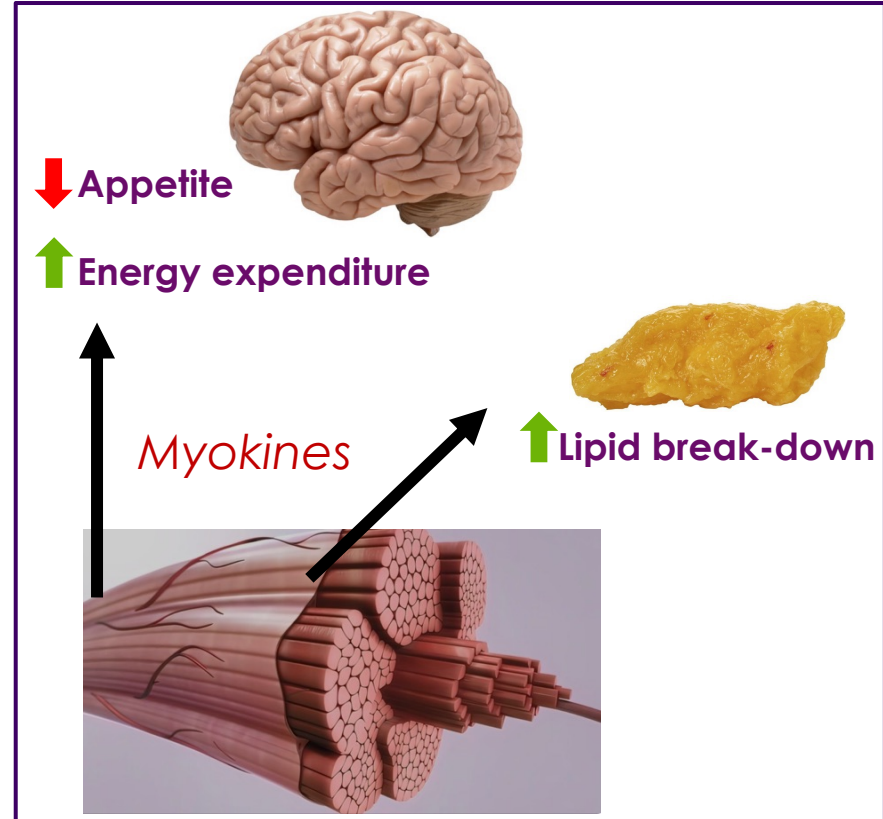
Figure 7. Change from baseline (%) in body weight (Study 3 on left and Study 4^a on right)



Depleted muscle- low energy balance



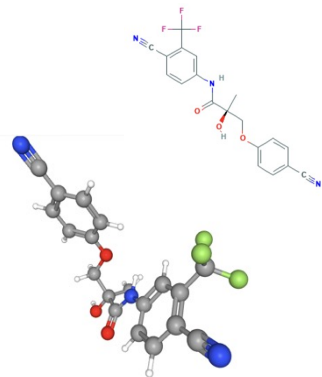
Normal muscle – normal energy balance



¹ Dulloo A Obesity 25:277-279, 2017 | ²Grannell A et al. Muscles 1:26-47, 2022

veru | Enobosarm is a novel oral selective androgen receptor modulator (SARM) designed to reduce fat mass and increase lean mass (muscle and bone)

- Enobosarm (Ostarine, MK2866, GTx-024) is a nonsteroidal, selective androgen receptor modulator^{1,2}
- Data from clinical trials and preclinical studies support enobosarm's potential:
 - Once-a-day oral dosing
 - Activates the androgen receptor, a well-established mechanism
 - Tissue selective
 - Improves muscle mass and physical function^{2,6}
 - Stimulates lipolysis, inhibits lipogenesis, and decreases fat mass^{7,8}
 - Builds and heals bone-potential to treat bone loss/osteoporosis³⁻⁵
 - Safety
 - Lack of masculinizing effects in women
 - Not converted to estrogen or dihydrotestosterone
 - No liver toxicity- no drug induced liver toxicity observed in clinical studies (27 clinical studies)



Chemical structure of enobosarm

¹ Narayanan R et al. Mol Cell Endocrinol 2017 | ² Dalton JT et al. Curr Opin Support Palliat Care 7:345-351, 2013 | ³ Kamrakova M et al Calcif Tissue Int 106:147-157,2020 | ⁴ Hoffman DB et al. J Bone Metab 37:243-255, 2019 | ⁵ Kearbey JD et al Pharm Res 26:2471-2477, 2009 | ⁶ Dobs AS et al. Lancet Oncol 14:335-45, 2013 | ⁷ Dalton JT et al. J Cachexia Sarcopenia Muscle 2:153-161, 2011 | ⁸ Leciejewska N et al. J Phys and Pharma 70:525-533, 2019



Enobosarm clinical data from 5 clinical trials approx. 1,000 patients conducted by GTx or Merck in subjects with and without muscle wasting

Subjects (n=)	Phase	Population	Purpose	Muscle (LBM)	Muscle strength/function	Fat Mass	Duration	Source
120 (24 received enobosarm 3mg)	2	Males over 60 years of age and postmenopausal women (Study G200501)	Dose-finding (0.1mg-3mg) placebo controlled	3mg=1.25 kg increase (p<0.001 compared to placebo) 3.1% increase from baseline	3mg Increase SCP (p=0.049 compared to placebo)	3mg=0.32 kg decrease (p=0.049 compared to placebo) 2-5% decrease in fat mass	12 weeks	Dalton JT J Cachexia Sarcopenia Muscle 2:153, 2011 and CSR
48 (12 received enobosarm 3mg)	2	Sarcopenic postmenopausal women (Study 003)	Double-blind placebo controlled (3mg)	3mg=1.54 kg increase (p<0.001 compared to placebo) 3.7% increase from baseline.	Bilateral leg press 3mg 21.96 lbs. increase from baseline vs placebo 1.5 lbs. increase from baseline	Not collected	12 weeks	Merck study Clinical study report (on file)
159 (41 received enobosarm 3mg)	2b	Muscle wasting cancer (Study G200502)	Double-blind placebo controlled (1 and 3 mg)	3mg = 1.27 kg (2.8%) increase (p=0.041 compared to baseline)	3mg 16.8 watt increase SCP. (p=0.001 compared to baseline)	3mg= 0.76 kg decrease in total fat mass (p=0.086 compared to placebo) 4% decrease of total fat mass	16 weeks	Dobs AS Lancet Oncology 14:335, 2013 And CSR
321 (160 received enobosarm 3mg)	3	Lung cancer muscle wasting receiving cisplatin + taxane chemotherapy (Study G300504)	Double-blind placebo controlled (3mg)	0.8 kg Increase in LBM at Day 84 (p<0.001 from baseline) Higher mean slope of the change from baseline than placebo (p=0.0002 Day 84 and p<0.0001 Day 147)	5.17% Increased in SCP at Day 84 vs. -1.27% in the placebo Higher mean slope of the change from baseline (p=0.0147 at Day 84, p=0.049 at Day 147)	Not collected	21 weeks	Clinical study report (on file)
320 (159 received enobosarm 3mg)	3	Lung cancer muscle wasting receiving cisplatin + nontaxane chemotherapy (Study G300505)	Double-blind placebo controlled (3mg)	0.73 kg Increase in LBM Day 84 and 0.67 kg increase at Day 147 (p=0.013) Higher mean slope of the change from baseline compared to placebo (p=0.0111 at Day 84, and p=0.0028 at Day 147)	SCP N.S.	Not collected	21 weeks	Clinical study report (on file)

Sarcopenic= presence of low muscle mass; LBM= lean body mass; SCP= stair climb power (Watts), power exerted in a 12-step stair climb; CSR=clinical study report ; N.S.=not significant

Healthy elderly men (>60 yo) and postmenopausal women receiving enobosarm in Phase 2 double-blind placebo controlled clinical trial (G200501) demonstrated improved lean body mass and physical function

- 120 subjects enrolled
- 12 weeks of treatment

% Change in lean mass

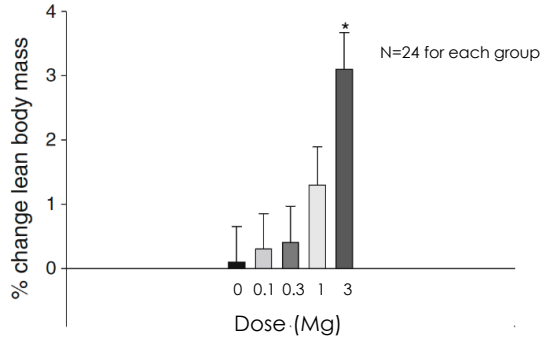


Fig. 1 Percentage change from baseline to day 86/EOS in total lean body mass: evaluable population. EOS end of study, * $P < 0.001$ 3 mg vs. placebo (T test)

% Change in stair climb power

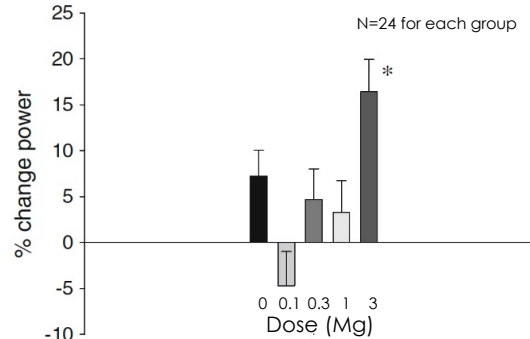
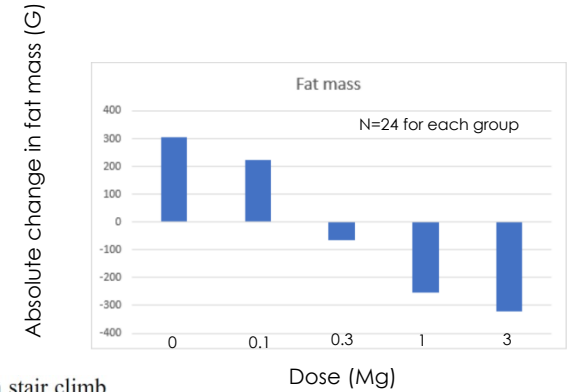


Fig. 2 Percentage change from baseline to day 86/EOS in stair climb power: evaluable population. EOS end of study, * $P = 0.013$ 3 mg vs. placebo (T test)

Mean change in fat mass



Metabolic changes

Blood glucose was significantly decreased by an average of 6.9 ± 2.5 mg/dL in the enobosarm 3mg versus placebo ($n=24$; $P = 0.006$)

Blood insulin was reduced by 2.2 ± 1.1 μ U/mL in the enobosarm 3mg versus placebo ($n=24$; $P = 0.052$)

Insulin resistance (HOMA-IR) was reduced in the enobosarm 1-mg and 3-mg treatment groups (placebo = $2.6\% \pm 8.6$, 1 mg = $-9.3\% \pm 5.5$, 3 mg = $-27.5\% \pm 7.6$) ($P = 0.013$ 3 mg vs. placebo)

- Mean age >60 yo
- 159 subjects enrolled
- 16 weeks of treatment

Change in total lean mass at Day 113/EOS compared to baseline

	Placebo	Enobosarm 1 mg	Enobosarm 3 mg
N	34	32	34
Mean (SD), kg	0.1 (2.7)	1.5 (2.7)	1.3 (3.5)
Median (range), kg	0.02 (-5.8 to 6.7)	1.5 (-2.1 to 12.6)	1.0 (-4.8 to 11.5)
p value [*]	0.88	0.0012	0.046

P < 0.041 enobosarm 3mg vs placebo

Change in stair climb time and power at Day 113/EOS compared to baseline

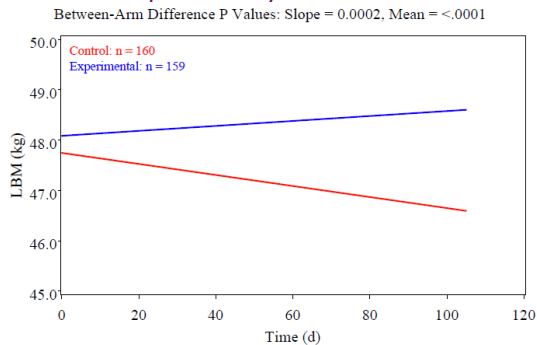
	Placebo	Enobosarm 1 mg	Enobosarm 3 mg
Stair climb time (s)			
N	36	32	28
Mean (SD)	0.20 (2.98)	-1.63 (3.39)	-2.22 (7.05)
Median (range)	-0.14 (-4.61 to 14.54)	-0.84 (-12.67 to 5.56)	-0.46 (-31.01 to 5.06)
p value [*]	0.26	0.0019	0.0065
Stair climb power (watts)[†]			
N	36	31	28
Mean (SD)	2.21 (39.30)	14.26 (53.77)	16.81 (31.08)
Median (range)	11.34 (-156.36 to 56.37)	19.93 (-235.34 to 110.14)	12.84 (-77.74 to 93.15)
p value [*]	0.11	0.0008	0.0006

veru | Phase 3 randomized, double-blind, placebo-controlled 504 clinical trial of enobosarm on muscle wasting in patients with non-small cell lung cancer on first line platinum plus a taxane chemotherapy¹

3mg enobosarm treatment in 321 subjects enrolled for 21 weeks

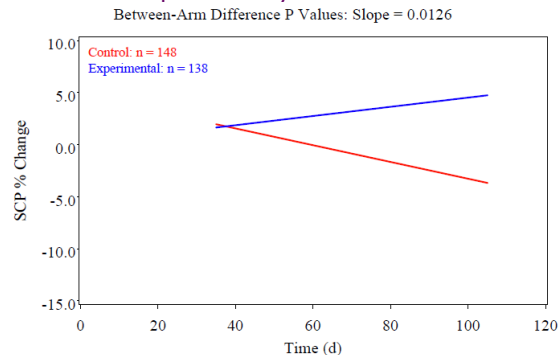
Lean body mass (muscle)

Up to Day 84 visit

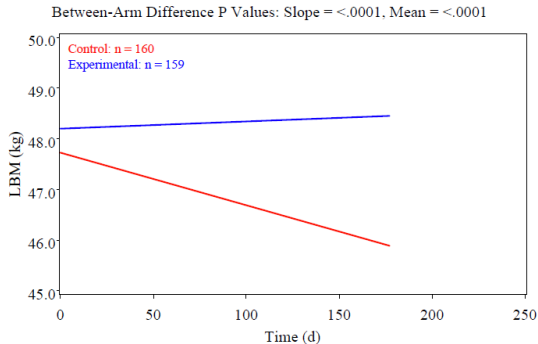


Stair climb power

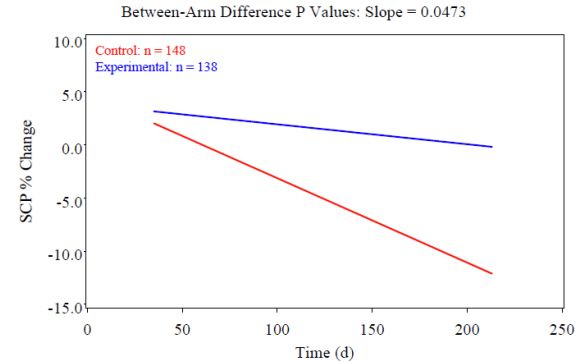
Up to Day 84 visit



Up to Day 147 visit



Up to Day 147 visit

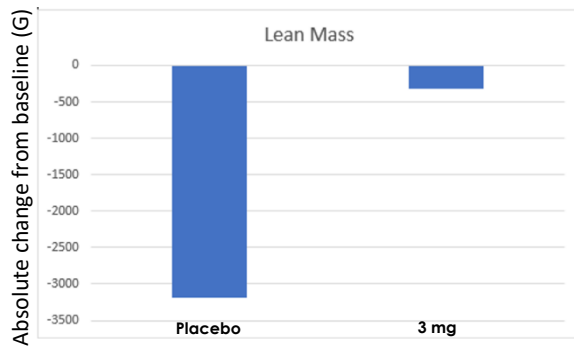


¹ Study G300504 CSR data on file Veru

Post-hoc analysis of obese subpopulation (BMI ≥ 30)

Total lean body mass

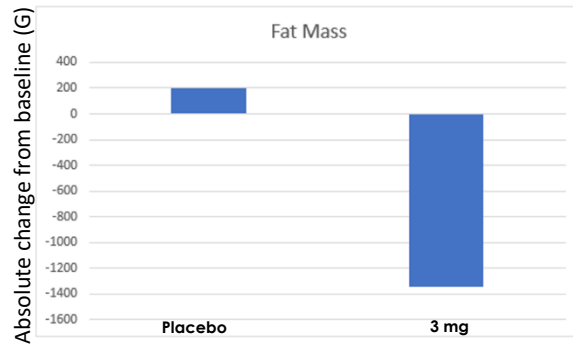
Up to Day 84 visit



Placebo N=15, Treated N=14
Placebo corrected % change = +4.96%

Total fat mass

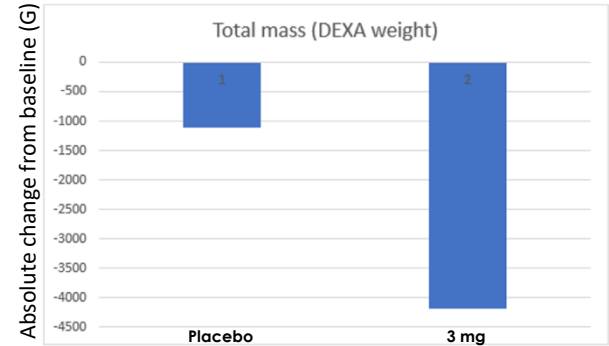
Up to Day 84 visit



Placebo N=15, Treated N=14
Placebo corrected % change = -5.77%

Total body weight*

Up to Day 147 visit



Placebo N=12, Treated N=12
Placebo corrected % change = -4.51%

Total Fat mass
Placebo corrected % change = -14.4%

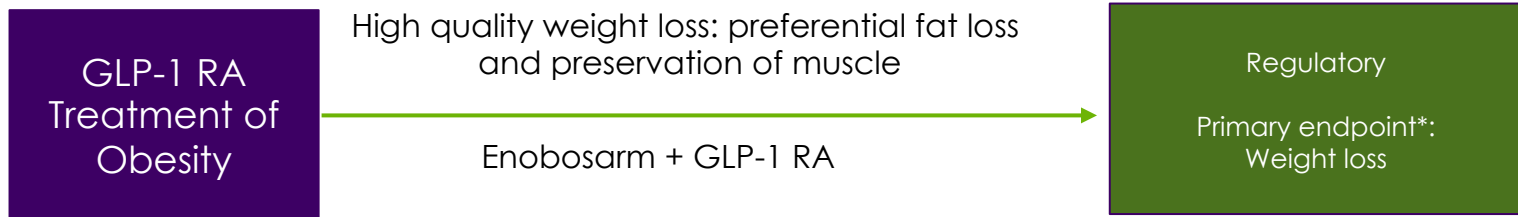
¹ Study G300504 CSR data on file Veru

Enobosarm +/- GLP-1 RA for the treatment of obesity

Clinical and regulatory strategy for all patients who are overweight or obese

- **New drug in combination with GLP-1 RA should show incremental increase in weight loss at 1 year**
- **Enobosarm potential direct effects:**
 - Prevents muscle loss: active protein synthesis in muscle
 - Increases fat loss: increase in lipolysis and decrease in lipogenesis

Strategy 1 - Entire obesity population



If muscle is preserved, can there still be significant weight loss?

The amount of fat mass compartment is greater than the muscle mass one



Preventing muscle loss (FFM deficit) blocks the trigger to increase in appetite¹

Collateral Fattening: When a Deficit in Lean Body Mass Drives Overeating

Abdul G. Dulloo

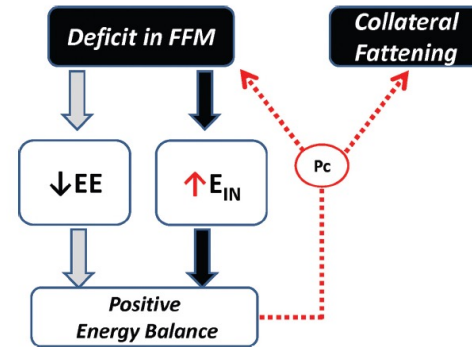
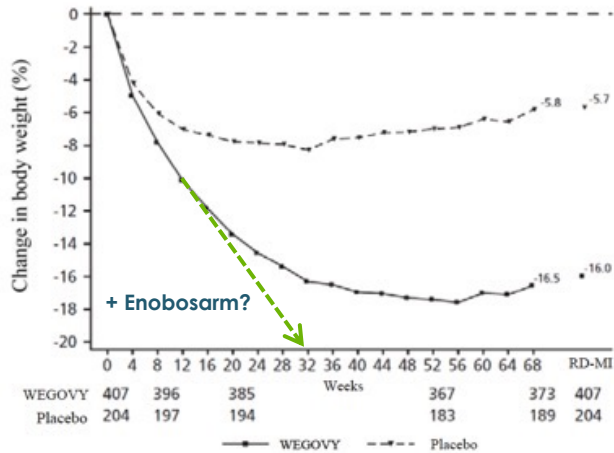


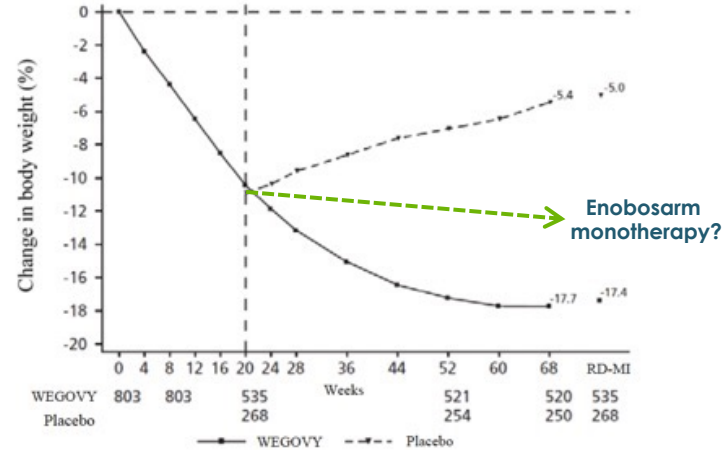
Figure 2 Concept of collateral fattening. A deficit in fat-free mass (FFM) results not only in a lower energy expenditure (EE) and hence lower energy needs for weight maintenance, but also in the activation a feedback loop that drives energy intake (E_{IN}) in an attempt to restore FFM through the lean-to-fat partitioning characteristic (P_c) of the individual (4).

¹ Dulloo A Obesity 25:277-279, 2017

Figure 7. Change from baseline (%) in body weight (Study 3 on left and Study 4^a on right)



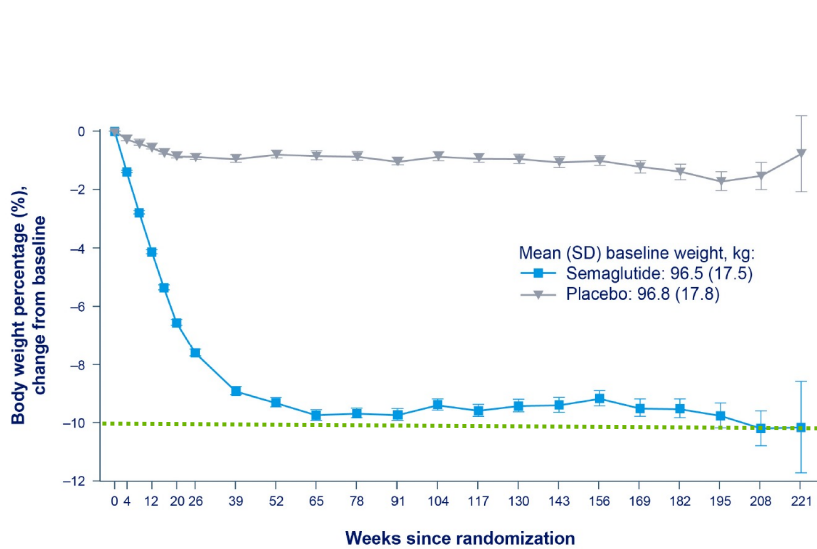
Greater amount of fat loss and weight loss ?



Prevent rebound fat and weight gain?

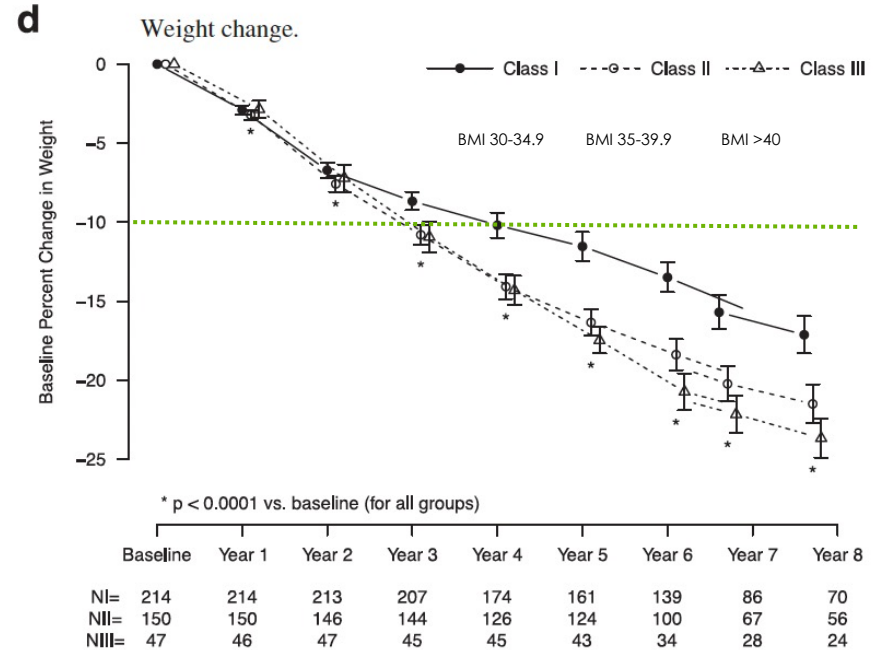
If muscle is preserved, could there be greater weight loss without a plateau?

SELECT Trial:
Effect of semaglutide vs placebo on body weight
(4.25 years)¹



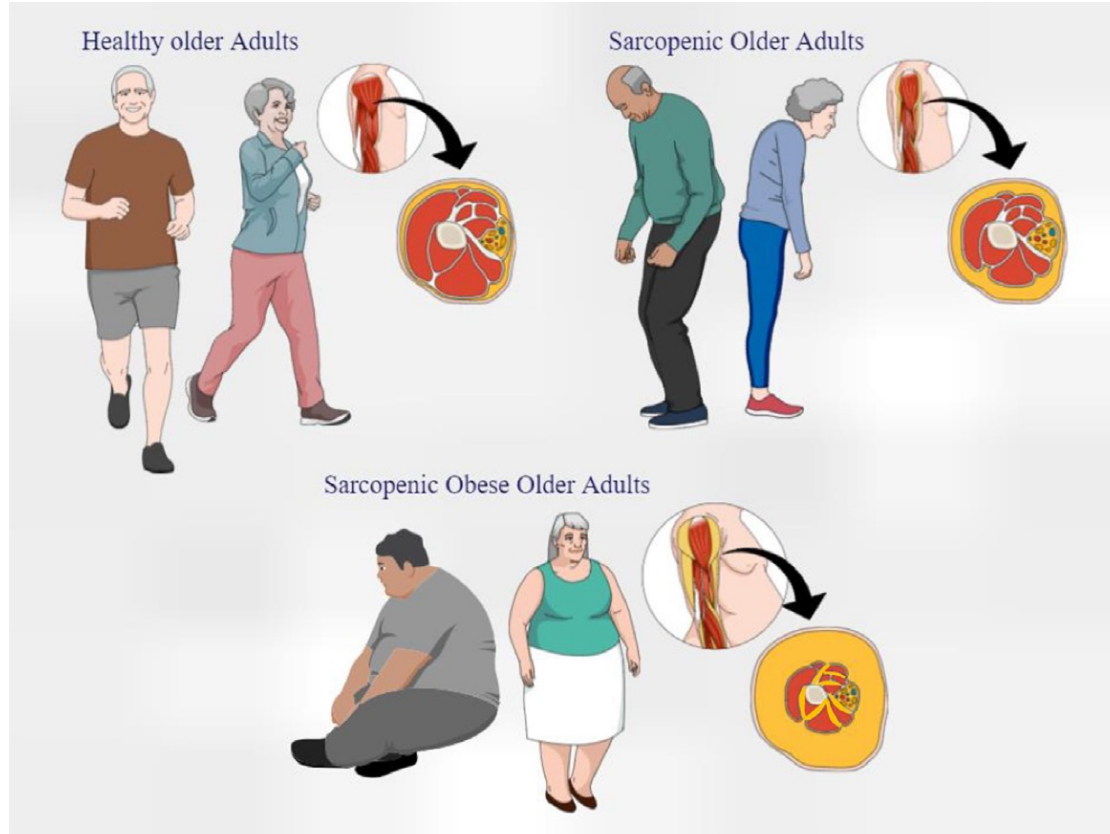
Semaglutide, N	8,803	7,647	7,493	6,690	7,290	6,447	7,282	6,460	7,474	5,991	5,898	4,686	5,085	3,650	2,954	1,737	921	157
Placebo, N	8,801	7,715	7,516	6,704	7,269	6,340	7,272	6,392	7,378	5,871	5,879	4,583	5,014	3,560	2,890	1,698	898	152

Effect of long-term testosterone in hypogonadal men with obesity (8 years)²



¹Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes obesity without diabetes. N Engl J Med 2023;389:2221-32. DOI: 10.1056/NEJMoa2307563 | ² Saad F et al. Int J Obesity 40: 162-170, 2016.

Sarcopenic obese or overweight elderly patients at risk for developing muscle weakness and functional limitations when receiving GLP-1 RA for weight loss

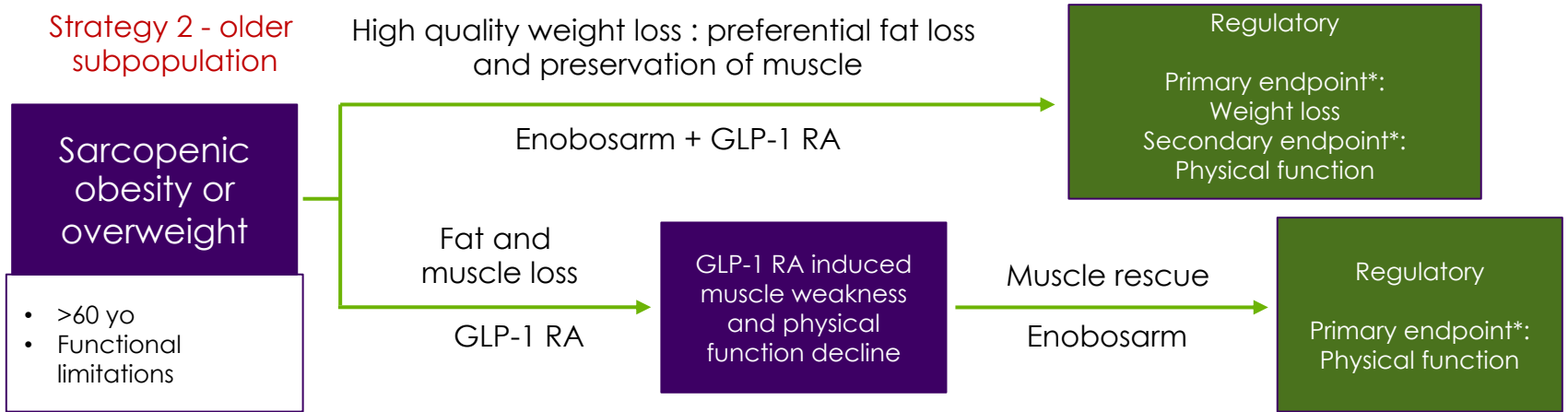


¹ Taken from Malandrino N et al. Endocrinol Metab Clin N Am 52 (2023) 317–339

Enobosarm +/- GLP-1 RA for the treatment of obesity

Clinical and regulatory strategy for older patients with low muscle reserve

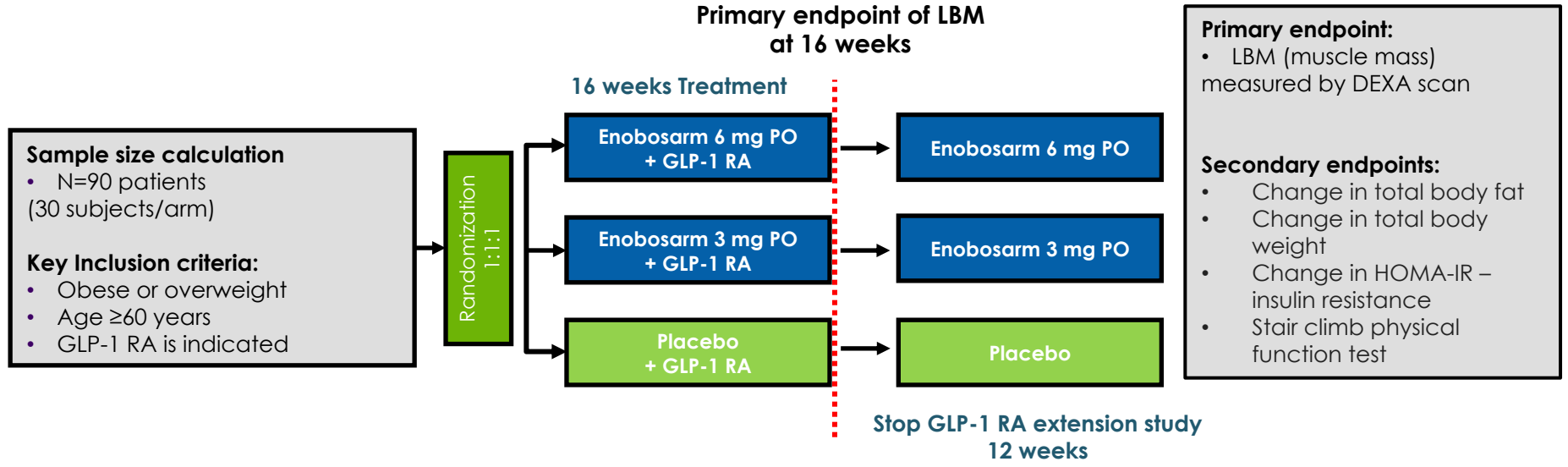
- New drug in combination with GLP-1 RA should show incremental increase in weight loss and physical function benefit
- **Enobosarm potential direct effects:**
 - Prevents muscle loss: active protein synthesis in muscle
 - Increases fat loss: increase in lipolysis and decrease in lipogenesis



Enrolling - Phase 2 double-blind, placebo controlled, randomized, dose finding trial of enobosarm in preventing muscle loss and increasing fat loss in patients receiving a GLP-1 RA for weight loss

Enobosarm and GLP-1 RA combination study

Primary endpoint of LBM at 16 weeks



- Semaglutide treatment for obesity¹
 - 6.92 kg of lean body mass lost by 68 weeks (40% of total weight loss)
 - 49% of total weight loss at 68 weeks occurred by 16 weeks

- Study Power Assumptions
 - $\alpha=0.05$ (two-sided), power = 80%
 - 1.6 kg loss in lean mass at 16 weeks in placebo group
 - Expect between 1.6 and 3.4 kg lean mass loss
 - 0.3 kg loss in lean mass at 16 weeks in enobosarm groups
 - Expect between 0.3 kg loss and 0.4 kg gain in lean mass

¹ Wilding JPH et al. NEJM 384:989-1002, 2021

- **Prevent loss of muscle to preserve physical function**
 - Older adults with sarcopenic obesity are at risk for developing physical function decline; accelerated development of frailty
- **Preserve muscle to stop the GLP-1 weight loss plateau**
 - Loss of muscle creates a muscle deficit that triggers increase in appetite that counters the hypocaloric benefit of GLP-1 drugs leading to the weight loss plateau
 - Without muscle deficit, GLP-1 drugs may potentially remove more fat mass in a maintained hypocaloric state
- **Adequate muscle reserve upon cessation of GLP-1 drugs may prevent fat mass rebound weight regain**
 - Muscle deficit when stopping the GLP-1 drives over-eating and collateral fattening
 - Fat is preferentially regained over muscle; rebound total weight gain is primarily fat



HEALTH

The Ozempic Plateau

Everyone hits a weight-loss plateau, but the race is on for next-generation drugs that can help patients lose even more weight.

By Sarah Zhang



Illustration by the Atlantic. Source: Getty

JANUARY 17, 2024, 8 AM ET

SHARE SAVE



Enobosarm has an extensive safety database

Combined Safety data from 5 Phase 2 and 3 clinical trials in cancer and healthy subjects and Phase 1 studies

Percentage of healthy and cancer subjects in all 5 clinical and Phase 1 clinical trials reporting a **treatment-emergent adverse event** with a frequency of $\geq 0.5\%$

MedDRA Preferred Term	Enobosarm (N=896) n(%)	Placebo (N=437) n(%)	All subjects (N=1333) n(%)
<i>Any treatment related adverse event</i>	219 (24.4)	73 (16.7)	292 (21.9)
Headache	51 (5.7)	10 (2.3)	61 (4.6)
Nausea	27 (3.0)	12 (2.7)	39 (2.9)
Alanine aminotransferase increased	19 (2.1)	2 (0.5)	21 (1.6)
Diarrhoea	19 (2.1)	12 (2.7)	31 (2.3)
Dizziness	18 (2.0)	2 (0.5)	20 (1.5)
Back pain	13 (1.5)	2 (0.5)	15 (1.1)
Constipation	12 (1.3)	3 (0.7)	15 (1.1)
Vomiting	12 (1.3)	4 (0.9)	16 (1.2)
Pain In extremity	11 (1.2)	4 (0.9)	15 (1.1)
Hyperhidrosis	9 (1.0)	1 (0.2)	10 (0.8)
Pruritus	9 (1.0)	3 (0.7)	12 (0.9)
Somnolence	9 (1.0)	0 (0)	9 (0.7)
Dyspnoea	8 (0.9)	0 (0)	8 (0.6)
Fatigue	8 (0.9)	5 (1.1)	13 (1.0)
Abdominal Pain	7 (0.8)	2 (0.5)	9 (0.7)
Hot Flush	6 (0.7)	2 (0.5)	8 (0.6)
Muscle Spasms	6 (0.7)	1 (0.2)	7 (0.5)
Myalgia	6 (0.7)	1 (0.2)	7 (0.5)
Dizziness Postural	5 (0.6)	0 (0)	5 (0.4)
Insomnia	5 (0.6)	1 (0.2)	6 (0.5)
Rash	5 (0.6)	0 (0)	5 (0.4)

Percentage of healthy and cancer subjects in all 5 clinical and Phase 1 clinical trials reporting a **treatment-emergent serious adverse event** with a frequency of $\geq 1\%$

MedDRA Preferred Term	Enobosarm (N=896) n(%)	Placebo (N=437) n(%)
<i>Any serious adverse event</i>	157 (17.5)	145 (33.2)
Disease progression	34 (3.8)	45 (10.3)
Anaemia	18 (2.0)	14 (3.2)
Pneumonia	15 (1.7)	11 (2.5)
Neutropenia	14 (1.6)	14 (3.2)
Malignant neoplasm progression	12 (1.3)	8 (1.8)
Febrile neutropenia	10 (1.1)	6 (1.4)
Thrombocytopenia	10 (1.1)	6 (1.4)
Pulmonary haemorrhage	4 (0.4)	5 (1.1)
Dehydration	3 (0.3)	7 (1.6)

¹Taken from GTx Investigator Brochure 2017

- Evaluated in 27 clinical trials comprising >1580 subjects dosed (235 subjects dosed at \geq 9mg)

- Data reported from 12 Phase 1 studies:

- No QT effects
- No significant drug-drug interactions²
- No significant food effect
- No significant renal or hepatic effects
- Major metabolites analysis and route of elimination- renal elimination and only metabolite is enobosarm glucuronide
- Cytochrome P450 3A4- enobosarm is not an inhibitor

Safety of special interest:

Elderly healthy volunteers G200501 Phase 2 study conducted by GTx¹

	Baseline	SD	Absolute change	SD	P value
Total cholesterol (mg/dL)					
Placebo	195.9	35.83	4.8	17.46	
0.1 mg	197.8	27.31	-6.3	20.03	0.088
0.3 mg	204.4	29.84	-14.3	19.88	0.004*
1 mg	197.1	29.87	-19	26.34	<.001*
3 mg	203.1	35.1	-15.3	26.95	0.003*
HDL (mg/dL)					
Placebo	49.9	10.2	0	4.88	
0.1 mg	50.9	9.49	-4.3	4.72	0.027*
0.3 mg	55.3	13.99	-6.3	4.86	0.001*
1 mg	52.1	10.44	-8.9	6.18	<.001*
3 mg	52.8	10.99	-14.7	10.58	<.001*
LDL (mg/dL)					
Placebo	130	34.02	7.5	13.95	
0.1 mg	128	22.91	5.5	16.48	0.734
0.3 mg	130.7	31.57	-0.2	15.67	0.206
1 mg	125.2	23.83	3.9	27.16	0.564
3 mg	130.6	29.68	4.6	27.44	0.629
Triglycerides (mg/dL)					
Placebo	114.8	39.66	7.2	34.43	
0.1 mg	137.4	76.17	5.8	46.96	0.952
0.3 mg	126	80.69	2.4	50.18	0.838
1 mg	112.9	49.14	-12.8	31.14	0.4
3 mg	153.5	182.89	-36.6	155.64	0.06

HDL changes are similar to what has been observed for testosterone replacement

- **Enobosarm is a nonsteroidal, selective androgen receptor modulator that targets the androgen receptor, a well-established mechanism of action^{1,2}**
- **Data from clinical trials and preclinical studies support enobosarm's potential:**
 - Administration: Once-a-day oral dosing
 - Efficacy
 - Avoidance of muscle loss - improves muscle mass and physical function^{2,6}
 - Reduction of fat mass - stimulates lipolysis and inhibits lipogenesis^{7,8}
 - Metabolic effects- decrease glucose, lowers insulin, and reduces insulin resistance
 - Builds and heals bone-potential to treat bone loss/osteoporosis³⁻⁵
 - Safety
 - Large safety database
 - Not converted to estrogen or dihydrotestosterone
 - Lack of masculinizing effects in women
 - No liver toxicity - no DILI observed in clinical studies (27 clinical studies)
 - Minimal GI side effects: frequencies of nausea, vomiting, and diarrhea are similar to placebo⁹

¹ Narayanan R et al. Mol Cell Endocrinol 2017 | ² Dalton JT et al. Curr Opin Support Palliat Care 7:345-351, 2013 | ³ Kamrakova M et al Calcif Tissue Int 106:147-157,2020 | ⁴ Hoffman DB et al. J Bone Metab 37:243-255, 2019 | ⁵ Kearbey JD et al Pharm Res 26:2471-2477, 2009 | ⁶ Dobs AS et al. Lancet Oncol 14:335-45, 2013 | ⁷ Dalton JT et al. J Cachexia Sarcopenia Muscle 2:153-161, 2011 | ⁸ Leciejewska N et al. J Phys and Pharma 70:525-533, 2019 | ⁹: Taken from GTX Investigator Brochure 2017