S-OXPRENOLOL FOR PRESERVING MUSCLE MASS, BONE DENSITY, AND CARDIAC FUNCTION IN WEIGHT LOSS TREATMENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/636,664, filed on April 19, 2024; U.S. Provisional Application No. 63/668,732, filed on July 8, 2024; GB 2410016.6, filed on July 10, 2024; GB 2415544.2, filed on October 22, 2024; and GB 2500384.9, filed on January 13, 2025; all of which are incorporated by reference herein in their entireties.

FIELD OF THE INVENTION

The present disclosure relates to the use of beta-blockers to inhibit loss of muscle mass and/or function and/or bone mass and/or density that may occur due to a variety of conditions, such as, e.g., aging, treatment of disease, weight loss, e.g., when a subject is treated with a diabetes drug or weight loss drug, such as, e.g., a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and/or a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

The present invention also relates to a method of restoring muscle mass in a patient who has undergone a weight loss treatment.

The present invention relates to new combination treatments involving (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and (b) a weight loss treatment (e.g. a GLP1 agonist). Such combinations are useful in treating or preventing loss of muscle mass in a patient in need thereof, for example during bodyweight reduction when the patient is overweight or obese.

BACKGROUND OF THE INVENTION

Obesity and being overweight (pre-obesity) are medical conditions defined by excessive fat accumulation in the body. Obesity is a leading cause of preventable death worldwide and is a known risk factor for the development of many diseases particularly cardiovascular diseases, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis.

When diet and exercise alone do not suffice in reducing the body mass index (BMI) to an acceptable level, treatment with glucagon-like peptide 1 (GLP1) receptor agonists has been shown to cause weight loss in obese and overweight individuals. For example, semaglutide is a glucagon-like peptide 1 (GLP1) receptor agonist and is the active pharmaceutical ingredient in a marketed product, Wegovy, approved for weight management. In addition, liraglutide is a glucagon-like peptide 1 (GLP1) receptor agonist and is the active pharmaceutical ingredient in a marketed product, Saxenda, also approved for weight management. In addition, tirzepatide is a glucagon-like peptide 1 (GLP1) receptor agonist and is the active pharmaceutical ingredient in a marketed product, Mounjaro, also approved for weight management.

Loss of muscle mass and/or function and/or bone density is an unfortunate result of the natural aging process and many diseases, including obesity and diabetes, and/or the therapeutic interventions used to treat them. For example, age-related low muscle mass and/or function is defined as sarcopenia, and sarcopenic obesity describes loss of muscle and function in obese individuals. (Murdock DJ, Wu N, Grimsby JS, Calle RA, Donahue S, Glass DJ, Sleeman MW, Sanchez RJ. The prevalence of low muscle mass and/or function associated with obesity in the USA. Skelet Muscle. 2022 Dec 21;12(1):26) The elderly population is at risk for the development of sarcopenia alone as well as for the development of sarcopenic obesity for the same reasons; hormonal shifts, chronic inflammation, lifestyle factors and an increase in precipitating events that lead to a more sedimentary state. (Prado CM, Batsis JA, Donini LM, Gonzalez MC, Siervo M. Sarcopenic obesity in older adults: a clinical overview. Nat Rev Endocrinol. 2024 Feb 6. doi: 10.1038/s41574-023-00943-z. Epub ahead of print. PMID: 38321142). It is estimated that 28.3% of people in the U.S. aged 60 and over have sarcopenic obesity. (Murdock DJ, Wu N, Grimsby JS, Calle RA, Donahue S, Glass DJ, Sleeman MW, Sanchez RJ. The prevalence of low muscle mass and/or function associated with obesity in the USA. Skelet Muscle. 2022 Dec 21;12(1):26) Paradoxically, sarcopenic obesity can occur in the diametrically opposing metabolic scenarios of either weight gain or weight loss. In the context of weight gain, individuals can evolve in two ways. They might accrue an average amount of muscle alongside the additional body weight, resulting in a condition of general obesity. Alternatively, if their rate of muscle accretion is low while they gain weight, they might develop sarcopenic obesity. Conversely, a similar transformation can occur in individuals experiencing considerable weight loss. The weight loss in these individuals can induce varying degrees of muscle loss, potentially leading to the development of sarcopenic obesity, especially if the loss in muscle mass and/or function is substantial. (Prado CM, Batsis JA, Donini LM, Gonzalez MC, Siervo M. Sarcopenic obesity in older adults: a clinical overview. Nat Rev Endocrinol. 2024 Feb 6.) For this reason, an

increase in sarcopenic obesity is being observed in younger age groups secondary to weight loss treatments such as GLP-1R agonists etc. With all age groups considered, an estimated 28.7 million Americans (15.9%) are estimated to have sarcopenic obesity (Murdock DJ, Wu N, Grimsby JS, Calle RA, Donahue S, Glass DJ, Sleeman MW, Sanchez RJ. The prevalence of low muscle mass and/or function associated with obesity in the USA. Skelet Muscle. 2022 Dec 21;12(1):26). In addition, treatment with medications for type 2 diabetes mellitus (T2DM) or obesity, e.g., GLP-1R agonists and SGLT2 inhibitors, can result in loss of muscle and/or bone (see, e.g., Pan R. et al. (2022) PLoS ONE 17(12): e0279889; Ida S. et al., (2021) Current Diabetes Reviews 17: 293-303; Sargeant, J.A. et al. (2019) Endocrinol Metab 34:247-262; Hansen, M.S. et al. (2023) Lancet; Malandrino, N. et al. (2023) Endocrin Metab Clin N Am 52:317-339; and Zhao, C. et al, (2017) Front. Endocrinol. 8:98). SGLT2 inhibitors have been shown to increase the risk of sarcopenia, as a meta-analysis of 18 studies showed that in addition to the significant reduction of body weight, there was also a significant reduction in lean mass and skeletal muscle mass and/or function (Pan, R. et al. (2022) PLoS One 17(12):e0279889). Diabetic patients are more susceptible to muscle loss compared with non-diabetic ones, potentially due to increased oxidative stress, proinflammatory state, and decreased physical activity (Ida, S. (2021) Curr. Diabetes. Rev. 17(3):293-303). This loss of muscle mass and/or function accompanied by weight loss has been observed in diabetic patients on GLP-1R agonists (McCrimmon, R.J. et al. (2020) Diabetologia 63(3):473-85), as well as SGLT2 inhibitors (Bolinder, J. et al. (2012) J. Clin. Endocrinol. Metab. 97(3):1020-31). The amount of fat-free mass (FFM) loss (an index of muscle mass and/or function) accounted for up to 40% of weight loss in patients taking semaglutide (Ida, S. (2021) Curr. Diabetes. Rev. 17(3):293-303). GLP-1 activation is also associated with the sympathetic nervous system and the body's stress response (Diz-Chaves, Y. et al. (2020) Nutrients 12(11)).

One significant challenge with weight loss is weight-loss-associated loss of muscle mass. The potential health benefits of weight loss can be compromised by associated loss of muscle mass for example as discussed in Nutrients, 2021, 13(7), p2473, "Weight Loss Strategies and the Risk of Skeletal Muscle Mass Loss" McCarthy *et al.* Other weight loss treatments, such as bariatric surgery, can also be associated with weight-loss-associated loss of muscle mass.

In addition to the issues related to the loss of muscle mass during a weight loss treatment, it has also been observed that patients struggle to restore muscle mass following the conclusion of the weight loss treatment. It is also desirable to reduce loss of bone mineral content and/or bone density and/or bone mass during a weight loss treatment.

There is, therefore, a need for pharmaceutical interventions that can address excess adiposity without detrimental effects on muscle mass. There is a need in the art for improved methods for preventing, inhibiting or reducing muscle loss and/or function and/or bone loss resulting from treatment with therapeutic agents that cause this, such as, e.g., GLP1R agonists. Moreover, there is a recognized need for improved methods for treating diabetes, including both type 1 diabetes mellitus (T1DM) and T2DM and obesity with GLP-1R agonists and SGLT2 inhibitors, and other anti-obesity drugs, which result in reduced loss of muscle and/or bone.

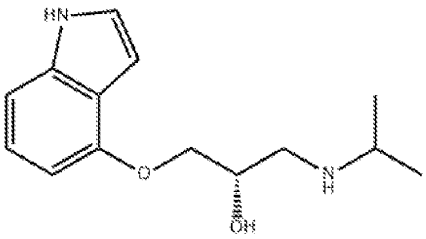
There is also a need to develop treatments to restore muscle mass following weight loss, particularly in the case of rapid and/or substantial weight loss.

SUMMARY OF THE INVENTION

It has been found that beta-blockers (and in particular a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) provide promising treatments for preventing or reducing loss of muscle mass and/or muscle strength during weight loss treatments, and for restoring muscle mass lost following a weight loss treatment. A combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist may be referred to herein as a beta-blocker.

It has also been found that a combination therapy of a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist with a GLP1 agonist results in a noticeable improvement in therapeutic efficacy in reducing detrimental effects on muscle mass as compared to the corresponding GLP1 agonist monotherapies. The enhanced therapeutic effect that is observed with the combination therapy is highly advantageous from a clinical perspective.

Compounds that are antagonists or partial agonists of both beta-adrenergic receptors and 5-HT_{1A} receptors have been described for uses in a number of disorders. Examples of such compounds include S-pindolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol and S-oxprenolol. A particular example is S-pindolol which is an anabolic/catabolic transforming agent which shows β_1 receptor antagonism, partial β_2 receptor agonism and central 5-HT1A antagonism. S-pindolol is also known as (-)-pindolol, S(-)-pindolol, or Espindolol and has the systematic name (2S)-1-(1*H*-indol-4-yloxy)-3-(1-methylethylamino)propan-2-ol. The structure of S-pindolol is shown below.



The treatment of wasting disorders such as cachexia and sarcopenia using enantiomerically enriched S-pindolol is described in WO 2008/068477 A1, WO 2010/125348 A1 and WO 2014/016585 A1.

Thus, the present invention provides a beta-blocker for use in a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

The invention also provides a beta-blocker for use in a method for increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

The present invention provides a pharmaceutical composition which comprises:
(a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) a GLP1 agonist.

Also provided is a composition of the invention for use in the treatment of the human or animal body.

Also provided is a composition of the invention for use in treating or preventing loss of muscle mass in a patient in need thereof.

Also provided is use of a composition of the invention in the manufacture of a medicament for use in the treatment of the human or animal body.

Also provided is use of a composition of the invention in the manufacture of a medicament for use in treating or preventing loss of muscle mass in a patient in need thereof.

Also provided is a product comprising (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein and (b) a GLP1 agonist as defined herein, for simultaneous, concurrent, separate or sequential use in the treatment of the human or animal body.

Also provided is a product comprising (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein and (b) a GLP1 agonist as defined herein, for simultaneous, concurrent, separate or sequential use in treating or preventing loss of muscle mass in a patient in need thereof.

Also provided is a combination comprising (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein and (b) a GLP1 agonist as defined herein, for simultaneous, concurrent, separate or sequential use in the treatment of the human or animal body.

Also provided is a combination comprising (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein and (b) a GLP1 agonist as defined herein, for simultaneous, concurrent, separate or sequential use in treating or preventing loss of muscle mass in a patient in need thereof.

Also provided is use of (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist and (b) a GLP1 agonist as defined herein in the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in the treatment of the human or animal body.

Also provided is use of (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein and (b) a GLP1 agonist defined herein in the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in treating or preventing loss of muscle mass in a patient in need thereof.

Also provided is a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for use in the treatment of the human or animal body, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist thereof as defined herein.

Also provided is a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist thereof as defined herein for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined herein.

Also provided is a GLP1 agonist for use in the treatment of the human or animal body, by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein.

Also provided is a GLP1 agonist for use in reducing body mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein.

Also provided is a GLP1 agonist for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein.

Also provided is use of a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein in the manufacture of a medicament for use in the treatment of the human or animal body by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist thereof as defined herein.

Also provided is use of a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined in herein in the manufacture of a medicament for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined herein.

Also provided is use of a GLP1 agonist as defined herein in the manufacture of a medicament for use in the treatment of the human or animal body by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined in herein.

Also provided is use of a GLP1 agonist as defined herein in the manufacture of a medicament for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a

combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined in herein.

Also provided is a method of treatment of a patient in need thereof, which method comprises administering to said patient a combination or composition as defined herein.

Also provided is a method of treating or preventing loss of muscle mass in a patient in need thereof, which method comprises administering to said patient a combination or composition as defined herein.

Also provided is a kit of parts comprising a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein, together with instructions for simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined herein for the treatment of a human or animal patient.

Also provided is a kit of parts comprising a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein, together with instructions for simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined herein for the treatment of a patient suffering from or susceptible to loss of muscle mass.

Also provided is a package comprising a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein, and a GLP1 agonist as defined herein for the simultaneous, concurrent, separate or sequential use in the treatment of a human or animal patient.

Also provided is a package comprising a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein, and a GLP1 agonist as defined herein for the simultaneous, concurrent, separate or sequential use in the treatment of a patient suffering from or susceptible to loss of muscle mass.

Also provided is use of (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in combination with (b) a GLP1 agonist as defined herein for the treatment of the human or animal body.

Also provided is use of (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for the preparation of a medicament, for simultaneous,

concurrent, separate or sequential use in combination with (b) a GLP1 agonist as defined herein for the treatment or prevention of loss of muscle mass in a patient in need thereof.

Also provided is use of (b) a GLP1 agonist as defined herein for the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in combination with (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for the treatment of the human or animal body.

Also provided is use of (b) a GLP1 agonist as defined herein for the preparation of a medicament, for simultaneous, concurrent, separate or sequential use in combination with (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for the treatment or prevention of loss of muscle mass in a patient in need thereof.

Also provided is a method of treatment of a patient in need thereof, which method comprises administering a combination or composition as defined herein.

Also provided is a method of treatment of a patient suffering from or susceptible to loss of muscle mass, which method comprises administering a combination or composition as defined herein.

The invention also provides a beta-blocker (such as a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) for use in a method for treating or preventing loss of muscle mass and/or muscle strength in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. The weight loss treatment typically comprises a GLP1 agonist and the beta-blocker is typically S-pindolol or a pharmaceutically acceptable salt thereof.

The invention also provides a beta-blocker (such as a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) for use in a method for treating or preventing loss of bone mineral content in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. The weight loss treatment typically comprises a GLP1 agonist and the beta-blocker is typically S-pindolol or a pharmaceutically acceptable salt thereof.

The invention also provides a beta-blocker (such as a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) for use in a method for protecting cardiac muscle and/or cardiac function in a subject during a weight loss treatment, which method

comprises providing to the subject an effective amount of the beta-blocker. The weight loss treatment typically comprises a GLP1 agonist and the beta-blocker is typically S-pindolol or a pharmaceutically acceptable salt thereof. The beta-blocker may protect against hypotension and/or increased heartrate caused by the weight loss treatment.

The invention also provides a beta-blocker (such as a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) for use in a method for increasing or restoring muscle mass and/or muscle strength in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. The weight loss treatment typically comprises a GLP1 agonist and the beta-blocker is typically S-pindolol or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 shows XRPD diffractograms of S-oxprenolol free base and Pattern 1 of S-oxprenolol dihydrogenphosphate.

FIG. 2 shows XRPD diffractograms of S-oxprenolol free base, S-oxprenolol oxalate Patterns 1 and 2, and oxalic acid.

FIG. 3 shows an XRPD diffractograms of Pattern 2 of S-oxprenolol dihydrogenphosphate.

FIG. 4 shows an XRPD diffractograms of Pattern 3 of S-oxprenolol dihydrogenphosphate.

FIG. 5 is a diagram of a phase IIb study of treatment with a combination of a GLP1R agonist and a beta-blocker.

FIG. 6 is a diagram of a phase IIb study of treatment of sarcopenic obesity with a beta-blocker.

FIG. 7 shows S-oxprenolol preventing muscle wasting in a murine model of KPC-induced cachexia.

FIGS. 8A & 8B show S-oxprenolol preserving muscle and function in a murine model of LLC-induced cachexia.

FIG. 9 shows S-oxprenolol can preserve lean body mass in a Yoshida AH-130 hepatoma model.

FIG. 10 shows S-oxprenolol can reduce atrophy in skeletal muscle in a Yoshida AH-130 hepatoma model.

FIGS. 11A – 11C shows schematics of Phase 1 (11A), Phase 2 (11B) and Phase 3 (11C) of a murine obesity model.

FIG. 12 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on body composition in DIO mice treated with semaglutide (DEXA body composition, comparison vs baseline).

FIG. 13 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on total muscle in DIO mice treated with semaglutide.

FIG. 14 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on cardiac muscle in DIO mice treated with semaglutide.

FIG. 15 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on grip strength normalised to body weight in DIO mice treated with semaglutide.

FIG. 16 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on appetite in DIO mice treated with semaglutide.

FIG. 17 shows a diagram of the basic study design in DIO mice.

FIGS. 18A & 18B show the body weight change from baseline at the indicated timepoints following the indicated treatments. At TP4/Final of FIG. 18A, the lines from top to bottom correspond to: vehicle; semaglutide; semaglutide + low dose FDY-8801; semaglutide + mid dose FDY-8801; and semaglutide + high dose FDY-8801. In FIG. 18B, MMRM = mixed model repeated measures; SE = standard error; and MMRM Model: change from baseline = baseline value + timepoint + treatment + treatment*timepoint + error.

FIGS. 19A and 19B show fat change from baseline at the indicated timepoints following the indicated treatments. At TP3 of FIG. 19A, the lines from top to bottom correspond to: vehicle; semaglutide; semaglutide + mid dose FDY-8801; semaglutide + low dose FDY-8801; and semaglutide + high dose FDY-8801. In FIG. 19B, MMRM = mixed model repeated

measures; SE = standard error; and MMRM Model: change from baseline = baseline value + timepoint + treatment + treatment*timepoint + error.

FIG. 20 shows the weight of various muscles (body weight normalized) following the indicated treatments.

FIGS. 21A & 21B show normalized force (21A) and normalized force @ 100 Hz (21B) following the indicated treatments. In FIG. 21A, at 50 Hz, the lines from top to bottom correspond to: S+FDY-8801 (75 mg/kg); S+FDY-8801 (25 mg/kg); semaglutide (S); and S+FDY-8801 (10 mg/kg). The S+FDY-8801 (25 mg/kg) curve is slightly obscuring the S+FDY-8801 (75 mg/kg) curve in the graph.

FIG. 22 shows adiponectin levels (ng/mL) following the indicated treatments.

FIG. 23 shows FDY-8801 (in form of S-oxprenolol) activity in an ADRB3 biosensor assay. Data was normalized to the maximal and minimal response observed in the presence of control ligand and vehicle.

FIG. 24 shows nitric oxide release following treatment of HUVEC with the indicated concentrations of FDY-8801. The data is expressed as mean $\pm$ SEM.

FIG. 25 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on total muscle weight and gastrocnemius weight in DIO mice following semaglutide treatment.

FIG. 26 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on epididymal and retroperitoneal fat in DIO mice following semaglutide treatment.

FIG. 27 shows the effect of S-pindolol, DHEA and (S)-(-)-carvedilol on the change in bone mineral content at day 57 following semaglutide treatment in DIO mice, compared with bone mineral content at day 28.

FIG. 28 shows the effect of semaglutide alone or in combination with S-pindolol on (A) fat mass (%) change from baseline, (B) lean mass (%) change from baseline and (C) lean/fat ratio (%) change in baseline in DIO mice.

FIG. 29 shows the effect of semaglutide alone or in combination with S-pindolol on (a) total muscle weight and (B) heart weight (in each case normalised to tibia length) in DIO mice.

FIG. 30 shows the effect of semaglutide alone or in combination with S-pindolol on blood pressure and heart rate in DIO mice.

DETAILED DESCRIPTION OF THE INVENTION

Reducing and restoring muscle loss from weight loss treatment

The method may reduce the negative effects of a weight loss treatment on muscle mass and/or muscle strength. The method may treat or reduce loss of muscle mass and/or muscle strength in a subject, which loss is caused by a weight loss treatment.

The beta-blocker may be for use in a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. As such, the method may reduce the negative effects of a weight loss treatment on muscle mass and/or function and/or bone density. The method may prevent, inhibit, or reduce loss of muscle mass and/or function and/or bone density in a subject, which loss is caused by a weight loss treatment.

The subject is typically undergoing a weight loss treatment when the beta-blocker is provided to the subject, or the patient may have undergone a weight loss treatment shortly before (for instance less than one month before) the beta-blocker is provided to the subject. The method may prevent, inhibit, or reduce loss of muscle mass and/or function and/or bone density in a subject who is undergoing a weight loss treatment.

The subject is typically undergoing a weight loss treatment when the beta-blocker is provided to the subject, or the patient may have undergone a weight loss treatment shortly before (for instance less than one month before) the beta-blocker is provided to the subject, The method may treat or reduce loss of muscle mass and/or muscle strength in a subject who is undergoing a weight loss treatment. The method may treat or reduce loss of bone mineral content in a subject who is undergoing a weight loss treatment.

Typically, the method is a method for preventing, inhibiting, or reducing loss of muscle mass in a subject resulting from a weight loss treatment. For instance, the method may reduce loss of muscle mass in a subject resulting from a weight loss treatment. Muscle mass may

be referred to, or determined as, lean body mass. As such, the method may be a method for preventing, inhibiting, or reducing loss of lean body mass.

The weight loss treatment may comprise (i) administration of a therapeutic agent which is a diabetes or weight loss drug and/or (ii) bariatric surgery. The weight loss treatment typically comprises deliberate reduction in the total weight of the subject.

Typically, the weight loss treatment comprises administration of a therapeutic agent which is a diabetes or weight loss drug. The weight loss treatment may comprise administration of the therapeutic agent for at least one week or at least one month prior to first treatment with the beta-blocker. For instance, the patient may have been administered the therapeutic agent at least once a week for at least one month prior to first treatment with the beta-blocker. Alternatively, the subject may begin treatment with the therapeutic agent which is a diabetes or weight loss drug at the same time or after the first treatment with the beta-blocker. For instance, the subject may be first treated with the therapeutic agent and first treated with the beta-blocker within one week, or within two weeks.

The beta-blocker may be used in situations where significant weight loss of the subject is anticipated during the weight loss treatment. For instance, the subject may be expected to undergo (or have undergone) a reduction in BMI of at least 15%, at least 20% or at least 25% as a result of the weight loss treatment (for instance compared with the BMI of the subject when the weight loss treatment was started).

The diabetes or weight loss drug may be selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

Typically, the diabetes or weight loss drug is a GLP1R agonist. The GLP1R agonist may for instance be selected from the group consisting of: semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a salt or solvate of any of the foregoing. Typically, the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide and tirzepatide, or a salt or solvate of any of the foregoing. Preferably, the weight loss drug is semaglutide.

The diabetes or weight loss drug may be a SGLT2 inhibitor, optionally selected from the group consisting of: bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin,

ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, sotagliflozin, tofogliflozin, henagliflozin, and pharmaceutically acceptable salts or solvates of any of the foregoing.

The diabetes or weight loss drug may be an amylin analogue. The amylin analogue may be petrelintide, cagrilintide or pramlintide, or a pharmaceutically acceptable salt or solvate thereof.

The weight loss treatment may comprise bariatric surgery. For instance, the patient may have undergone bariatric surgery. The patient may have undergone bariatric surgery no greater than one month before first administration of the beta-blocker. The patient may undergo bariatric surgery at least one week after first administration of the beta-blocker. The beta-blocker may prevent, inhibit, or reduce loss of muscle mass and/or function and/or bone density in a subject arising following the bariatric surgery. The beta-blocker may treat or reduce loss of muscle mass and/or muscle strength and/or bone mineral content in a subject arising following the bariatric surgery.

The bariatric surgery may comprise one or more of sleeve gastrectomy, gastric bypass surgery, biliopancreatic diversion with duodenal switch, vertical banded gastroplasty, gastric plication, or a gastric implant (for instance a gastric band, intragastric balloon, or implantable gastric stimulation).

The beta-blocker may be selected from the group consisting of: pindolol, oxprenolol, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, celeprolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, propanolol, sotalol, esmolol, carvedilol, timolol, bopindolol, medroxalol, bucindolol, levobunolol, metipranolol, celiprolol, tertatolol, and propafenone, or a pharmaceutically acceptable salt thereof.

The beta-blocker may be in racemic form or the beta-blocker may be in enantiomerically enriched form. Typically the beta-blocker is enantiomerically enriched for the S-enantiomer. For instance, the beta-blocker may have an enantiomeric excess of at least 10% (or at least about 50%) of the S-enantiomer. Typically, the beta-blocker has an enantiomeric excess of at least 90% or at least 95% of the S-enantiomer. The beta-blocker may be in single enantiomer form (for instance substantially only in the form of the S-enantiomer).

Typically, the beta-blocker is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist. For instance, the beta-blocker may be a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist selected from the group consisting of: S-pindolol,

S-oxprenolol, S-bucindolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol, and pharmaceutically acceptable salts thereof.

The beta-blocker is preferably selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. Typically, the beta-blocker is selected from the group consisting of: S-pindolol and S-oxprenolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. As such, the beta-blocker may comprise an enantiomerically enriched beta-blocker with is S-pindolol and S-oxprenolol, or a pharmaceutically acceptable salt thereof.

In one embodiment, the beta-blocker is S-pindolol or a pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salt of S-pindolol may be selected from the benzoate, the succinate or the fumarate. For instance, the beta-blocker may be S-pindolol benzoate. For instance, the beta-blocker may be S-pindolol succinate. The enantiomeric excess of S-pindolol may be at least 10%, at least 50% or at least 95%.

The beta-blocker may be S-pindolol or a pharmaceutically acceptable salt thereof and the total daily dose of the beta-blocker may be from 5 to 50 mg as the free base equivalent, for instance a total daily dose of about 10 mg, about 20 mg or about 30 mg as the free base equivalent.

In one embodiment, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof. For instance, the beta-blocker may be S-oxprenolol dihydrogenphosphate. The enantiomeric excess of S-oxprenolol may be at least 10%, at least 50% or at least 95%.

The beta-blocker may be administered once or twice a day. The beta-blocker may be administered at least three times per week (for instance once or twice a day) for at least two weeks, for instance for from two to twenty-four weeks.

Typically, the subject is overweight or obese. The subject may have a body mass index of 30 or greater (for instance of 35 or greater). The subject may have a body mass index of of ≥ 27 kg/m^2 to < 30 kg/m^2 in the presence of at least one weight-related comorbidity. The subject may be seeking to lose weight.

The subject may have sarcopenic obesity. As such, the patient may be obese and have a pre-existing loss of muscle mass and function (sarcopenia). The patient may be obese and have a pre-existing loss of muscle mass and muscle strength (sarcopenia).

The method may result in decreased loss of muscle mass and/or function and/or bone density as compared to the weight loss treatment in the absence of treatment with the beta-blocker. The method may result in decreased loss of muscle mass and/or muscle strength as compared to the weight loss treatment in the absence of treatment with the beta-blocker. As such, the beta-blocker typically reduces the loss of muscle mass experienced during or following the weight loss treatment.

The method may result in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or function and/or bone density. The method may result in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or muscle strength and/or bone mineral content. For instance, during the treatment the overall weight of the subject may reduce, but the percentage of muscle mass in the subject may increase. The method may result in the ratio of (mass of muscle):(mass of adipose tissue and fat) in the subject increasing, for instance by at least 2%, by at least 5%, by at least 10% or by at least 20% (optionally relative to the ratio in the subject when first treated with the beta-blocker).

The ratio may be as determined using body composition analysis, for instance using dual-energy X-ray absorptiometry (DEXA).

The method may inhibit or prevent the reduction of bone density and/or bone mineral content of the subject caused by the weight loss treatment. The method may increase the bone density and/or bone mineral content of the subject during the weight loss treatment.

The weight loss treatment and the beta-blocker may be administered during an overlapping time period. For instance, the weight loss treatment may be administration of a therapeutic agent which is a diabetes or weight loss drug, and the subject may be administered each of the beta-blocker and the therapeutic agent at least once during a period of one week. Typically, the subject may be administered each of the beta-blocker and the therapeutic agent at least twice during a period of one month.

Typically, the weight loss treatment comprises administration of a therapeutic agent which is a diabetes or weight loss drug, and the method comprises administering the beta-blocker and the therapeutic agent simultaneously, concurrently, separately, concomitantly or sequentially.

The invention also provides a beta-blocker for use in a method for increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. As such, the subject may have undergone a weight loss treatment and the method may result in an increase in the muscle mass and/or function and/or bone density in the subject. Typically, the method may restore muscle mass and/or function and/or bone density that the subject has lost as a consequence of the weight loss treatment.

The invention also provides a beta-blocker for use in a method for increasing or restoring muscle mass and/or muscle strength and/or bone mineral content in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker. As such, the subject has undergone a weight loss treatment and the method results in an increase in the muscle mass and/or muscle strength and/or bone mineral content in the subject. Typically, the method may restore muscle mass and/or muscle strength and/or bone mineral content that the subject has lost as a consequence of the weight loss treatment.

The method may prevent or inhibit a reduction in (mass of muscle):(mass of adipose tissue and fat) ratio of the subject following a weight loss treatment.

The beta-blocker may be as defined herein (for instance S-pindolol or S-oxprenolol, or a salt thereof). The weight loss treatment may be as defined herein (for instance administration of a GLP1 agonist). The beta-blocker may be S-pindolol or a salt thereof and the weight loss treatment may comprise administration of a GLP1 agonist.

Typically, the method is a method for increasing or restoring muscle mass in a subject following a weight loss treatment. Muscle mass may be referred to, or determined as, lean body mass. As such, the method may be a method for increasing or restoring lean body mass.

In some embodiments, the subject is undergoing the weight loss treatment at the time the subject is provided with the beta-blocker. In other embodiments, the subject has completed the weight loss treatment at the time the subject is provided with the beta-blocker. By completion of the weight loss treatment, it is meant that that particular course of weight loss has been completed. It may be the case that the subject undergoes a further weight loss

treatment in future. The method may comprising first administering the beta blocker within one month (for instance within one week) of cessation of the weight loss treatment.

The subject has typically lost weight as a result of the weight loss treatment such that the BMI of the patient has been reduced by at least 5 % relative to the BMI at the beginning of said weight loss treatment (for instance at least 10 % or at least 20 %). The reduction in BMI may have occurred within a period of no greater than 1 year prior to first provision of the beta-blocker to the subject, for instance than no greater than 6 months prior to first provision of the beta-blocker to the subject. As such, the subject may have undergone rapid weight loss due to the weight loss treatment.

The method may cause weight regain after a weight loss treatment not to be predominantly fat or adipose tissue. For instance, the subject may undergo an increase in total body weight following the cessation of the weight loss treatment, and the method may cause at least 1 %, at least 5 % or at least 10 % of that total weight gain to correspond to a gain in muscle weight. The subject may undergo an increase in total body weight following the cessation of the weight loss treatment, and the method may cause at least 50 % or at least 60 % of that total weight gain to correspond to a gain in muscle weight.

The reduction in loss of muscle mass and/or function may comprise a reduction in loss of cardiac muscle mass and/or function in the subject. The method for increasing or restoring muscle mass and/or function in a subject following a weight loss treatment may comprise increasing or restoring cardiac muscle mass and/or function in the subject.

The reduction in loss of muscle mass and/or muscle strength may comprise a reduction in loss of cardiac muscle mass and/or muscle strength in the subject. The method for increasing or restoring muscle mass and/or muscle strength in a subject following a weight loss treatment may comprise increasing or restoring cardiac muscle mass and/or muscle strength in the subject.

The method may protect cardiac muscle during a weight loss treatment. As such, the method may prevent or reduce the loss of cardiac muscle mass in the subject during a weight loss treatment. The cardiac muscle mass may be left and/or right ventricular muscle mass. For instance, the method may prevent or reduce the loss of left ventricular cardiac muscle mass in the subject during a weight loss treatment. The method may prevent or treat a weight-loss induced increase in heart rate.

The method may protect cardiac function during a weight loss treatment. The method may accordingly prevent or reduce a loss in cardiac function during a weight loss treatment. The cardiac function may be left and/or right ventricular function. The method may prevent or reduce a loss in diastolic cardiac function, a loss in systolic cardiac function, or both. In each case, the cardiac function may be left and/or right ventricular function.

The method may protect against hypotension (i.e. low blood pressure) in a subject during a weight loss treatment. Hypotension may be defined as a blood pressure reading of less than 90/60mmHg. The method may protect against increased heart rate in a subject during a weight loss treatment.

The invention also provides a beta-blocker which is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use in a method of restoring cardiac muscle mass (as defined herein) and/or cardiac function (as defined herein) in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker as defined herein.

The invention also provides a beta-blocker which is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use in a method for treating or preventing weight-loss associated increased heart rate in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

The invention also provides a beta-blocker for use in a method of treating a subject in need thereof for sarcopenic obesity or osteosarcopenic adiposity syndrome (OSA), which method comprises providing to the subject an effective amount of a beta-blocker. As such, the treatment may prevent or reduce sarcopenia in an obese subject. OSA includes coexistence of osteopenia (or osteoporosis), sarcopenia, and excess adiposity. The method may accordingly reduce sarcopenia in a subject with OSA.

The invention also provides a product comprising (a) a beta-blocker and (b) a therapeutic agent which is a diabetes or weight loss drug for simultaneous, concurrent, concomitant, separate or sequential use in: (i) preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment; and/or (ii) increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment. The beta-blocker may be S-pindolol or a salt thereof and the therapeutic agent may be a GLP1 agonist.

The invention also provides a product comprising (a) a beta-blocker and (b) a therapeutic agent which is a weight loss drug for simultaneous, concurrent, concomitant, separate or sequential use in: (i) preventing, inhibiting, or reducing loss of muscle mass and/or muscle strength in a subject resulting from a weight loss treatment; and/or (ii) increasing or restoring muscle mass and/or muscle strength and/or bone mineral content in a subject following a weight loss treatment. The beta-blocker may be S-pindolol or a salt thereof and the therapeutic agent may be a GLP1 agonist.

The invention also provides a product comprising (a) a beta-blocker and (b) a therapeutic agent which is a diabetes or weight loss drug for simultaneous, concurrent, concomitant, separate or sequential use in a method as described herein.

The invention also provides a therapeutic agent for use in a method of treating a subject in need thereof for diabetes and/or to induce weight loss in combination with an effective amount of a beta-blocker, which method comprises providing to the subject an effective amount of the therapeutic agent, which therapeutic agent is a diabetes or weight loss drug. For instance, the invention may provide a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, or a SGLT2 inhibitor for use in a method of treating a subject in need thereof for diabetes and/or to induce weight loss in combination with an effective amount of a beta-blocker (for instance S-pindolol or S-oxprenolol or a salt thereof).

Typically the beta-blocker is administered orally. For instance, the beta-blocker may be administered orally in the form of a tablet or capsule.

Alternatively, the beta-blocker may be administered by injection, for instance by intravenous, intramuscular or subcutaneous injection. The subject may be administered by injection in a form which provides a delayed release of the beta-blocker during and/or following the weight loss treatment. For instance, the beta-blocker may be administered in the form of a depot injection. A depot injection typically injects the beta-blocker in a formulation which allows slow release of the beta-blocker. The depot injection of the beta-blocker may be administered within one month of first administration of the weight loss treatment. For instance, the depot injection of the beta-blocker may be administered within one week of first administration of the weight loss treatment.

Combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist

The present invention provides a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist as defined herein for use in treating or preventing loss of muscle mass in a patient treated with a GLP1 agonist as defined herein.

The present invention utilizes dual-acting compounds to interact with both beta- adrenergic receptors and 5-HT_{1A} receptors and as a result to provide the means for the treatment described herein. This invention envisages the use of any compound that interacts with both the beta-adrenergic receptors and the 5-HT_{1A} receptor as either an antagonist or a partial agonist.

In some embodiments, the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is selected from the group consisting of S-pindolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol, S-oxprenolol and pharmaceutically acceptable salts thereof. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is selected from the group consisting of S-pindolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol and pharmaceutically acceptable salts thereof. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is selected from the group consisting of S-oxprenolol, S-pindolol and pharmaceutically acceptable salts thereof. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol and pharmaceutically acceptable salts thereof. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-oxprenolol and pharmaceutically acceptable salts thereof.

In some embodiments, the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol or a pharmaceutically acceptable salt thereof. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is a pharmaceutically acceptable salt of S-pindolol and benzoic acid. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol benzoate. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol benzoate crystalline polymorph Pattern 1 having an x-ray powder diffraction pattern comprising peaks at 8.1°, 11.4° and 17.0° ±0.2° 2θ. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol benzoate crystalline polymorph Pattern 2 having an x-ray powder diffraction pattern comprising peaks at 16.9°, 18.9° and 20.1° ±0.2° 2θ. Such polymorphs are described in WO 2021/205144.

In some embodiments, the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is a pharmaceutically acceptable salt of S-pindolol and succinic acid. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol succinate. In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol succinate in the form of S-pindolol succinate crystalline polymorph Pattern 1 having an x-ray powder diffraction pattern comprising peaks at 13.3°, 16.7° and 19.5° ± 0.2° 2θ.

In some embodiments, the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol or a pharmaceutically acceptable salt thereof; wherein the S-pindolol or a pharmaceutically acceptable salt thereof is provided as a solid pharmaceutical formulation suitable for oral administration comprising: (a) an active agent which is S-pindolol or a pharmaceutically acceptable salt thereof; (b) a starch excipient in an amount of at least 15.0 % by weight relative to the total weight of the formulation; and (c) a cellulose excipient in an amount of at least 40.0 % by weight relative to the total weight of the formulation. S-pindolol benzoate is a particularly preferred pharmaceutically acceptable salt of S-pindolol.

A typical dose of the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist will be in the range of 0.1-1000 mg for a single dose, preferably 1-15 mg for a single dose. In some embodiments, the dose is 2.5 mg, 5 mg or 10 mg. In some embodiments the dose is 15 mg per day, or 20 mg per day, or 30 mg per day or 45 mg per day, or 60 mg per day. In some embodiments, the dose is at least 10 mg a day, or at least 15 mg a day, or at least 20 mg a day, or at least 30 mg a day. In some embodiments, the dose is at least 10 mg two times a day. In some embodiments, the dose is 10 mg two times a day. Where the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is in the form of a pharmaceutically acceptable salt, the dose will be an amount to provide an equivalent amount of the free acid or free base compound.

Where the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is S-pindolol, the typical dose will be in the range 0.1-1000 mg for a single dose, preferably 1-15 mg for a single dose. In some embodiments, the S-pindolol dose is 2.5 mg, 5 mg or 10 mg. In some embodiments the S-pindolol dose is 15 mg per day, or 20 mg per day, or 30 mg per day or 45 mg per day, or 60 mg per day. In some embodiments, the S-pindolol dose is at least 10 mg a day, or at least 15 mg a day, or at least 20 mg a day, or at least 30 mg a day.

In some embodiments, the S-pindolol dose is at least 10 mg two times a day. In some embodiments, the S-pindolol dose is 10 mg two times a day.

In some embodiments, the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is administered once, twice or three times a day. Preferably the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is administered once a day or two times a day. More preferably the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is administered two times a day.

Glucagon-like peptide-1 receptor agonist (GLP1 agonist or GLP1R agonist)

The present invention utilizes a GLP1 agonist to provide the means for the treatment described herein. GLP1 agonists are known for use in body mass reduction.

In some embodiments, the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, mazdutide, retatrutide, and pharmaceutically acceptable salts thereof. In some embodiments the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, and pharmaceutically acceptable salts thereof. In some embodiments, the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide, tirzepatide, and pharmaceutically acceptable salts thereof. In some embodiments, the GLP1 agonist is selected from the group consisting of semaglutide, tirzepatide, and pharmaceutically acceptable salts thereof.

In some embodiments, the GLP1 agonist is administered once weekly. In some embodiments, the GLP1 agonist is administered in a solution by subcutaneous injection. In some embodiments, the GLP1 agonist is administered in a solution by subcutaneous injection once weekly.

In some embodiments, the GLP1 agonist is administered once daily. In some embodiments, the GLP1 agonist is administered orally. In some embodiments, the GLP1 agonist is administered orally once daily.

In some embodiments, the GLP1 agonist is semaglutide. In some embodiments the semaglutide dose is 0.1-30 mg. In some embodiments the semaglutide dose is selected from the group consisting of 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg 3 mg, 7 mg and 14 mg. In some embodiments the semaglutide dose is administered in a solution by subcutaneous

injection once weekly. In some embodiments the semaglutide dose is administered orally once daily.

In some embodiments, the GLP1 agonist is liraglutide. In some embodiments the liraglutide dose is 0.1-10 mg. In some embodiments the liraglutide dose is selected from the group consisting of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3 mg. In some embodiments the liraglutide dose is administered in a solution by subcutaneous injection once daily.

In some embodiments the GLP1 agonist is also a GIP (glucose-dependent insulinotropic polypeptide) receptor agonist. An example of a dual GLP1 and GIP receptor agonist is tirzepatide.

In some embodiments the GLP1 agonist is tirzepatide. In some embodiments the tirzepatide dose is 0.1-30 mg. In some embodiments the tirzepatide dose is selected from the group consisting of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg and 15 mg. In some embodiments the tirzepatide dose is administered in a solution by subcutaneous injection once weekly.

In some embodiments the GLP1 agonist is also a glucagon receptor agonist. An example of a dual GLP1 and glucagon receptor agonist is mazdutide.

In some embodiments the GLP1 agonist is also an agonist of both the GIP (glucose-dependent insulinotropic polypeptide) receptor and the glucagon receptor. An example of a triple agonist of the GLP1, GIP and glucagon receptors is retatrutide (also known as LY3437943).

Treatment or prevention

The term "therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

In some embodiments, the combinations as described herein are for use in treating loss of muscle mass in a patient in need thereof. For example, in treating loss of muscle mass associated with body mass reduction.

In some embodiments, a beta blocker described herein, e.g., S-oxprenolol, is used to treat obesity or pre-obesity, or to induce or promote weight loss in a patient in need thereof. In

some embodiments, the patient has sarcopenic obesity or another condition disclosed herein.

The term "treatment" as used herein refers to the treatment of a disease or medical condition in a human or animal patient which includes:
(a) preventing the disease or medical condition from occurring, i.e., prophylactic treatment of a patient;
(b) ameliorating the disease or medical condition, i.e., causing regression of the disease or medical condition in a patient, for example restoring loss of muscle mass;
(c) suppressing the disease or medical condition, i.e., slowing the development of the disease or medical condition in a patient; and/or
(d) alleviating the symptoms of the disease or medical condition in a patient.

In some embodiments, the combinations as described herein are for use in preventing loss of muscle mass in a patient in need thereof. For example, in preventing loss of muscle mass during body mass reduction. As such, the invention may provide combined a beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use in preventing sarcopenia in a patient who is losing weight. The patient may be undergoing a weight loss treatment.

The term “prevention” as used herein in relation to a disease or condition, relates to prophylactic or preventative therapy, as well as therapy to reduce the risk of developing the disease or condition. The term “prevention” includes both the avoidance of occurrence of the disease or condition, and the delay in onset of the disease or condition. Any statistically significant ($p < 0.05$) avoidance of occurrence, delay in onset or reduction in risk as measured by a controlled clinical trial may be deemed a prevention of the disease or condition. Subjects amenable to prevention include those at heightened risk of a disease or condition.

Body composition including muscle mass can be measured by dual-energy X-ray absorptiometry (DEXA). J Clin Med. 2019 Jul; 8(7), p 1040 “Clinical Value of Muscle Mass Assessment in Clinical Conditions Associated with Malnutrition” Mareschal et al. describes methods of assessing muscle mass. Body composition may alternatively be as measured by skin fold callipers and calculation (of total weight gain minus fat gain), by bioimpedance methods, or by using a labelled tracer.

Muscle strength may be as measured by determining grip strength of a subject (for instance grip strength normalised to body weight). Muscle strength may be as measured using isometric dynamometry, the Oxford Scale (also known as the Medical Research Council Manual Muscle Testing scale), stair climbing power, the short physical performance battery, the Heel-Raise Test or Sit-to-Stand Tests.

Patient

The patient may be any human or other animal. Typically, the patient is a human.

In some embodiments, the combinations as described herein are for use in treating or preventing loss of muscle mass during body mass reduction in a patient in need thereof. In some embodiments, the body mass reduction of the patient is 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15% or 20% of the total body mass. In some embodiments, the body mass reduction is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

In some embodiments, the combinations as described herein are for use in treating or preventing loss of muscle mass during fat mass reduction in a patient in need thereof. In some embodiments, the fat mass reduction of the patient is 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15% or 20% of the total body fat mass. In some embodiments, the fat mass reduction is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8. 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

In some embodiments, the patient has a body mass index of 22 or greater. In some embodiments the patient has a body mass index of 25 or greater. In some embodiments, the patient has a BMI of 27 or greater. In some embodiments, the patient has a body mass index of 30 or greater. In some embodiments, the patient has a body mass index of 32 or greater. In some embodiments, the patient has a body mass index of 35 or greater. In some embodiments, the patient has a body mass index of 37 or greater. In some embodiments, the patient has a body mass index of 40 or greater.

Body mass index (BMI) is a value derived from the mass (weight) and height of a person. The BMI is defined as the body mass divided by the square of the body height, and is expressed in units of kg/m^2, resulting from mass in kilograms (kg) and height in metres (m).

Adult BMI classifications are underweight (under 18.5 kg/m^2), normal weight (18.5 to 24.9), overweight (also known as pre-obesity) (25 to 29.9), and obese (30.0 or more).

In some embodiments, the patient has one or more co-morbid condition selected from the group consisting of hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, and type 2 diabetes mellitus.

In some embodiments, the patient has a BMI of 27 or greater and has one or more comorbid condition. Examples of comorbid conditions include conditions selected from the group consisting of hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, and type 2 diabetes mellitus.

In some embodiments, the patient is at risk of a condition associated with loss of muscle mass. In some embodiments the patient has a condition associated with loss of muscle mass. Examples of conditions associated with loss of muscle mass include sarcopenia and cachexia.

In some embodiments, the loss of muscle mass of the patient is no more than about 10% (for example no more than about any of 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1%) of the total body muscle mass. In some embodiments, there is no loss of muscle mass of the patient. In some embodiments muscle mass of the patient increases by about 1% (for example about any of 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9% or 10%) of the total body muscle mass. In some embodiments, the loss of muscle mass is evaluated over a time period of about 1 month to 2 years (for example, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 months).

In some embodiments, the patient is 18 years of age or older. In some embodiments, the patient is 45 years of age or older. In some embodiments, the patient is 60 years of age or older. In some embodiments the patient is 70 years of age or older.

In some embodiments, the patient is an adolescent of 12 years of age or older and less than 18 years of age, is obese, and has a body weight above 60 Kg. BMI cut-off points for obesity for adolescents by age and sex are:

Age (years)	**BMI (Kg/m^2) at 95th percentile**	
	Male	**Female**

12	24.2	25.2
12.5	24.7	25.7
13	25.1	26.3
13.5	25.6	26.8
14	26.0	27.2
14.5	26.4	27.7
15	26.8	28.1
15.5	27.2	28.5
16	27.5	28.9
16.5	27.9	29.3
17	28.2	29.6
17.5	28.6	30.0

Administration

The present invention involves the use of a combination of (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist and (b) a GLP1 agonist. The combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist and GLP1 agonist are herein referred to as “active ingredients”.

In one aspect, the present invention provides a pharmaceutical composition that comprises: (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist and (b) GLP1 agonist. Pharmaceutical compositions according to the invention will typically further comprise one or more pharmaceutically acceptable excipients or carriers.

In some embodiments the invention provides:
(a) S-pindolol or a pharmaceutically acceptable salt thereof as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) semaglutide as the GLP1 agonist.

In some embodiments the invention provides:
(a) S-pindolol or a pharmaceutically acceptable salt thereof as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) tirzepatide as the GLP1 agonist.

In some embodiments the invention provides:

(a) S-pindolol or a pharmaceutically acceptable salt thereof as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) liraglutide as the GLP1 agonist.

In some embodiments the invention provides:
(a) S-pindolol benzoate as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) semaglutide as the GLP1 agonist.

In some embodiments the invention provides:
(a) S-pindolol benzoate as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) tirzepatide as the GLP1 agonist.

In some embodiments the invention provides:
(a) S-pindolol benzoate as the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist; and
(b) liraglutide as the GLP1 agonist.

The combination of the present invention extends to situations where the active ingredients discussed above are co-administered. When the active ingredients are co-administered they can be present either in a single pharmaceutical composition or in separate pharmaceutical compositions, including in separate pharmaceutical compositions optimized for administration either by the same mode or a different mode. For example, the active ingredients may both be administered intravenously, either in a single pharmaceutical composition or, more preferably, in separate pharmaceutical compositions.

For the avoidance of doubt, in the product comprising (a) a combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist and (b) GLP1 agonist, as a combined preparation for simultaneous, concurrent, separate or sequential use, the product may comprise either a single pharmaceutical composition that comprises both (a) and (b) (i.e. a unit dosage form) or alternatively, and preferably, a first pharmaceutical composition that comprises (a) and a second (i.e., separate) pharmaceutical composition that comprises (b).

In some embodiments the combination comprises sequential use of the GLP1 agonist followed by the 5-HT_{1A} receptor antagonist or partial agonist.

In some embodiments the 5-HT_{1A} receptor antagonist or partial agonist is for use following discontinuation of the use of the GLP1 agonist. In some embodiments the 5-HT_{1A} receptor antagonist or partial agonist is for use in treating loss of muscle mass, wherein the 5-HT_{1A} receptor antagonist or partial agonist is for use following discontinuation of the use of the GLP1 agonist. In some embodiments the 5-HT_{1A} receptor antagonist or partial agonist is for use in treating loss of muscle mass associated with body mass reduction, wherein the 5-HT_{1A} receptor antagonist or partial agonist is for use following discontinuation of the use of the GLP1 agonist.

The pharmaceutical formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

Co-administration of the active ingredients according to the present invention includes simultaneous, concurrent, separate and sequential administration.

When combinations of actives are used, it is contemplated that all active agents would be administered at the same time, or very close in time. Alternatively, one active could be taken in the morning and the other later in the day. Or in another scenario, one active could be taken once or twice daily and the other once weekly, either at the same time as one of the once or twice-a-day dosing occurred, or separately.

Pharmaceutical compositions

The term “pharmaceutically acceptable salt” refers to a salt prepared from a base or acid which is acceptable for administration to a patient, such as a human or animal e.g. a mammal. Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids.

In some embodiments the combined beta-adrenergic and 5-HT_{1A} receptor antagonist or partial agonist is in the form of a pharmaceutically acceptable salt.

In some embodiments the GLP1 agonist is in the form of a pharmaceutically acceptable salt.

The active ingredients of the present invention can be used both in their free base form and their acid addition salt form. For the purposes of this invention, a “salt” of a compound of the present invention includes an acid addition salt. Acid addition salts are addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for

example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulfuric or phosphoric acid); or organic acids such as organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothenic or pamoic acid), organic sulfonic acids (for example, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, benzenesulfonic, toluene-p-sulfonic, naphthalene-2-sulfonic or camphorsulfonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono-, di-, tri- or multi-acid addition salt. A preferred salt is a benzoic acid addition salt.

The active ingredients of the present invention can also be used both in their free acid form and their salt form. For the purposes of this invention, a “salt” of a compound of the present invention includes one formed between a protic acid functionality (such as a carboxylic acid group) of a compound of the present invention and a suitable cation. Suitable cations include, but are not limited to lithium, sodium, potassium, magnesium, calcium and ammonium. The salt may be a mono-, di-, tri- or multi-salt. Preferably the salt is a mono- or di-lithium, sodium, potassium, magnesium, calcium or ammonium salt.

The active ingredients of the present invention may be anhydrous or in the form of a hydrate (e.g. a hemihydrate, monohydrate, dihydrate or trihydrate) or other solvate. Such other solvates may be formed with common organic solvents, including but not limited to, alcoholic solvents e.g. methanol, ethanol or isopropanol.

The active ingredients of the present invention may contain at least one chiral centre. The active ingredients may therefore exist in at least two isomeric forms. The present invention encompasses racemic mixtures of the active ingredients as well as enantiomerically enriched and substantially enantiomerically pure isomers. For the purposes of this invention, a “substantially enantiomerically pure” isomer of a compound comprises less than 5% of other isomers of the same compound, more typically less than 2%, more typically less than 0.5% by weight, more typically less than 0.1% by weight and most typically less than 0.01% by weight.

The active ingredients of present invention may be in any polymorphic or amorphous form.

Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, “Aulton’s Pharmaceutics - The Design and

Manufacture of Medicines", M. E. Aulton and K. M. G. Taylor, Churchill Livingstone Elsevier, 4th Ed., 2013.

Pharmaceutically acceptable excipients including adjuvants, diluents or carriers that may be used in the pharmaceutical compositions of the invention are those conventionally employed in the field of pharmaceutical formulation, and include, but are not limited to, sugars, sugar alcohols, starches, ion exchangers, alumina, aluminium stearate, lecithin, serum proteins such as human serum albumin, buffer substances such as phosphates, glycerine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinylpyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Pharmaceutical compositions of the invention may comprise additional active ingredients, such as an additional therapeutic or prophylactic agent intended, for example, for the treatment of the same condition or a different one, or for other purposes such as amelioration of side effects.

Any of the medicaments employed in the present invention can be administered by oral, parenteral (including intravenous, subcutaneous, intramuscular, intradermal, intratracheal, intraperitoneal, intraarticular, intracranial and epidural), airway (aerosol), rectal, vaginal, ocular or topical (including transdermal, buccal, mucosal, sublingual and topical ocular) administration.

For oral administration, the active ingredients of the present invention will generally be provided in the form of tablets, capsules, hard or soft gelatine capsules, caplets, troches or lozenges, as a powder or granules, or as an aqueous solution, suspension or dispersion.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose. Corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatine. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a

material, such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract. Tablets may also be effervescent and/ or dissolving tablets.

Capsules for oral use include hard gelatine capsules in which the active ingredient is mixed with a solid diluent, and soft gelatine capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Powders or granules for oral use may be provided in sachets or tubs. Aqueous solutions, suspensions or dispersions may be prepared by the addition of water to powders, granules or tablets.

Any form suitable for oral administration may optionally include sweetening agents such as sugar, flavouring agents, colouring agents and/or preservatives.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or a salicylate.

For parenteral use, active ingredients of the present invention will generally be provided in a sterile aqueous solution or suspension, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride or glucose. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinylpyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate. Active ingredients of the invention may also be presented as liposome formulations.

For transdermal and other topical administration, active ingredients of the invention will generally be provided in the form of ointments, cataplasms (poultices), pastes, powders, dressings, creams, plasters or patches.

Suitable suspensions and solutions can be used in inhalers for airway (aerosol) administration.

The dose of the active ingredients of the present invention will, of course, vary for example with the severity of the disease or condition to be treated or prevented. In general, a suitable dose will be in the range of 0.01 to 500 mg per kilogram body weight of the recipient per day.

The desired dose may be presented at an appropriate interval such as once a week, once every other day, once a day, twice a day, three times a day or four times a day.

The desired dose may be administered in unit dosage form, for example, containing 0.1 mg to 5 g of active ingredient per unit dosage form.

For the avoidance of doubt, insofar as is practicable any embodiment of the present invention may occur in combination with any other embodiment of the present invention.

Additional discussion of the invention

In general, the present disclosure relates to compositions and methods for treating various disease or disorders, e.g., diabetes and inducing weight loss, that comprise use of a beta-blocker or a combination of both a therapeutic agent and a beta-blocker. The compositions and methods disclosed herein advantageously inhibit or prevent loss of muscle mass and/or function and/or bone mass and/or density that can result from treatment with therapeutic agents such as diabetes and weight loss drugs, e.g., GLP1R agonists.

In a first aspect, the disclosure provides a method of treating a subject in need thereof for diabetes and/or to induce weight loss, comprising providing to the subject an effective amount of a diabetes or weight loss drug in combination with an effective amount of a beta-blocker. In certain embodiments, the beta-blocker is a beta-1 adrenergic antagonist (β1 antagonist) and/or a beta-2 adrenergic antagonist (β2 antagonist). In certain embodiments, the beta-blocker is additionally a beta-3 adrenergic agonist (β3 agonist). In certain embodiments, the beta blocker is additionally a β3 agonist and/or a serotonin 1A receptor (5-HT1A receptor) antagonist or partial agonist. In certain embodiments, the beta blocker is additionally a β3 agonist and a serotonin 1A receptor (5-HT1A receptor) antagonist. In particular embodiments, the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor. In certain embodiments, the subject is treated for diabetes, e.g., type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). In certain embodiments, the diabetes or weight loss drug is not a beta-blocker. In certain embodiments, the subject is treated to induce weight loss. In certain embodiments, the subject is overweight or obese. In certain embodiments, the subject has sarcopenic obesity.

In a second aspect, the disclosure provides a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density resulting from treatment of a subject with a therapeutic agent, comprising providing to the subject an effective amount of a beta-blocker in combination with the therapeutic agent, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to the subject without the beta-blocker. In certain embodiments, the beta-blocker is a beta-1 adrenergic antagonist (β1 antagonist) and/or a beta-2 adrenergic antagonist (β2 antagonist). In certain embodiments, the beta-blocker is additionally a beta-3 adrenergic agonist (β3 agonist). In certain embodiments, the beta blocker is additionally a β3 agonist and a serotonin 1A receptor (5-HT1A receptor) antagonist. In particular embodiments, the therapeutic agent is a diabetes or weight loss drug, optionally a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, or a SGLT2 inhibitor.

In a third aspect, the disclosure provides a method for increasing or promoting weight loss resulting from treatment of a subject with a therapeutic agent, comprising providing to the subject an effective amount of a beta-blocker in combination with the therapeutic agent, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to the subject without the beta-blocker. In certain embodiments, the beta-blocker is a beta-1 adrenergic antagonist (β1 antagonist) and/or a beta-2 adrenergic antagonist (β2 antagonist). In certain embodiments, the beta-blocker is a beta-3 adrenergic agonist (β3 agonist). In certain embodiments, the beta blocker is a β3 agonist and a serotonin 1A receptor (5-HT1A receptor) antagonist. In particular embodiments, the therapeutic agent is a diabetes or weight loss drug, optionally a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, or a SGLT2 inhibitor.

In a fourth aspect, the disclosure provides a method of treating a subject in thereof for sarcopenic obesity, osteosarcopenia, osteoporosis, or osteosarcopenic adiposity syndrome (OSA), comprising providing to the subject an effective amount of a beta-blocker. In certain embodiments, the beta-blocker is a beta-1 adrenergic antagonist (β1 antagonist) and/or a beta-2 adrenergic antagonist (β2 antagonist). In certain embodiments, the beta-blocker is additionally a beta-3 adrenergic agonist (β3 agonist). In certain embodiments, the beta blocker is additionally a β3 agonist and a serotonin 1A receptor (5-HT1A receptor) antagonist.

In a fifth aspect, the disclosure provides a pharmaceutical composition comprising a therapeutic agent and a beta blocker, and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker. In particular embodiments, the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

In a sixth aspect, the disclosure provides a kit comprising: a container comprising a pharmaceutical composition comprising a therapeutic agent and a pharmaceutically acceptable excipient, diluent, or carrier; and a container comprising a beta blocker and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker. In certain embodiments, the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

In particular embodiments of the first, second, third, fifth, and sixth aspects aspects, the drug or therapeutic agent is a GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments of the first, second, third, fifth, and sixth aspects aspects, the drug or therapeutic agent is a SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments of any of the first, second, third, fourth, fifth and sixth aspects, the beta-blocker is selected from the group consisting of: oxprenolol or pindolol, or a

pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiments, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

In particular embodiments of the first, second, third, fifth, and sixth aspects, the subject is provided, or the composition or kit comprises: S-oxprenolol dihydrogenphosphate and exenatide; S-oxprenolol dihydrogenphosphate and lixisenatide; S-oxprenolol dihydrogenphosphate and liraglutide; S-oxprenolol dihydrogenphosphate and dulaglutide; S-oxprenolol dihydrogenphosphate and semaglutide; S-oxprenolol dihydrogenphosphate and tirzepatide; S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943); S-oxprenolol dihydrogenphosphate and empagliflozin; S-oxprenolol dihydrogenphosphate and canagliflozin; S-oxprenolol dihydrogenphosphate and dapagliflozin; or S-oxprenolol dihydrogenphosphate and ipragliflozin.

In particular embodiments of aspect 1, aspect 2, and aspect 3, the therapeutic agent, e.g., diabetes or weight loss drug, and the beta-blocker are administered during an overlapping time period.

In particular embodiments of aspect 1, aspect 2, aspect 3, and aspect 4, the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the beta-blocker.

Definitions and Nomenclature

Unless otherwise defined herein, scientific and technical terms used in this application shall have meanings that are commonly understood by those of ordinary skill in the art. Generally, nomenclature used in connection with, and techniques of, chemistry, molecular biology, cell and cancer biology, immunology, microbiology, pharmacology, and protein and nucleic acid chemistry, described herein, are those well-known and commonly used in the art.

As used herein, the following terms have the meanings ascribed to them in the art unless specified otherwise.

Throughout this specification, the word “comprise” or variations such as “comprises” or “comprising” will be understood to imply the inclusion of a stated integer (or components) or group of integers (or components), but not the exclusion of any other integer (or components) or group of integers (or components).

The singular forms “a,” “an,” and “the” include the plurals unless the context clearly dictates otherwise. The term “including” is used to mean “including but not limited to.” “Including” and “including but not limited to” are used interchangeably.

The terms “patient,” “subject,” and “individual” may be used interchangeably and refer to either a human or a non-human animal. These terms include mammals such as humans, primates, livestock animals (e.g., bovines, porcines), companion animals (e.g., canines, felines) and rodents (e.g., mice and rats). The term “mammal” refers to any mammalian species such as a human, mouse, rat, dog, cat, hamster, guinea pig, rabbit, livestock, and the like.

“About” when referring to a value includes the stated value +/- 10% of the stated value. For example, about 50% includes a range of from 45% to 55%, while about 20 molar equivalents includes a range of from 18 to 22 molar equivalents. Accordingly, when referring to a range, “about” refers to each of the stated values +/- 10% of the stated value of each end of the range. For instance, a ratio of from about 1 to about 3 (weight/weight) includes a range of from 0.9 to 3.3.

“Pharmaceutically acceptable excipient” includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

As used herein, by "pharmaceutically acceptable" or "pharmacologically compatible" is meant a material that is not biologically or otherwise undesirable, e.g., the material may be incorporated into a pharmaceutical composition administered to an individual without causing any significant undesirable biological effects or interacting in a deleterious manner

with any of the other components of the composition in which it is contained. “Pharmaceutically acceptable” may refer to compounds, salts, compositions, dosage forms and other materials which are useful in preparing a pharmaceutical composition that is suitable for veterinary or human pharmaceutical use.

The term "salt thereof” means a compound formed when a proton of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. By way of example, salts of the disclosed compounds include those wherein the compound is protonated by an inorganic or organic acid to form a cation, with the conjugate base of the inorganic or organic acid as the anionic component of the salt. It will be appreciated that the term "or a salt thereof” is intended to include all permutations of salts, such as a pharmaceutically acceptable salt, of a subject compound. The term "pharmaceutically acceptable salt" means a salt which is acceptable for administration to a subject, such as a mammal (salts with counterions having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids. Thus, the term “pharmaceutically acceptable salt,” as used herein, represents salts or zwitterionic forms of compounds that are suitable for treatment of diseases without undue toxicity, irritation, and allergic response; which are commensurate with a reasonable benefit/risk ratio, and which are effective for their intended use. Representative acid addition salts include acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, formate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproprionate, picrate, pivalate, propionate, succinate, tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-toluenesulfonate, and undecanoate. Examples of acids which can be employed to form therapeutically acceptable addition salts include, but are not limited to, inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. A pharmaceutically acceptable salt may suitably be a salt chosen, e.g., among acid addition salts and basic salts. Examples of acid addition salts include chloride salts, citrate salts and acetate salts. Examples of basic salts include salts where the cation is selected among alkali metal cations, such as sodium or potassium ions, alkaline earth metal cations, such as calcium or magnesium ions, as well as substituted ammonium ions, such as ions of the type NX_4^+ (wherein X is C1-C6 alkyl). Also included are base addition salts, such as sodium or potassium salts. Other examples of pharmaceutically acceptable salts are described in “Remington’s Pharmaceutical Sciences”,

17th edition, Alfonso R. Gennaro (Ed.), Mark Publishing Company, Easton, PA, USA, 1985 (and more recent editions thereof), in the “Encyclopaedia of Pharmaceutical Technology”, 3rd edition, James Swarbrick (Ed.), Informa Healthcare USA (Inc.), NY, USA, 2007, and in J. Pharm. Sci. 66: 2 (1977). Also, for a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley- VCH, 2002). Other suitable base salts are formed from bases which form non-toxic salts. Representative examples include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine, and zinc salts. Hemisalts of acids and bases may also be formed, e.g., hemisulphate and hemicalcium salts.

Compounds disclosed herein, or their pharmaceutically acceptable salts, may contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. Where compounds are represented in their chiral form, it is understood that the aspect encompasses, but is not limited to, the specific diastereomerically or enantiomerically enriched form (unless the context indicates otherwise). Where chirality is not specified but is present, it is understood that the aspect is directed to either the specific diastereomerically or enantiomerically enriched form; or a racemic or scalemic mixture of such compound(s). As used herein, “scalemic mixture” is a mixture of stereoisomers at a ratio other than 1:1.

The term "isomers" or "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. “Stereoisomer” and “stereoisomers” refer to compounds that differ in the chirality of one or more stereocenters. Stereoisomers include enantiomers and diastereomers. The compounds may exist in stereoisomeric form, if they possess one or more asymmetric

centers or a double bond with asymmetric substitution and, therefore, can be produced as individual stereoisomers or as mixtures. Unless otherwise indicated, the description is intended to include individual stereoisomers as well as mixtures. In the chemical structures where a chiral center exists in a structure, but no specific stereochemistry is shown for the chiral center, both enantiomers associated with the chiral structure are encompassed by the structure. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (see, e.g., Chapter 4 of Advanced Organic Chemistry, 4th ed., J. March, John Wiley and Sons, New York, 1992).

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "diastereomers" refers to stereoisomers with two or more centers of dissymmetry and whose molecules are not mirror images of one another.

The term "enantiomers" refers to two stereoisomers of a compound which are non-superimposable mirror images of one another. An equimolar mixture of two enantiomers is called a "racemic mixture" or a "racemate."

“Tautomer” refers to alternate forms of a compound that differ in the position of a proton, such as enol-keto and imine-enamine tautomers, or the tautomeric forms of heteroaryl groups containing a ring atom attached to both a ring -NH- and a ring =N- such as pyrazoles, imidazoles, benzimidazoles, triazoles, and tetrazoles.

The term "enantiomerically enriched" means that the racemic mixture (i.e., 50/50 mixture of the enantiomers) has been purified such that one enantiomer comprises greater than 50% of the total amount of the compound present, For example, a composition that is enantiomerically enriched for S-oxprenolol is a composition wherein more than 50% of the oxprenolol is the S- enantiomer of oxprenolol (S-oxprenolol). The degree of enantiomeric enrichment of a composition can be determined by "enantiomeric excess," or ee. "Enantiomeric excess" represents the percentage of one enantiomer in excess of the other. For instance, a composition having a 75:25 mixture of S-oxprenolol and R-oxprenolol has a 75 - 25 = 50 % ee, while a 50:50 racemic mixture has a 50 - 50 = 0 % ee. The value of ee will be a number from 0 to 100, 0 being racemic and 100 being pure, single enantiomer.

"Therapeutically effective amount" or "effective amount" as used herein refers to an amount that is effective to elicit the desired biological or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to affect such treatment for the disease. The effective amount will vary depending on the compound, the disease, and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts. As is understood in the art, an effective amount may be in one or more doses, i.e., a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved. Suitable doses of any co-administered compounds may optionally be lowered due to the combined action (e.g., additive or synergistic effects) of the compounds.

"Treatment" or "treat" or "treating" as used herein refers to an approach for obtaining beneficial or desired results. For purposes of the present invention, beneficial or desired results include, but are not limited to, alleviation of a symptom and/or diminishment of the extent of a symptom and/or preventing a worsening of a symptom associated with a disease or condition. In one aspect, "treatment" or "treating" includes one or more of the following: (a) inhibiting the disease or condition (e.g., decreasing one or more symptoms resulting from the disease or condition, and/or diminishing the extent of the disease or condition); (b) slowing or arresting the development of one or more symptoms associated with the disease or condition (e.g., stabilizing the disease or condition, delaying the worsening or progression of the disease or condition); (c) relieving the disease or condition, e.g., causing the regression of clinical symptoms, ameliorating the disease state, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival; and (d) preventing the disease, condition or disorder in a subject who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease. In some embodiments, treating refers to inhibiting or ameliorating the disease. In some embodiments, treating is preventing the disease.

"Co-administration" or "to administer in combination with" as used herein refers to administration of unit dosages of one of the therapeutic agents disclosed herein (e.g., a diabetes or weight loss drug) before or after administration of unit dosages of one or more additional therapeutic agents (e.g., a beta-blocker), for example, administration of a therapeutic agent within seconds, minutes, or hours of the administration of a beta-blocker. For example, in some aspects, a unit dose of a therapeutic agent (e.g., a diabetes or weight

loss drug) is administered first, followed within seconds or minutes by administration of a unit dose of a beta-blocker. Alternatively, in other aspects, a unit dose of a beta-blocker is administered first, followed by administration of a unit dose of a therapeutic agent (e.g., a diabetes or weight loss drug) within seconds or minutes. In some aspects, a unit dose of a compound of the invention is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more additional therapeutic agents. In other aspects, a unit dose of a therapeutic agent (e.g., a diabetes or weight loss drug) is administered first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a beta-blocker. Co-administration of a therapeutic agent (e.g., a diabetes or weight loss drug) with a beta-blocker generally refers to simultaneous or sequential administration of a therapeutic agent (e.g., a diabetes or weight loss drug) and a beta-blocker, such that therapeutically effective amounts of each agent are present in the body of the patient at some time, and in some embodiment, during an overlapping time period.

The term "simultaneous administration," as used herein, means that a first therapy and second therapy are administered with a time separation of no more than about 15 minutes, such as no more than about any of 10, 5, or 1 minutes. When the first and second therapies are administered simultaneously, the first and second therapies may be contained in the same composition (e.g., a composition comprising both a first and second therapy) or in separate compositions (e.g., a first therapy in one composition and a second therapy is contained in another composition).

As used herein, the term "sequential administration" means that the first therapy and second therapy in a combination therapy are administered with a time separation of more than about 15 minutes, such as more than about any of 20, 30, 40, 50, 60, or more minutes. Either the first therapy or the second therapy may be administered first. The first and second therapies are contained in separate compositions, which may be contained in the same or different packages or kits.

As used herein, the term "concurrent administration" means that the administration of the first therapy and that of a second therapy in a combination therapy overlap with each other.

Beta-Blockers

The methods described herein comprise administration of beta-blockers or compositions comprising beta-blockers. Beta-blockers are drugs that lower blood pressure may also be referred to as beta-adrenergic blocking agents. Beta-blockers block the effects of the

hormone epinephrine, also known as adrenaline. Beta-blockers cause the heart to beat more slowly and with less force, thus lowering blood pressure. In certain embodiments, beta-blockers are primarily used to treat heart and circulatory disorders, but they are also used to treat other disorders, such as, e.g., essential tremor, glaucoma, and hyperthyroidism.

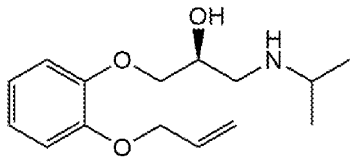
The disclosure contemplates the use of any beta-blocker. In some embodiments, the beta-blocker targets or inhibits signalling via the beta-1 receptor, the beta-2 receptor, and/or the beta-3 receptor. In certain embodiments, the beta-blocker is a beta-1 adrenergic antagonist (β1 antagonist) and/or a beta-2 adrenergic antagonist (β2 antagonist). In certain embodiments, the beta-blocker is additionally a beta-3 adrenergic receptor agonist (β3 agonist or receptor B3 agonist). As used herein, the terms “agonist” and “antagonist” include partial agonists and partial antagonists, respectively. In certain embodiments, the beta-blocker is a β3 agonist and a serotonin 1A receptor (5-HT1A receptor) antagonist. While not wishing to be bound to any particular theory, it is believed that beta-blockers with β3 agonist activity increase fat loss via β3 receptor agonism pathways, e.g., by increasing thermogenesis, improving insulin sensitivity, increasing glucose homeostasis, and/or increasing lipolysis. In some embodiments, the beta blocker is selected from the group consisting of acebutolol, atenolol, betaxolol, bisoprolol, carteolol, celeprolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propanolol, sotalol, esmolol, carvedilol, timolol, bopindolol, medroxalol, bucindolol, levobunolol, metipranolol, celiprolol and propafenone, or a pharmaceutically acceptable salt thereof. In particular embodiments, the beta-blocker is in racemic form or in single enantiomer form, e.g., S-pindolol.

In certain embodiments, the beta-blocker is oxprenonol or a particular enantiomer or salt thereof, e.g., S-oxprenolol. S-oxprenolol is a receptor B2 antagonist, a receptor B1 antagonist, a 5-HT1A antagonist, and a receptor B3 partial agonist. Without wishing to be bound to any particular theory, it is believed that S-oxprenolol may: (1) increase fat loss via β3 receptor agonism pathways, e.g., by increasing thermogenesis, improving insulin sensitivity, improving glucose homeostasis, improving B cell function, and/or increasing lipolysis (2) reduce fatigue through 5-HT1A antagonism (3) increase muscle mass by anti-catabolic and pro-anabolic activity though non-selective β1 and β2 receptor antagonism; and (4) increase bone density via 5-HT1A antagonism and non-selective β1 and β2 receptor antagonism.

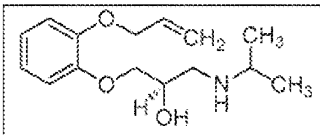
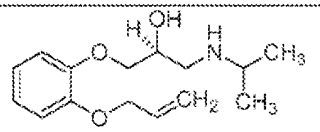
In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral centers). The prefixes "d" and 'T' or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the

compound, with (-) or 1 meaning that the compound is "levorotatory" and with (+) or d meaning that the compound is "dextrorotatory." There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. For a given chemical structure, these compounds, called "stereoisomers," are identical except that they are mirror images of one another. A specific stereoisomer can also be referred to as an "enantiomer," and a mixture of such isomers is often called an "enantiomeric" or "racemic" mixture. When a compound has one chiral center, there are two enantiomers: the S-enantiomer and the R- enantiomer.

S-oxprenolol is a β-adrenergic receptor antagonist and is also known as (-)-oxprenolol. The systematic name for S-oxprenolol is (S)-1-(2-(allyloxy)phenoxy)-3-(isopropylamino)propan-2-ol and the structure of this compound is shown below.



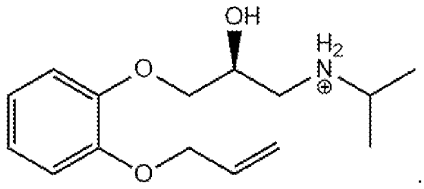
Oxprenolol is a compound with one chiral center. As a racemic mixture, there is a mixture of (R)-(+)-oxprenolol and (S)-(-)-oxprenolol. Analytical methods, such as HPLC, can be used for separation and quantification of (R)-(+)-oxprenolol and (S)-(-)-oxprenolol in mixtures. The structures of (R)-(+)-oxprenolol and (S)-(-)-oxprenolol are shown below.

	(*R*)-(+)-oxprenolol or R-oxprenolol (*R*)-1-(2-(allyloxy)phenoxy)-3-(isopropylamino)propan-2-ol
	(*S*)-(−)-oxprenolol or S-oxprenolol (*S*)-1-(2-(allyloxy)phenoxy)-3-(isopropylamino)propan-2-ol

In particular embodiments, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof. S-oxprenolol has affinity for both beta-adrenergic receptors and 5-HT1a receptors and is useful in treating a number of disorders. WO 2014/138806 A1 describes the treatment of cachexia with S-oxprenolol, and WO 2014/138814 A1 describes the treatment of amyotrophic lateral sclerosis with S-oxprenolol. Oxprenolol is authorized for the treatment of conditions such as angina pectoris in the form of the racemate. It has been found that S-

oxprenolol is the more pharmacologically active enantiomer for certain conditions. In some embodiments, the composition comprises an enantiomeric excess of at least about 10% (such as at least about any one of 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, or 99.9%) of S-oxprenolol. In particular embodiments, the composition is enantiomerically enriched for S-oxprenolol or a pharmaceutically acceptable salt thereof, wherein more than 80%, more than 90%, more than 95%, more than 95%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol (S-oxprenolol) or a pharmaceutically acceptable salt thereof.

In particular embodiments, the beta-blocker is a salt of S-oxprenolol formed with phosphoric acid, e.g., an acid addition salt of: (a) S-oxprenolol and (b) phosphoric acid. The acid addition salt is a salt of S-oxprenolol and therefore comprises a cation formed from S-oxprenolol. The cation formed from S-oxprenolol typically has the following structure:



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The enantiomeric excess of the S-enantiomer of the cation of oxprenolol in the pharmaceutically acceptable salt is typically at least 80% or at least 90%. The enantiomeric excess is typically at least 95%. The cation of S-oxprenolol in the pharmaceutically acceptable acid addition salt is typically substantially in the S-configuration and therefore may have an enantiomeric excess of at least 90%, at least 95%, at least 98% or at least 99%. Enantiomeric excess may be measured by any standard technique, for instance by measuring optical rotation or using chiral high performance liquid chromatography (HPLC). Thus, of the cations in the salt, at least 80 mol% are typically in the S-configuration. For instance, at least 90 mol% or at least 95 mol% of the oxprenolol cations in the salt may be in the S-configuration. Preferably, at least 99 mol% of the oxprenolol cations in the salt are in the S-configuration. The pharmaceutically acceptable acid addition salt typically does not therefore comprise greater than 10 mol% of the R- enantiomer of oxprenolol or a salt comprising a cation which is a protonated R-oxprenolol molecule. The pharmaceutically acceptable acid addition salt typically comprises less than 5.0 mol% of the R-enantiomer of oxprenolol or a salt comprising a cation which is a protonated R- oxprenolol molecule. For instance, the pharmaceutically acceptable acid addition salt is typically substantially free of

the R-enantiomer of oxprenolol or a salt comprising a cation which is a protonated R-oxprenolol molecule.

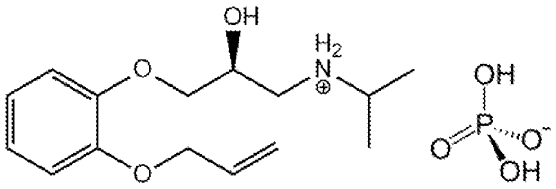
The pharmaceutically acceptable acid addition salt is typically crystalline. The salt accordingly may have a three dimensional crystal structure comprising repeating unit cells. The pharmaceutically acceptable acid addition salt may be in a solid form, for instance a solid form comprising crystals or crystallites of the pharmaceutically acceptable acid addition salt.

The pharmaceutically acceptable acid salt may be in the form of a solvate. A solvate of a salt is a solid form of the salt which comprises molecules of a solvent. For instance, the salt may be a hydrate. Typically, the salt is not a solvate. For example, the pharmaceutically acceptable acid addition salt may be anhydrous.

The salt may be in the form of a hydrate, and the hydrate may comprise from 0.1 to 0.5 molecules of water per molecule of the salt (for instance about 0.25 molecules of water per molecule of the salt). The salt may be in the form of an ethanol solvate, and the ethanol solvate may comprise from 0.1 to 1.0 molecules of ethanol per molecule of the salt (for instance about 0.5 molecules of ethanol per molecule of the salt).

The pharmaceutically acceptable acid addition salt may comprise the cation derived from S-oxprenolol and one or more anions selected from a phosphate anion ($[PO_4]^{3-}$), hydrogenphosphate ($[HPO_4]^{2-}$) and a dihydrogenphosphate anion ($[H_2PO_4]^-$). As used herein, S-oxprenolol phosphate includes forms of oxprenolol comprising the cation derived from S-oxprenolol and one or more anions selected from a phosphate anion ($[PO_4]^{3-}$), hydrogenphosphate ($[HPO_4]^{2-}$) and a dihydrogenphosphate anion ($[H_2PO_4]^-$). In particular embodiments, the beta- blocker is S-oxprenolol dihydrogenphosphate, including but not limited to S-oxprenolol dihydrogenphosphate in the form of a crystalline polymorph of S-oxprenolol dihydrogenphosphate designated as Pattern 1, Pattern 2, or Pattern 3.

The pharmaceutically acceptable acid addition salt may be S-oxprenolol dihydrogenphosphate. The salt may accordingly comprise the cation derived from S-oxprenolol and a dihydrogenphosphate anion (i.e., ($[H_2PO_4]^-$). The stoichiometry of the cation and anion is typically about 1:1, for instance from 0.9:1.0 to 1.1:1.0 (i.e., for each mole of the anion, there may be from 0.9 to 1.1 moles of the cation). As such, the S-oxprenolol dihydrogenphosphate is typically S-oxprenolol mono-dihydrogen-phosphate. Accordingly, the salt may be of formula $[C_{15}H_{23}NO_3]^+[H_2PO_4]^-$, as shown below.



The stoichiometry of the cation and anion may alternatively be about 3:1, about 2:1 or about 1:2. In particular embodiments, the composition comprises S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

The pharmaceutically acceptable acid addition salt may be formed by any suitable method. Typically, free base S-oxprenolol is combined with the acid from which the counterion is derived (for instance phosphoric acid) in a solvent. For instance, S-oxprenolol may be dissolved in a solution of the acid in a solvent. The solvent may comprise water, an alcohol (such as methanol, ethanol, 1-propanol or isopropanol), a ketone (for instance acetone), an ester (ethyl acetate) or an ether (for instance tetrahydrofuran (THF), ethyl ether or tert-butyl methyl ether). Preferably, the solvent comprises an alcohol. The solvent may comprise at least 40 vol% of an alcohol. The solvent typically comprises ethanol.

The process for producing the pharmaceutically acceptable acid addition salt may comprise: (a) combining S-oxprenolol and phosphoric acid in a solvent comprising an alcohol to produce a solution of the pharmaceutically acceptable acid addition salt in the solvent comprising the alcohol; (b) adding a solvent comprising an alkane to the solution of the pharmaceutically acceptable acid addition salt in the solvent comprising the alcohol to produce a precipitate of the pharmaceutically acceptable acid addition salt; and (c) isolating the precipitate of the pharmaceutically acceptable acid addition salt, for instance by filtration. The process for producing the pharmaceutically acceptable acid addition salt may comprise: (a) combining S-oxprenolol and phosphoric acid in ethanol to produce a solution of the pharmaceutically acceptable acid addition salt in ethanol; (b) adding hexane or heptane to the solution of the pharmaceutically acceptable acid addition salt in ethanol to produce a precipitate of the pharmaceutically acceptable acid addition salt; and (c) isolating the precipitate of the pharmaceutically acceptable acid addition salt, for instance by filtration.

The pharmaceutically acceptable acid addition salt produced may be dissolved in the solvent or may precipitate out of solution. The pharmaceutically acceptable acid addition salt may be isolated by a suitable method, for instance by filtration or by solvent evaporation.

The pharmaceutically acceptable acid addition salt is typically crystalline. As stated herein, values of °2θ are as measured using an x-ray wavelength of CuK α1 radiation (λ = 1.54060 Å). If an x-ray powder diffraction pattern comprises a peak, the relative intensity of that peak is typically at least 5% or at least 10%. Error margins for the values of °2θ are typically ± 0.2° 2θ, but the error margin may alternatively be ± 0.1° 2θ.

The S-oxprenolol dihydrogenphosphate may be in the form of the crystalline polymorph of S-oxprenolol dihydrogenphosphate designated as Pattern 3. Pattern 3 of S-oxprenolol dihydrogenphosphate typically has an x-ray powder diffraction (XRPD) pattern comprising peaks at 4.8°, 7.1° and 8.2° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 4.8°, 7.1° and 8.2° ± 0.1° 2θ. The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 typically further comprises peaks at 22.5°, 22.7° and 23.2° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 22.5°, 22.7° and 23.2° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 may comprise seven or more peaks selected from 4.8°, 7.1°, 8.2°, 14.2°, 14.4°, 22.5°, 22.7°, 23.2°, 23.5° and 23.8° ± 0.2° 2θ. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 may comprise five or more peaks selected from 4.8°, 7.1°, 7.2°, 8.2°, 14.2°, 14.4°, 22.5°, 22.7°, 23.2°, 23.5°, 23.8° and 24.0° ± 0.2° 2θ. The XRPD pattern may comprise seven or more of these peaks. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 may comprise the following peaks: 4.8°, 7.1°, 8.2°, 9.6°, 11.6°, 13.4°, 14.2°, 14.4°, 17.9°, 20.9°, 21.6°, 22.5°, 22.7°, 23.2°, 23.5°, 23.8°, 25.0°, 25.8° and 27.0° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 may comprise the following peaks.

S-oxprenololdihydrogenphosphate Pattern 3	
Pos. [°2θ]	Rel. Int. [%]
4.8	100.0
7.1	49.6
7.2	20.9
8.2	28.7
9.6	11.9
11.6	12.9
13.4	11.7
14.2	17.8
14.4	16.2
18.0	12.4
20.9	11.8
21.6	13.2
22.5	31.2
22.7	53.9

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 3 may be substantially as shown in Figure 4.

S-oxprenolol dihydrogenphosphate Pattern 3 may have the following unit cell parameters (as determined by single crystal analysis).

Orthorhombic P21
a = 7.76070(10) Å α = 90°
b = 36.7729(6) Å β = 94.0602(11)°
c = 12.9496(2) Å γ = 90°
Volume = 3686.33(10) $Å^3$
Z = 8, Z` = 4
Temperature = 100 K

The infrared spectrum of S-oxprenolol dihydrogenphosphate Pattern 3 typically comprises peaks at about 1210 to 1260 cm^{-1} (C-O-C functional group) and at about 1590 cm^{-1} (N-H

bending). The melting point of S-oxprenolol dihydrogenphosphate Pattern 3 is typically in the range of 85.0 to 90.0°C, for instance about 88 °C. The melting point may be as measured by DSC analysis.

S-oxprenolol dihydrogenphosphate Pattern 3 may be produced by a process comprising recrystallizing S-oxprenolol dihydrogenphosphate from a solvent which is ethanol, isopropanol, acetone, a mixture of acetone and water, di-isopropyl ether, n-heptane, n-hexane, methanol, methyl isobutyl ketone, tert-butyl methyl ether, tetrahydrofuran or toluene. Typically, the solvent for the recrystallization contains at least 90 % by volume of the stated solvent component.

S-oxprenolol dihydrogenphosphate Pattern 3 may be obtainable by addition of a THF anti-solvent into a 90% acetone:10% water solution of S-oxprenolol dihydrogenphosphate and storing the resulting mixture at 25°C for two weeks.

S-oxprenolol dihydrogenphosphate Pattern 3 is typically a hydrate and the unit cell typically comprises about 0.25 molecules of water per molecule of S-oxprenolol dihydrogenphosphate.

The S-oxprenolol dihydrogenphosphate may be in the form of the crystalline polymorph of S-oxprenolol dihydrogenphosphate designated as Pattern 2. Pattern 2 of S-oxprenolol dihydrogenphosphate typically has an x-ray powder diffraction (XRPD) pattern comprising peaks at 6.8°, 7.8° and 22.5° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 6.8°, 7.8° and 22.5° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 typically further comprises peaks at 4.4°, 17.0° and 22.6° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 4.4°, 17.0° and 22.6° ± 0.1° 2θ. The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may comprise peaks at 4.4°, 6.8°, 7.8°, 17.0° and 22.5° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may comprise seven or more peaks selected from 4.4°, 6.8°, 7.8°, 17.0°, 22.5°, 22.9°, 23.5°, 23.6°, 24.2° and 25.1° ± 0.2° 2θ. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may comprise five or more peaks selected from 4.4°, 6.8°, 7.8°, 17.0°, 22.5°, 22.6°, 22.9°, 23.5°, 23.6°, 24.2° and 25.1°± 0.2° 2θ. The XRPD pattern may comprise seven or more of these peaks. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may comprise the following peaks: 4.4°, 6.8°, 7.8°, 13.0°, 17.0°, 17.2°, 19.3°, 21.9°, 22.5°, 22.9°, 23.5°, 23.6°, 24.2° and 25.1° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may comprise the following peaks.

S-oxprenolol dihydrogenphosphate Pattern 2	
Pos. [°2θ]	Rel. Int. [%]
4.1	14.4
4.4	52.5
6.8	97.4
7.8	35.0
12.9	21.0
13.7	13.7
17.0	23.0
17.2	21.1
19.3	20.0
21.9	11.1
22.5	100.0
22.6	79.6
22.9	23.8
23.5	96.1
23.6	61.2
24.2	23.3
25.1	21.3

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 2 may be substantially as shown in Figure 3.

S-oxprenolol dihydrogenphosphate Pattern 2 may have the following unit cell parameters (as determined by single crystal analysis).

Orthorhombic P212121	
a = 7.7822(4) Å	α = 90°
b = 13.2653(5) Å	β = 90°
c = 39.5732(15) Å	γ = 90°
Volume = 4085.3(3) $Å^3$	
Z = 4, Z` = 2	
Temperature = 100(2) K	

S-oxprenolol dihydrogenphosphate Pattern 2 may be produced by a process comprising recrystallizing S-oxprenolol dihydrogenphosphate from a solvent which is 1-propanol, 2-methyl- 1-propanol, acetonitrile, anisole, benzyl alcohol, butyl acetate, isopropyl acetate or methyl ethyl ketone).

S-oxprenolol dihydrogenphosphate Pattern 2 is typically an ethanol solvate and the unit cell typically comprises about 0.5 molecules of ethanol per molecule of S-oxprenolol dihydrogenphosphate.

The S-oxprenolol dihydrogenphosphate may be in the form of the crystalline polymorph of S-oxprenolol dihydrogenphosphate designated as Pattern 1. Pattern 1 of S-oxprenolol dihydrogenphosphate typically has an x-ray powder diffraction (XRPD) pattern comprising peaks at 4.6°, 11.0° and 20.6° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 4.6°, 11.0° and 20.6°± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 1 typically further comprises peaks at 17.1°, 18.4° and 22.9° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 17.1°, 18.4° and 22.9° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 1 may comprise five or more peaks selected from 4.6°, 11.0°, 13.8°, 17.1°, 18.4°, 20.6°, 21.8°, 22.9° and 26.3° ± 0.2° 2θ. The XRPD pattern may comprise seven or more of these peaks. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 1 may comprise the following peaks.

S-oxprenolol dihydrogenphosphate Pattern 1	
Pos. [°2θ]	Rel. Int. [%]
4.6	48.9
11.0	100.0
12.2	10.3
13.8	15.2
17.1	18.3
18.4	22.6
20.1	10.5
20.3	11.1
20.6	46.6
21.8	15.1
22.9	18.8
23.0	12.2
26.3	16.3

The XRPD pattern of S-oxprenolol dihydrogenphosphate Pattern 1 may be substantially as shown in Figure 1.

Also provided is S-oxprenolol dihydrogenphosphate, wherein the S-oxprenolol dihydrogenphosphate is characterized by an XRPD pattern comprising peaks at 4.8°, 7.1° and 8.2° ± 0.2° 2θ. The XRPD pattern may further comprises peaks at 22.5°, 22.7° and 23.2° ± 0.2° 2θ. The XRPD may comprise seven or more peaks selected from 4.8°, 7.1°, 8.2°, 14.2°, 14.4°, 22.5°, 22.7°, 23.2°, 23.5° and 23.8° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

Also provided is S-oxprenolol dihydrogenphosphate, wherein the S-oxprenolol dihydrogenphosphate is characterized by an x-ray powder diffraction pattern comprising peaks at 6.8°, 7.8° and 22.5° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 4.4°, 6.8°, 7.8°, 17.0° and 22.5° ± 0.2° 2θ. The XRPD pattern may comprise seven or more peaks selected from 4.4°, 6.8°, 7.8°, 17.0°, 22.5°, 22.9°, 23.5°, 23.6°, 24.2° and 25.1° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

Also provided is S-oxprenolol dihydrogenphosphate, wherein the S-oxprenolol dihydrogenphosphate is characterized by an x-ray powder diffraction pattern comprising

peaks at 4.6°, 11.0° and 20.6° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 17.1°, 18.4° and 22.9° ± 0.2° 2θ. The XRPD pattern may comprise five or more peaks selected from 4.6°, 11.0°, 13.8°, 17.1°, 18.4°, 20.6°, 21.8°, 22.9° and 26.3° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

The invention further provides a pharmaceutically acceptable acid addition salt of (i) S-oxprenolol and (ii) an acid selected from oxalic acid, 1-hydroxy-2-naphthoic acid (xinafoic acid), hippuric acid (N-benzoylglycine), acetic acid and naphthalene-1,5-disulfonic acid. The pharmaceutically acceptable acid addition salt formed from these acids may be as described above for the salt formed with phosphoric acid.

The pharmaceutically acceptable acid addition salt may be of (i) S-oxprenolol and (ii) oxalic acid, i.e., S-oxprenolol oxalate. The pharmaceutically acceptable acid addition salt may be S-oxprenolol hemi-oxalate ($[C_{15}H_{23}NO_3]^{2+}[O_2CCO_2]^{2-}$) or S-oxprenolol mono-oxalate ($[C_{15}H_{23}NO_3]^{+}[HO_2CCO_2]^{-}$). The salt is typically S-oxprenolol mono-oxalate (i.e. S-oxprenolol hydrogenoxalate).

The pharmaceutically acceptable acid addition salt of (i) S-oxprenolol and (ii) oxalic acid is typically crystalline. The S-oxprenolol oxalate may be in the form of the crystalline polymorph of S-oxprenolol oxalate designated as Pattern 1. Pattern 1 of S-oxprenolol oxalate typically has an x-ray powder diffraction (XRPD) pattern comprising peaks at 10.7°, 15.5° and 24.7° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 10.7°, 15.5° and 24.7° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol oxalate Pattern 1 typically further comprises peaks at 7.7°, 8.8° and 17.0° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 7.7°, 8.8° and 17.0° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol oxalate Pattern 1 may comprise five or more peaks selected from 7.7°, 8.8°, 10.7°, 15.5°, 17.0°, 17.4°, 17.7°, 18.7°, 19.7°, 20.3°, 22.9°, 23.3°, 24.3°, 24.7°, 25.6° and 26.3° ± 0.2° 2θ. The XRPD pattern may comprise seven or more of these peaks. The error margin may be ± 0.1° 2θ. The XRPD pattern may comprise all of these peaks.

The XRPD pattern of S-oxprenolol oxalate Pattern 1 may comprise the following peaks.

S-oxprenolol oxalate Pattern 1

Pos. [°2θ]	Rel. Int. [%]
27.0	12.6
26.3	16.9
25.6	33.9
25.6	37.8
25.3	13.8
24.7	62.4
24.3	30.5
24.3	31.5
23.3	17.4
22.9	38.6
21.4	11.2
20.3	25.5
19.7	21.4
18.7	17.9
17.7	15.5
17.4	16.6
17.0	40.4
15.5	61.2
10.7	100.0
8.8	52.6
7.7	40.4

The S-oxprenolol oxalate may be in the form of the crystalline polymorph of S-oxprenolol oxalate designated as Pattern 2. Pattern 2 of S-oxprenolol oxalate typically has an x-ray powder diffraction (XRPD) pattern comprising peaks at 9.0°, 22.5° and 24.4° ± 0.2° 2θ. The XRPD pattern may comprise peaks at 9.0°, 22.5° and 24.4° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol oxalate Pattern 2 typically further comprises peaks at 8.8°, 18.0° and 23.3° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 8.8°, 18.0° and 23.3° ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol oxalate Pattern 2 may comprise five or more peaks selected from 8.8°, 9.0°, 18.0°, 18.2°, 18.8°, 20.6°, 22.5°, 23.3°, 23.6°, 24.4° and 24.9° ± 0.2° 2θ.

The XRPD pattern may comprise seven or more of these peaks. The XRPD pattern may comprise all of these peaks. The error margin may be ± 0.1° 2θ.

The XRPD pattern of S-oxprenolol oxalate Pattern 2 may comprise the following peaks.

S-oxprenolol oxalate Pattern 2	
Pos. [°2θ]	Rel. Int. [%]
8.8	24.6
9.0	100.0
18.0	14.5
18.2	7.9
18.8	11.6
20.6	5.8
22.5	29.5
23.3	14.2
23.6	6.1
24.4	46.4
24.9	10.6

Also provided is S-oxprenolol oxalate characterized by an XRPD pattern comprising peaks at 10.7°, 15.5° and 24.7° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 7.7°, 8.8° and 17.0° ± 0.2° 2θ. The XRPD pattern may comprise five or more peaks selected from 7.7°, 8.8°, 10.7°, 15.5°, 17.0°, 17.4°, 17.7°, 18.7°, 19.7°, 20.3°, 22.9°, 23.3°, 24.3°, 24.7°, 25.6° and 26.3° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

Also provided is S-oxprenolol oxalate characterized by an XRPD pattern comprising peaks at 9.0°, 22.5° and 24.4° ± 0.2° 2θ. The XRPD pattern may further comprise peaks at 8.8°, 18.0° and 23.3° ± 0.2°. The XRPD pattern may comprise five or more peaks selected from 8.8°, 9.0°, 18.0°, 18.2°, 18.8°, 20.6°, 22.5°, 23.3°, 23.6°, 24.4° and 24.9° ± 0.2° 2θ. The error margin may be ± 0.1° 2θ.

Other Therapeutic Agents

The disclosure contemplates the use of beta-blockers in combination with other therapeutic agents, e.g., therapeutic agents that are not beta-blockers. In particular embodiments, the therapeutic agent causes or may cause a loss of muscle mass and/or function and/or a loss

of bone mass or bone density in patients treated with the therapeutic agent. In particular embodiments, the therapeutic agent is a GLP1R agonist, a GIPR agonist, a GCGR agonist, or a SGLT2 inhibitor.

In particular embodiments, the other therapeutic agent is any weight loss drug or diabetes drug. In particular embodiments, the weight loss drug or diabetes drug is a GLP1R agonist, a GIPR agonist, a GCGR agonist or a SGLT2 inhibitor. Weight loss and/or diabetes drugs include, but are not limited to, those described in Melson, E., Ashraf, U., Papamargaritis, D. et al. *What is the pipeline for future medications for obesity?*. Int J Obes (2024). https://doi.org/10.1038/s41366-024-01473-y (2024). Specific examples include, but are not limited to: semaglutide, orforglipron, tirzepatide, cagrisema, survodutide, mazdutide, retatrutide, danuglipron, cagrilintide, PYY 1875, efinopegdutide, pemvidutide, AMG 133, NNC0165-1875, dapiglutide, bimagrumab, S-309309, CT-996, long acting amylin agonist, AZD6234, ZP8396, HM15136, NNCO165-1562, Y-14, VK2735, SCO-094, CT-388, amycretin, Dacra QW II, HM- 15211, NNC0247-0829, JNJ-9090/CIN-109, SCO-267, and ZP6590. Additional examples of weight loss drugs include, but are not limited to, BIO101 (20-hydroxyecdysone; Biophytis), which is an oral, daily MAS receptor activator, LY3463251, a GDF-15 agonist, bimagrumab, which is an anti-activin type II receptor antibody currently being studied as co-administration with tirzepetide and as a monotherapy for sarcopenic obesity and pediatric obesity, and NA-931, a quadruple agonist targeting IGF-1, GLP-1, GIP, and glucagon receptors, which is currently being evaluated as a monotherapy or in combination with tirzepatide to reduce body weight, e.g., to treat type 2 diabetes and obesity.

GLP1R agonists are a class of drugs developed initially for the treatment of diabetes, but because of their efficacy for weight loss and reducing appetite, they are now prescribed as treatments for obesity. Glucagon-like peptide 1 (GLP-1) is an incretin hormone that has numerous direct and indirect effects on metabolism including: glucose-dependent stimulation of insulin secretion, decreased glucagon production, slowed gastric emptying (i.e., satiety) and reduction of food intake (Muller, T.D. et al. (2019 Mol. Metab. 30:72-130). Incretin therapies, such as GLP1R agonists, are suited for the treatment of diabetes, as they exert their actions during hyperglycemic conditions and help regulate body weight. GLP-1 infusion in humans results in reduced calorie intake and reduced appetite. In addition to the treatment of T2DM, GLP1R agonists are also being used as anti-obesity medications (AOMs) (Moore, P.W. et al. (2023) Adv. Ther. 40(3):723-42 and Drucker, D.J. (2022) Mol. Metab. 57:101351).

GLP1R agonists typically target the glucagon-like peptide-1 receptor (GLP1R), which is a G protein-coupled receptor (GPCR). GLP1R agonists may also target other receptors, and some are dual agonists of GLP1R and GIPR or tri-agonists of GLP1R, GIPR, and GCGR. In certain embodiments, the therapeutic agent is an incretin or GLP1R agonist. Various incretin therapy drugs have been approved by the FDA and MHRA to treat T2DM including: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), dulaglutide (Trulicity®) and tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, which are all GLP1R agonists, as well as Retatrutide (LY3437943) (an agonist of GLP1R, GIPR, and GCGR). The disclosure includes the use of any of these GLP1R agonists, as well as others.

In certain embodiments, the therapeutic agent is a human glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist. GIPR agonists stimulate insulin secretion through direct action on β cells.

In certain embodiments, the therapeutic agent is a human glucagon receptor (GCGR) agonist. GCGR agonist mimic the action of glucagon-like peptide 1 and stimulate the production of insulin when blood sugar levels rise after eating.

Sodium-glucose cotransporter 2 (SGLT2) is a kidney transporter involved in glucose reabsorption, and SGLT2 inhibitors cause an increase in urinary glucose excretion and have been demonstrated to reduce body weight, and improve cardiovascular and renal outcomes in patients with T2DM (Pan, R. et al. (2022) PLoS One 17(12):e0279889). Examples of SGLT2 inhibitors include, but are not limited to, empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin.

A variety of other diabetes and weight loss drugs, and other therapeutic agents, are known in the art and can be used according to the methods disclosed herein, including but not limited to those disclosed, in, e.g., PCT Patent Application Publication Nos. WO2017077378, WO2021178368, WO2022058947, WO2020204998, WO2015055802, WO2014096150, WO2011160633, WO2006121860, WO2003059372, WO2017077378, U.S. Patent Application Publication Nos: US20100016425, US20210121468, and US20220073583, and U.S. Patent Nos: US9975939 and US11890325.

Methods of Use

The disclosure provides methods related to inhibiting loss of muscle mass and/or function and/or decrease in bone density (e.g., bone mineral density), e.g., resulting from aging, weight loss, disease, or from treatment of a subject with a therapeutic agent that can cause loss of muscle mass and/or function and/or decrease in bone density, e.g., a GLP1R agonist, a GIPR agonist, a GCGR agonist, or a SGLT2 inhibitor. As such, the disclosure also includes methods for inducing weight loss and/or treating a disease or disorders, comprising providing to a subject a beta-blocker in combination with another therapeutic agent, optionally wherein the other therapeutic agent is not a beta-blocker, including but not limited to any disclosed herein.

Obesity is associated with a number of medical conditions / comorbidities, including insulin resistance, glucose intolerance, diabetes mellitus, nonalcoholic fatty liver disease (NAFLD), hypertension, dyslipidemia, sleep apnea, arthritis, hyperuricemia, gall bladder disease, certain types of cancer, heart and coronary artery disease, and stroke. There are numerous drugs used as weight-reducing agents, including drugs intended for prolonged use for treatment of nonsyndromic obesity, such as, e.g., orlistat, phentermine-topiramate, naltrexone-bupropion, liraglutide, and semaglutide. Weight loss may be considered to be poor quality weight loss when muscle mass and/or function and/or bone density is lost in addition to loss of adipose tissue and fat. The loss of muscle mass and/or function and/or bone density can promote frailty and have negative effects on quality of life. According to the CDC, 41.5% of older adults have obesity in the United States and could benefit from a weight loss medication. Up to 34.4% of these obese patients over the age of 60 have sarcopenic obesity. This large subpopulation of sarcopenic obese patients is especially at risk for taking GLP-1 drugs for weight loss as they already have critically low amount of muscle due to age-related muscle loss. Further loss of muscle mass and/or function when taking a GLP-1 RA medication may lead to muscle weakness leading to poor balance, decreased gait speed, mobility disability, loss of independence, falls, bone fractures and increased mortality which is a condition like age-related frailty. Because of the magnitude and speed of muscle loss while on GLP-1 RA therapy for weight loss, GLP-1 RA drugs may accelerate the development of frailty in older obese or overweight elderly patients. https://www.globenewswire.com/news-release/2024/02/06/2824317/0/en/Veru-Announces-FDA-Clearance-of-IND-Application-to-Initiate-Phase-2b-Clinical-Trial-with-Enobosarm-to-Treat-Muscle-Loss-Associated-with-Weight-Loss-Drugs.html.

In certain embodiments, the methods inhibit or reduce loss of muscle mass and/or function and/or decrease in bone density associated with weight loss, e.g., as compared to when the subject is not treated with a beta-blocker. In certain embodiments, the methods increase or

promote weight loss, e.g., as compared to when the subject is treated with a weight loss or diabetes drug but is not treated with a beta-blocker. In certain embodiments, the methods result in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or function and/or bone density, e.g., as compared to when the subject is not treated with a beta-blocker. Thus, in particular embodiments, the methods result in less loss of lean body mass (LBM) and/or fat-free mass (FFM), e.g., as compared to when the subject is not treated with a beta-blocker. The weight loss may result from a variety of underlying causes, such as, e.g., pharmacological intervention, such as treatment with a weight loss drug or other therapeutic agent, disease, or diet, e.g., fasting or a reduced calorie diet. The weight loss may be desired or an unintended consequence. In certain embodiments, the weight loss is the results of a disease, such as a cancer. In certain embodiments, the weight loss results from treatment with a therapeutic agent. The therapeutic agent may be intended to cause weight loss, e.g., a weight loss drug, and/or the weight loss is an intended or unintended result of treatment with the therapeutic agent, e.g., treatment of diabetes with a GLP1R agonist or SGLT2 inhibitor. In related embodiments, the methods disclosed herein may be used to reduce or inhibit muscle loss or preserve lean mass, reduce or inhibit bone loss or preserve bone mass or bone quality, or enhance or promote fat loss

In particular embodiments of any of the disclosed methods, the subject is over the age of 60. In particular embodiments of any of the disclosed methods, the subject is overweight or obese. Approximately 42% of older adults (> 60 years old) have obesity or are overweight and could benefit from weight loss drugs. In particular embodiments, the subject is > 60 years old, obese or overweight, and may have low muscle mass and/or function and/or functional limitations. In certain embodiments, the subject has diabetes, e.g., T1DM or T2DM, and may also be overweight or obese. In certain embodiments, the subject is overweight or obese, has diabetes, e.g., T1DM or T2DM, and is over 60 years old. As used herein, for adults, overweight is a body mass index (BMI) greater than or equal to 25, and obesity is a BLI greater than or equal to 30.

In some embodiments, the subject has sarcopenic obesity, which may also be referred to as obesity with low lean muscle mass and/or function (OLLMM) (Murdock, D. J. et al. The prevalence of low muscle mass and/or function associated with obesity in the USA. Skelet. Muscle 12, 26 (2022)). Sarcopenic obesity may be caused by various things, including, e.g., aging (which may be related to, e.g., inflammation oxidative stress, hormonal imbalances, declining neuromuscular function, impaired muscle/bone/fat cross talk), diet (which may be related to, e.g., eating disorders, bariatric surgery, weight loss medication, nutrient poor diet,

and/or extreme or chronic dieting), and lack of movement or exercise (which may be related to, e.g., stroke, illness, falls, fractures, depression, isolation, telecommuting, and/or driving). Sarcopenic obesity can result in increased fat mass, lipotoxicity, reduced muscle mass and/or function and function, and/or reduced bone mass or density. Sarcopenic obesity is associated with abnormal and excessive fat accumulation and loss of skeletal muscle mass and/or function and function. It may be characterized by excessive fat gain and loss of muscle mass and/or function. At the tissue level, it may be associated in fat tissue with chronic inflammation, insulin resistance, and/or impaired signaling, in bone tissue with alternations in bone structure and/or impaired signaling, and in muscle tissue with decreased muscle anabolism, increased muscle catabolism, mitochondrial dysfunction, and/or myosteatosis. In some embodiments, the subject has sarcopenic obesity and is greater than 60 years old. 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 and/or function, have the greatest risk to develop muscle weakness because of critically low muscle mass and/or function with eight-loss drug treatment (Wennamethee, S.G. et al. (2023) Current Diabetes Reports; Spanoudake, M. et al. (2023) Life 13:1242; and Roh, E. et al. (2020) Front Endocrinol 11). Patients with sarcopenic obesity have a higher risk of frailty and 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 mortality. In certain embodiments, methods disclosed herein, including those used to treat sarcopenic obesity, may result in increased lipolysis, increased muscle anabolism and reduced muscle catabolism, reduced fatigue and reduced bone resorption. In related embodiments, the methods disclosed herein for treatment of sarcopenic obesity may also be used for the treatment of osteosarcopenia, osteoporosis, osteosarcopenia, adiposity syndrome, sarcopenia, and OSA.

In certain embodiments, the disclosure provides a method of preventing, inhibiting, or reducing loss of muscle mass and/or function and/or decrease in bone density, e.g., resulting from weight loss, disease, or from treatment of a subject with a therapeutic agent that can cause loss of muscle mass and/or function and/or decrease in bone density, e.g., a GLP1R agonist, a GIPR agonist, a GCGR agonist, or a SGLT2 inhibitor, comprising administering to the subject in need thereof a beta-blocker in combination with one or more therapeutic agents. In particular embodiments, the subject is treated with the therapeutic treatment to treat any disease or disorder for which the therapeutic agent is indicated or expected to have a therapeutic effect. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol

dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In certain embodiments, the disclosure provides a method of increasing, promoting, or enhancing weight loss from treatment of a subject with a diabetes or weight loss drug, e.g., a GLP1R agonist, a GIPR agonist, a GCGR agonist, or a SGLT2 inhibitor, comprising administering to the subject in need thereof a beta-blocker in combination with one or more diabetes or weight loss drugs. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In some embodiments, the disclosure provides a method for treating a disease or disorder as disclosed herein in a subject. The method comprises administering to the subject in need thereof a beta-blocker in combination with one or more therapeutic agents or therapies. In certain embodiments, one or more therapeutic agents or therapies are provided to the subject concurrently with the beta-blocker, e.g., before and/or simultaneously with and/or after the beta-blocker is administered to the subject. In particular embodiments of any of the disclosed methods that comprise providing to a subject both a beta-blocker and another therapeutic agent, treatment with the beta-blocker is commenced within about one week, about two weeks, about one month, about two months, about six months, or about one year after or before treatment with the other therapeutic agent is commenced. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In certain embodiments, the disclosure provides a method for treating obesity or inducing weight loss, the method comprising administering to a subject in need of such a treatment an effective amount of a weight loss drug, or a pharmaceutically acceptable salt or solvate thereof, in combination with a beta-blocker, or a pharmaceutically acceptable salt or solvate thereof. In particular embodiments, the subject is administered a composition comprising the

beta-blocker, S- oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In one embodiment, the disclosure provides a method for treating diabetes, e.g., T1DM or T2DM, the method comprising administering to a subject with diabetes, e.g., T1DM or T2DM, an effective amount of a diabetes drug, e.g., a T1DM or T2DM drug, or a pharmaceutically acceptable salt or solvate thereof, in combination with a beta-blocker, or a pharmaceutically acceptable salt or solvate thereof. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In particular embodiments, the disclosure provides method of treating a subject in need thereof for diabetes and/or to induce weight loss, comprising providing to the subject an effective amount of a diabetes or weight loss drug in combination with an effective amount of a beta-blocker or pharmaceutically acceptable salt thereof. In particular embodiments, the subject is treated for diabetes, e.g., T1DM or T2DM and/or the subject is treated to induce weight loss. In particular embodiments, the subject is overweight or obese. In certain embodiments, the subject has sarcopenic obesity. In certain embodiments, the diabetes or weight loss drug and the beta-blocker are administered concurrently and/or during an overlapping time period. In particular embodiments, the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the beta-blocker. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In particular embodiments, the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-

dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor, including but not limited to any of those disclosed herein. In particular embodiments, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof, e.g., S-oxprenolol dihydrogenphosphate. In certain embodiments, the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the diabetes or weight loss drug is the GIPR agonist. In certain embodiments, the diabetes or weight loss drug is the GCGR agonist. In certain embodiments, the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S- oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate. In particular embodiments, the oxprenolol is enriched for S-enantiomer, wherein more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol.

In particular embodiments, the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

In particular embodiments, the subject is provided a composition enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In certain embodiment, the disclosure provides a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density resulting from treatment of a subject with a therapeutic agent, comprising providing to the subject an effective amount of a beta- blocker in combination with the therapeutic agent, wherein the therapeutic agent is not a beta- blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to the subject without the beta-blocker. In particular embodiments, the subject is treated for diabetes, e.g., T1DM or T2DM and/or the subject is treated to induce weight loss. In particular embodiments, the subject is overweight or obese. In certain embodiments, the subject has sarcopenic obesity. In certain embodiments, the diabetes or weight loss drug and the beta-blocker are administered concurrently and/or during an overlapping time period. In particular embodiments, the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the beta-blocker. In particular embodiments, the subject is administered a composition comprising the beta-blocker, S-oxprenolol dihydrogenphosphate, and in particular embodiments, the composition is enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In particular embodiments, the therapeutic agent is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor. In certain embodiments, the therapeutic agent is a corticosteroid, chemotherapeutic agent, a diabetes drug, or a weight loss drug.

In particular embodiments, the therapeutic agent is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor, including but not limited to any of those disclosed herein. In particular embodiments, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof, e.g., S-oxprenolol dihydrogenphosphate. In certain embodiments, the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the therapeutic agent is the GIPR agonist. In certain embodiments, the therapeutic agent is the GCGR agonist. In certain embodiments, the therapeutic agent is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S- oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

In particular embodiments, the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

In particular embodiments, the subject is provided a composition enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In certain embodiments, the disclosure provides a method for treating sarcopenic obesity in a subject, comprising providing to the subject a beta-blocker. In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S- oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate. In particular embodiments, the subject is provided a composition enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In certain embodiments, the disclosure provides a method for treating osteosarcopenia, osteoporosis, or osteosarcopenic adiposity syndrome (OSA) in a subject, comprising providing to the subject a beta-blocker. In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or

pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate. In particular embodiments, the subject is provided a composition enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate). Osteosarcopenia describes the co-existence of osteoporosis and sarcopenia, two chronic musculoskeletal conditions associated with ageing. Osteoporosis, a condition of low bone mass and micro-architectural deterioration of bone, and sarcopenia, the loss of muscle mass and/or function, strength and function, often co-exist in a frail subset of the elderly population, leading to significantly worsened outcomes than seen in either condition alone (Paintin J, Cooper C, Dennison E. Osteosarcopenia. Br J Hosp Med (Lond). 2018 May 2;79(5):253-258). Osteosarcopenic adiposity syndrome (OSA) is the concurrent deterioration of bone (osteopenia/osteoporosis), muscle (sarcopenia) and adipose tissue expansion (Ilich JZ. Osteosarcopenic adiposity syndrome update and the role of associated minerals and vitamins. Proc Nutr Soc. 2021 Aug;80(3):344-355).

The therapeutically effective dose of beta-blocker and other therapeutic agent may be decided by the attending physician within the scope of sound medical judgment, e.g., based on the approved prescribed dosage. The specific therapeutically effective dose level for any particular subject may depend upon a variety of factors including: a) the disorder being treated and the severity of the disorder; b) activity of the specific compound employed; c) the specific composition employed, the age, body weight, general health, sex and diet of the patient; d) the route of administration; and e) the duration of the treatment, and like factors well known in the medical arts.

In some embodiments, the amount of an S-enantiomerically enriched composition of a beta blocker or a pharmaceutically acceptable salt thereof (e.g., S-oxprenolol) administered is within any of the following ranges: about 0.5 to about 5 mg, about 5 to about 10 mg, about 10 to about 15 mg, about 15 to about 20 mg, about 20 to about 25 mg, about 20 to about 50 mg, about 25 to about 50 mg, about 50 to about 75 mg, about 50 to about 100 mg, about 75 to about 100 mg, about 100 to about 125 mg, about 125 to about l50 mg, about 150 to about 175 mg, about 175 to about 200 mg. In some embodiments, the amount of an S-enantiomerically enriched composition of a beta blocker or a pharmaceutically acceptable

salt thereof (e.g., S-oxprenolol) administered is about 20 to about 160 mg, including for example about 50 to about 150 mg, 80 to about 150 mg, about 90 to about 140 mg, about 100 to about 120 mg. In some embodiments, the amount of an S- enantiomerically enriched composition of a beta blocker or a pharmaceutically acceptable salt thereof (e.g., S-oxprenolol) in the composition is about 80 to about 160 mg.

In some embodiments, the amount of an S-enantiomerically enriched composition of a beta blocker or a pharmaceutically acceptable salt thereof (e.g., S-oxprenolol) administered is at least about any of 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2.5 mg/kg, 5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg. In some embodiments, the amount of an S-enantiomerically enriched composition of a beta blocker or a pharmaceutically acceptable salt thereof (e.g., S-oxprenolol) in the composition includes less than about any of 35 mg/kg, 30 mg/kg, 25 mg/kg, 20 mg/kg, 15 mg/kg, 10 mg/kg, 5 mg/kg, 2.5 mg/kg, 2 mg/kg, 1 mg/kg, 0.5 mg/kg, or 0.1 mg/kg.

Illustrative dosing frequencies for the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, include, but are not limited to, daily without break; weekly without break; weekly; three out of four weeks; once every three weeks; once every two weeks; weekly, two out of three weeks. In some embodiments, the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, is administered about once a day, about twice a week, about once a week, about once every 2 weeks, about once every 3 weeks, about once every 4 weeks, about once every 6 weeks, or about once every 8 weeks. In some embodiments, the composition is administered at least about any of lx, 2x, 3x, 4x, 5x, 6x, or 7x (i.e., daily) a week. In some embodiments, the intervals between each administration are less than about any of 6 months, 3 months, 1 month, 20 days, 15, days, 12 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day. In some embodiments, the intervals between each administration are more than about any of 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, or 12 months. In some

The administration of the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, can be extended over an extended period of time, such as from about a month up to about seven years or life-long. In some embodiments, the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36, 48, 60, 72, or 84 months or life-long. In some embodiments, the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, is administered over a period of at least one month, wherein the interval between each administration is no more than about a week.

The compositions described herein can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intraportal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In some embodiments, sustained continuous release formulation of the composition may be used. In particular embodiments, the beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, are administered orally, intravenously, or subcutaneously.

Pharmaceutical Compositions and Kits

The beta-blocker and/or other therapeutic agent, e.g., GLP1R agonist, may be present in one or more pharmaceutical composition that further comprises one or more pharmaceutically acceptable carrier (or excipients).

A pharmaceutically-acceptable excipient is a substance that is non-toxic and otherwise biologically suitable for administration to a subject Such excipients facilitate administration of the compounds described herein and are compatible with the active ingredient. Examples of pharmaceutically-acceptable excipients include stabilizers, lubricants, surfactants, diluents, antioxidants, binders, coloring agents, bulking agents, emulsifiers, or taste-modifying agents. In some embodiments, the pharmaceutical composition is sterile.

In certain embodiments, the disclosure provides a pharmaceutical composition comprising a beta-blocker and another therapeutic agent. In particular embodiments, the pharmaceutical composition comprises the therapeutic agent and a beta blocker, and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker.

In particular embodiments of pharmaceutical compositions comprising both a beta- blocker and another therapeutic agent, the other therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

In certain embodiments, the therapeutic agent is a chemotherapeutic agent, a corticosteroid, a diabetes drug, or a weight loss drug.

In particular embodiments, the therapeutic agent is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor, including but not limited to any of those disclosed herein. In particular embodiments, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof, e.g., S-oxprenolol dihydrogenphosphate. In certain embodiments, the therapeutic agen is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the therapeutic agen is the GIPR agonist. In certain embodiments, the diabetes or weight loss drug is the GCGR agonist. In certain embodiments, the therapeutic agen is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S- oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

In particular embodiments, the pharmaceutical composition comprises:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

In particular embodiments, the pharmaceutical composition is enantiomerically enriched for S- oxprenolol dihydrogenphosphate, wherein more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

In other embodiments, the disclosure provides a kit comprising a beta-blocker and another therapeutic agent. In particular embodiments, the kit comprises: a) a first container comprising a pharmaceutical composition comprising the therapeutic agent and a pharmaceutically acceptable excipient, diluent, or carrier; and b) a second container comprising a pharmaceutical composition comprising a beta blocker and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker.

In certain embodiments, the therapeutic agent is a chemotherapeutic agent, a corticosteroid, a diabetes drug, or a weight loss drug.

In particular embodiments, the therapeutic agent is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor, including but not limited to any of those disclosed herein. In particular embodiments, the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof, e.g., S-oxprenolol dihydrogenphosphate. In certain embodiments, the therapeutic agen is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the therapeutic agen is the GIPR agonist. In certain embodiments, the therapeutic agen is the GCGR agonist. In certain embodiments,

the therapeutic agen is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

In particular embodiments, the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing. In certain embodiment, the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S- oxprenolol or a pharmaceutically acceptable salt or solvate thereof. In certain embodiments, the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

In particular embodiments, the kit comprises:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

In particular embodiments, the kit comprises a composition enantiomerically enriched for S-oxprenolol dihydrogenphosphate, wherein more than 50%, more than 60%, more than 70%, more than 80%, more than 90%, more than 95%, more than 95%, more than 98%, or more than 99% of the oxprenolol is the S-enantiomer of oxprenolol dihydrogenphosphate (S-oxprenolol dihydrogenphosphate).

First additional aspects of the invention

1. A method of treating a subject in need thereof for diabetes and/or to induce weight loss, comprising providing to the subject an effective amount of a diabetes or weight loss drug in combination with an effective amount of a beta-blocker, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker has b3 agonism activity.

2. The method of aspect 1, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

3. The method of aspect 2, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

4. The method of aspect 2, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

5. The method of any one of aspects 1-4, wherein the beta-blocker is selected from the group consisting of: oxprenolol or pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

6. The method of aspect 5, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

7. The method of aspect 6, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

8. The method of aspect 7, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

9. The method of any one of aspects 1-8, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;

e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);

h) S-oxprenolol dihydrogenphosphate and empagliflozin;

i) S-oxprenolol dihydrogenphosphate and canagliflozin;

j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or

k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

10. The method of any one of aspects 1-9, wherein the subject is treated for diabetes.

11. The method of aspect 10, wherein the diabetes is type 2 diabetes mellitus (T2DM).

12. The method of any one of aspects 1-9, wherein the subject is treated to induce weight loss.

13. The method of aspect 12, wherein the subject is overweight or obese.

14. The method of aspect 13, wherein the subject has sarcopenic obesity.

15. The method of any one of aspects 1-14, wherein the diabetes or weight loss drug and the beta-blocker are administered during an overlapping time period.

16. The method of any one of aspects 1-15, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the beta-blocker.

17. A method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density resulting from treatment of a subject with a therapeutic agent, comprising providing to the subject an effective amount of a beta-blocker in combination with the therapeutic agent, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to the subject without the beta-blocker, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker has b3 agonism activity.

18. The method of aspect 17, wherein the therapeutic agent is a diabetes or weight loss drug.

19. The method of aspect 18, wherein the therapeutic agent is a diabetes or weight loss drug selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

20. The method of aspect 19, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®),

tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

21. The method of aspect 19, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

22. The method of any one of aspects 17-21, wherein the beta-blocker is selected from the group consisting of: oxprenolol or pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

23. The method of aspect 22, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

24. The method of aspect 23, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

25. The method of aspect 24, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

26. The method of any one of aspects 17-25, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;

e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);

h) S-oxprenolol dihydrogenphosphate and empagliflozin;

i) S-oxprenolol dihydrogenphosphate and canagliflozin;

j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or

k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

27. The method of any one of aspects 17-26, wherein the subject is treated for diabetes.

28. The method of aspect 27, wherein the diabetes is type 2 diabetes mellitus (T2DM).

29. The method of any one of aspects 17-26, wherein the subject is treated to induce weight loss.

30. The method of aspect 29, wherein the subject is overweight or obese.

31. The method of aspect 29, wherein the subject has sarcopenic obesity.

32. The method of any one of aspects 17-31, wherein the diabetes or weight loss drug and the beta-blocker are administered during an overlapping time period.

33. The method of any one of aspects 17-32, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the therapeutic agent in the absence of treatment with the beta-blocker.

34. A method for increasing, enhancing, or promoting weight loss resulting from treatment of a subject with a diabetes or weight loss drug, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker also has b3 agonism activity.

35. The method of aspect 34, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

36. The method of aspect 5, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

37. The method of aspect 35, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

38. The method of any one of aspects 34-37, wherein the beta-blocker is selected from the group consisting of: oxprenolol or pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

39. The method of aspect 38, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

40. The method of aspect 39, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

41. The method of aspect 40, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the

oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

42. The method of any one of aspects 34-41, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;

e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);

h) S-oxprenolol dihydrogenphosphate and empagliflozin;

i) S-oxprenolol dihydrogenphosphate and canagliflozin;

j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or

k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

43. The method of any one of aspects 34-42, wherein the subject is treated for diabetes.

44. The method of aspect 43, wherein the diabetes is type 2 diabetes mellitus (T2DM).

45. The method of any one of aspects 34-42, wherein the subject is treated to induce weight loss.

46. The method of aspect 45, wherein the subject is overweight or obese.

47. The method of aspect 45, wherein the subject has sarcopenic obesity.

48. The method of any one of aspects 34-47, wherein the diabetes or weight loss drug and the beta-blocker are administered during an overlapping time period.

49. The method of any one of aspects 34-48, wherein the method results in increased loss of weight as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the beta-blocker.

50. A pharmaceutical composition comprising a therapeutic agent and a beta blocker, and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker also has b3 agonism activity.

51. The pharmaceutical composition of aspect 50, wherein the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

52. The pharmaceutical composition of aspect 51, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

53. The pharmaceutical composition of aspect 51, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

54. The pharmaceutical composition of any one of aspects 50-53, wherein the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

55. The pharmaceutical composition of aspect 54, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

56. The pharmaceutical composition of aspect 55, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

57. The pharmaceutical composition of aspect 56, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

58. The pharmaceutical composition of any one of aspects 50-57, comprising:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;

e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);

h) S-oxprenolol dihydrogenphosphate and empagliflozin;

i) S-oxprenolol dihydrogenphosphate and canagliflozin;

j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or

k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

59. A kit comprising:

a) a container comprising a pharmaceutical composition comprising a therapeutic agent and a pharmaceutically acceptable excipient, diluent, or carrier; and

b) a container comprising a beta blocker and a pharmaceutically acceptable excipient, diluent, or carrier,

wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the beta-blocker, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker also has b3 agonism activity.

60. The kit of aspect 59, wherein the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

61. The kit of aspect 60, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

62. The kit of aspect 60, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

63. The kit of any one of aspects 59-62, wherein the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

64. The kit of aspect 63, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

65. The kit of aspect 64, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

66. The kit of aspect 65, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

67. The kit of any one of aspects 59-66, comprising:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

68. A method of treating a subject in thereof for sarcopenic obesity, osteosarcopenia, osteoporosis, or osteosarcopenic adiposity syndrome (OSA), comprising providing to the subject an effective amount of a beta-blocker, optionally wherein the beta-blocker has b1 and/or b2 antagonism activity, and optionally wherein the beta-blocker also has b3 agonism activity.

69. The method of aspect 68, wherein the beta-blocker is oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

70. The method of aspect 69, wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate comprises at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

71. The method of aspect 70, wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

Second additional aspects of the invention

1. A pharmaceutical composition which comprises:
(a) a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist; and
(b) a GLP1 agonist.

2. The composition according to aspect 1, wherein the combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist is selected from the group consisting of S-pindolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol, S-oxprenolol and pharmaceutically acceptable salts thereof.

3. The composition according to aspect 2, wherein the combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist is S-pindolol or a pharmaceutically acceptable salt thereof.

4. The composition according to aspect 3, wherein the combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist is S-pindolol benzoate.

5. The composition according to any preceding aspect, wherein the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide and pharmaceutically acceptable salts thereof.

6. The composition according to any preceding aspect, wherein the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide and tirzepatide and pharmaceutically acceptable salts thereof.

7. A composition according to any preceding aspect, for use in the treatment of the human or animal body.

8. A composition according to any of aspects 1-6, for use in treating or preventing loss of muscle mass in a patient in need thereof.

9. A product comprising (a) a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 and (b) a GLP1 agonist as defined in aspects 1 or 5-6, for simultaneous, concurrent, separate or sequential use in the treatment of the human or animal body.

10. A product comprising (a) a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 and (b) a GLP1 agonist as defined in aspects 1 or 5-6, for simultaneous, concurrent, separate or sequential use in treating or preventing loss of muscle mass in a patient in need thereof.

11. The composition for use according to aspect 8 or product for use according to aspect 10, wherein the patient has a body mass index of 30 or greater.

12. A combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 for use in the treatment of the human or animal body, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined in aspects 1 or 5-6.

13. A combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined in aspects 1 or 5-6.

14. The combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use according to aspect 13, wherein said use is sequential use of the GLP1 agonist followed by the 5-HT1A receptor antagonist or partial agonist.

15. The combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use according to aspect 13 or 14, wherein the 5-HT1A receptor antagonist or partial agonist is for use following discontinuation of the use of the GLP1 agonist.

16. The combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use according to any of aspects 13-15, wherein the patient has a body mass index of 30 or greater.

17. A GLP1 agonist as defined in aspects 1 or 5-6 for use in the treatment of the human or animal body, by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4.

18. A GLP1 agonist as defined in aspects 1 or 5-6 for use in reducing body mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4.

19. The GLP1 agonist for use according to aspect 18, wherein the patient has a body mass index of 30 or greater.

20. Use of a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 in the manufacture of a medicament for use in the treatment of the human or animal body by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined in aspects 1 or 5-6.

21. Use of a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4 in the manufacture of a medicament for use in treating or preventing loss of muscle mass in a patient in need thereof, by simultaneous, concurrent, separate or sequential use in combination with a GLP1 agonist as defined in aspects 1 or 5-6.

22. A method of treating or preventing loss of muscle mass in a patient in need thereof, which method comprises administering to said patient a composition as defined in any of aspects 1-6.

23. A method of treating or preventing loss of muscle mass in a patient in need thereof, which method comprises co-administering to said patient a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist as defined in aspects 1-4, and a GLP1 agonist as defined in aspects 1 or 5-6.

24. The use of aspect 21 or the methods of aspect 22-23, wherein the patient has a body mass index of 30 or greater.

Third additional aspects of the invention

1. A beta-blocker for use in a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

2. A beta-blocker for use according to aspect 1, wherein the method is a method for preventing, inhibiting, or reducing loss of muscle mass in a subject resulting from a weight loss treatment.

3. A beta-blocker for use according to aspect 1 or aspect 2, wherein the weight loss treatment comprises (i) administration of a therapeutic agent which is a diabetes or weight loss drug and/or (ii) bariatric surgery.

4. A beta-blocker for use according to any one of the preceding aspects, wherein weight loss treatment comprises administration of a therapeutic agent which is a diabetes or weight loss drug.

5. A beta-blocker for use according to any one of the preceding aspects, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor, or

wherein the weight loss drug is a monoclonal antibody, optionally wherein the monoclonal antibody comprises bimagrumab or a salt thereof.

6. A beta-blocker for use according to aspect 5, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally wherein the GLP1R agonist is selected from the group consisting of: semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a salt or solvate of any of the foregoing,

preferably wherein the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide and tirzepatide, or a salt or solvate of any of the foregoing.

7. A beta-blocker for use according to aspect 5, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

8. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is selected from the group consisting of: pindolol, oxprenolol, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, celeprolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, propanolol, sotalol, esmolol, carvedilol, timolol, bopindolol, medroxalol, bucindolol, levobunolol, metipranolol, celiprolol and propafenone, or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist selected from the group consisting of: S-pindolol, S-oxprenolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol, and pharmaceutically acceptable salts thereof.

9. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing,

preferably wherein the beta-blocker is selected from the group consisting of: S-pindolol and S-oxprenolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

10. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is enantiomerically enriched for the S-enantiomer, optionally wherein the enantiomeric excess of the S-enantiomer is at least 50%,

optionally wherein the beta-blocker is in single enantiomer form.

11. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is S-pindolol or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is S-pindolol benzoate.

12. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is S-oxprenolol dihydrogenphosphate.

13. A beta-blocker for use according to any one of the preceding aspects, wherein the subject is overweight or obese, optionally wherein the subject has a body mass index of 30 or greater.

14. A beta-blocker for use according to any one of the preceding aspects, wherein the subject has sarcopenic obesity.

15. A beta-blocker for use according to any one of the preceding aspects, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to the weight loss treatment in the absence of treatment with the beta-blocker.

16. A beta-blocker for use according to any one of the preceding aspects, wherein the method results in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or function and/or bone density.

16. A beta-blocker for use according to any one of the preceding aspects, wherein the weight loss treatment and the beta-blocker are administered during an overlapping time period.

17. A beta-blocker according to any one of the preceding aspects, wherein the weight loss treatment comprises administration of a therapeutic agent which is a diabetes or weight loss

drug, and wherein the method comprises administering the beta-blocker and the therapeutic agent simultaneously, concurrently, separately, concomitantly or sequentially.

18. A beta-blocker for use in a method for increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

19. A beta-blocker for use according to aspect 18, wherein the beta-blocker is as defined in any of aspects 8 to 12 and/or the weight loss treatment is as defined in any one of aspects 3 to 7.

20. A beta-blocker for use according to aspect 18 or aspect 19, wherein the method is a method for increasing or restoring muscle mass in a subject following a weight loss treatment.

21. A beta-blocker for use according to aspect 18 or aspect 19, wherein (a) the subject is undergoing the weight loss treatment at the time the subject is provided with the beta-blocker or (b) the subject has completed the weight loss treatment at the time the subject is provided with the beta-blocker.

22. A beta-blocker for use according to any one of aspects 18 to 20, wherein the subject has lost weight as a result of the weight loss treatment such that the BMI of the patient has been reduced by at least 5 %, optionally wherein the reduction in BMI has occurred within a period of no greater than 1 year prior to first provision of the beta-blocker to the subject.

23. A beta-blocker for use in a method of treating a subject in need thereof for sarcopenic obesity or osteosarcopenic adiposity syndrome (OSA), which method comprises providing to the subject an effective amount of a beta-blocker.

24. A product comprising (a) a beta-blocker and (b) a therapeutic agent which is a diabetes or weight loss drug for simultaneous, concurrent, concomitant, separate or sequential use in: (i) preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment; and/or (ii) increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment

25. A therapeutic agent for use in a method of treating a subject in need thereof for diabetes and/or to induce weight loss in combination with an effective amount of a beta-blocker, which method comprises providing to the subject an effective amount of the therapeutic agent, which therapeutic agent is a diabetes or weight loss drug.

Fourth additional aspects of the invention

1. A beta-blocker which is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use in a method for treating or preventing loss of muscle mass and/or

muscle strength and/or bone mineral content in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

2. A beta-blocker which is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist for use in a method for protecting cardiac muscle and/or cardiac function in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

3. A beta-blocker which is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist) for use in a method for increasing or restoring muscle mass and/or muscle strength and/or bone mineral content in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the beta-blocker.

4. A beta-blocker for use according to any one of aspects 1 to 3, wherein the weight loss treatment comprises (i) administration of a therapeutic agent which is a weight loss drug and/or (ii) bariatric surgery.

5. A beta-blocker for use according to any one of the preceding aspects, wherein weight loss treatment comprises administration of a therapeutic agent which is a weight loss drug.

6. A beta-blocker for use according to any one of the preceding aspects, wherein the weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

7. A beta-blocker for use according to aspect 6, wherein the weight loss drug is the GLP1R agonist, optionally wherein the GLP1R agonist is selected from the group consisting of: semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a salt or solvate of any of the foregoing,

preferably wherein the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide and tirzepatide, or a salt or solvate of any of the foregoing.

8. A beta-blocker for use according to aspect 6, wherein the weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, sotagliflozin, tofogliflozin, henagliflozin, and pharmaceutically acceptable salts or solvates of any of the foregoing.

9. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is selected from the group consisting of: pindolol, oxprenolol, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, celeprolol, labetalol, metoprolol, nadolol, nebivolol, penbutolol, propanolol, sotalol, tertatolol, esmolol, carvedilol, timolol, bopindolol, medroxalol, bucindolol, levobunolol, metipranolol, celiprolol and propafenone, or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is a combined beta-adrenergic and 5-HT1A receptor antagonist or partial agonist selected from the group consisting of: S-pindolol, S-oxprenolol, S-propranolol, S-carteolol, S-penbutolol, S-alprenolol, S-tertatolol, S-mepindolol, S-bopindolol, and pharmaceutically acceptable salts thereof.

10. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is selected from the group consisting of: oxprenolol and pindolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing,

preferably wherein the beta-blocker is selected from the group consisting of: S-pindolol and S-oxprenolol, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

11. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is enantiomerically enriched for the S-enantiomer, optionally wherein the enantiomeric excess of the S-enantiomer is at least 50%,

optionally wherein the beta-blocker is in single enantiomer form.

12. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is S-pindolol or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is S-pindolol benzoate.

13. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is S-oxprenolol or a pharmaceutically acceptable salt thereof,

optionally wherein the beta-blocker is S-oxprenolol dihydrogenphosphate.

14. A beta-blocker for use according to any one of the preceding aspects, wherein the subject is overweight or obese, optionally wherein the subject has a body mass index of 30 or greater.

15. A beta-blocker for use according to any one of the preceding aspects, wherein the subject has sarcopenic obesity.

16. A beta-blocker for use according to any one of the preceding aspects, wherein the method results in decreased loss of muscle mass and/or muscle strength as compared to the weight loss treatment in the absence of treatment with the beta-blocker.

17. A beta-blocker for use according to any one of the preceding aspects, wherein the method results in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or muscle strength and/or bone mineral content.

18. A beta-blocker for use according to any one of the preceding aspects, wherein the weight loss treatment and the beta-blocker are administered during an overlapping time period.

19. A beta-blocker according to any one of the preceding aspects, wherein the weight loss treatment comprises administration of a therapeutic agent which is a weight loss drug, and

wherein the method comprises administering the beta-blocker and the therapeutic agent simultaneously, concurrently, separately, concomitantly or sequentially.

20. A beta-blocker for use according to any one of the preceding aspects, wherein the method is a method for increasing or restoring muscle mass in a subject following a weight loss treatment.

21. A beta-blocker for use according to aspect 20, wherein (a) the subject is undergoing the weight loss treatment at the time the subject is provided with the beta-blocker or (b) the subject has completed the weight loss treatment at the time the subject is provided with the beta-blocker.

22. A beta-blocker for use according to aspect 21 or aspect 22, wherein the subject has lost weight as a result of the weight loss treatment such that the BMI of the patient has been reduced by at least 5 % or at least 10 %, optionally wherein the reduction in BMI has occurred within a period of no greater than 1 year prior to first provision of the beta-blocker to the subject.

23. A beta-blocker for use in a method of treating a subject in need thereof for sarcopenic obesity, which method comprises providing to the subject an effective amount of a beta-blocker.

24. A beta-blocker for use according to any one of the preceding aspects, wherein the beta-blocker is administered orally, preferably wherein the beta-blocker is administered orally in the form of a tablet or capsule.

25. A therapeutic agent for use in a method of treating a subject in need thereof to induce weight loss in combination with an effective amount of a beta-blocker, which method comprises providing to the subject an effective amount of the therapeutic agent, which therapeutic agent is a weight loss drug.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

EXAMPLES

The following examples demonstrate certain specific embodiments of the present invention. It is to be understood that these examples are for illustrative purposes only and do not purport to be wholly definitive as to conditions or scope of the invention. As such, they should not be construed in any way as limiting the scope of the present invention.

Example 1

Efficacy studies in animal model receiving semaglutide

The aim of this study phase is to determine which treatment is best at *preserving* muscle mass during weight loss associated with GLP1 agonist treatment.

This phase of the study is a comparative assessment of lean muscle mass preservation in animals receiving semaglutide and either placebo (Group A) or S-pindolol benzoate (Group B). All products are for oral administration and for a treatment dosing period of 4 weeks.

Treatment groups for comparative study in animals receiving semaglutide:

Group	Treatment allocation
A	Placebo
B	S-pindolol benzoate

Animals are sacrificed at the end of the study and the following endpoint assessments made:

- Food & water intake and body weight
- Habitual activity counts
- Body composition
    - By DEXA scan
    - Post-mortem tissue samples

An improvement in the preservation of muscle mass may be observed in Group B compared to Group A.

Efficacy studies in obese animals previously treated with semaglutide

The aim of this study is to determine which treatment is best at *restoring* muscle mass after weight loss associated with GLP1 agonist treatment.

This study will evaluate the muscle:fat ratio of any weight gain in animals previously treated with semaglutide. In this study animals receive semaglutide for 4-weeks after which semaglutide treatment stops and the animals allocated to receive either placebo (Group A) or S-pindolol benzoate (Group B) for a period of 4 weeks.

Treatment groups for comparative study of anabolic agents in animals who have previously received semaglutide:

Group	Treatment allocation
A	Placebo
B	S-pindolol benzoate

Animals will be sacrificed at the end the study and the following assessments made:

- Food & water intake and body weight
- Habitual activity counts
- Body composition
    - By DEXA scan
    - Post-mortem tissue samples

An improvement in the restoration of muscle mass may be observed in Group B compared to Group A.

Example 2 - Clinical Data

A *post-hoc* analysis of data from the ACT-ONE proof of concept study of S-pindolol in patients with stage III and IV non-small cell lung cancer (NSCLC) and colorectal cancer with cachexia and reported body weight loss has been performed. S-pindolol was evaluated in this study, 10 mg BID. The treatment period was 16 weeks (112 days).

The analysis was performed for both the intent to treat population (ITT) and modified intent to treat (mITT) populations. The definition of modified intent to treat was a subset of the ITT population who are at least 80% compliant on investigational product through Study Day 28 per protocol.

A sub-group analysis of patients who gained weight between baseline and Day 112 of the

study showed that for both the ITT and mITT populations (Table 1), an improved percent change in lean mass was demonstrated for patients receiving S-pindolol compared to placebo (9.17% S-pindolol versus 3.51% placebo in the ITT population (Table 2) and 13.15% S-pindolol versus 3.51% placebo in the mITT population (Table 3).

Table 1. Patient populations: Patients who gained weight between baseline and Day 112		
ITT	**S-pindolol (N=42)**	**Placebo (N=31)**
Pts gain wt at Day 112	23 (54.8%)	10 (32.3%)
mITT	**S-pindolol (N=28)**	**Placebo (N=31)**
Pts gain wt at Day 112	16 (57.1%)	10 (38.5%)

Table 2. ITT: Lean Mass % change from BL (patients gaining weight at day 112)		
	S-pindolol (N= 23)	**Placebo (N=10)**
Number available	23 (100%)	10 (100%)
Mean (SD)	9.17 (21.87)	3.51 (2.69)
Median (25. 75th perc)	4.77 (2.22, 8.31)	2.98 (1.68, 5.70)
Table 3. mITT: Lean Mass % change from BL (patients gaining weight at day 112)		
	S-pindolol (N= 16)	**Placebo (N=10)**
Number available	16 (100%)	10 (100%)
Mean (SD)	13.15 (25.14)	3.51 (2.69)
Median (25. 75th perc)	6.04 (3.70, 10.92)	2.98 (1.68, 5.70)

A sub-group analysis was also performed for patients who continued to lose weight (>2.5% of body weight between baseline and Day 112) (Table 4). Patients receiving S-pindolol were able to gain lean tissue whilst still losing body weight (6.33% lean mass change for S-pindolol versus -4.27% placebo in the ITT population (Table 5) and 6.33% S-pindolol versus -4.88% placebo in the mITT population Table 6).

Table 4. Patient populations: Patients who lost >2.5% body wt at Day 112		
ITT	**S-pindolol (N=42)**	**Placebo (N=31)**
Pts lost wt at Day 112	2 (4.8%)	11 (35.5%)
mITT	**S-pindolol (N=28)**	**Placebo (N=26)**
Pts lost wt at Day 112	2 (7.1%)	10 (38.5%)

Table 5. ITT: Lean Mass % change from BL (patients who lost >2.5% body weight at day 112)		
	S-pindolol (N= 2)	**Placebo (N=11)**
Number available	2 (100.0%)	11 (100.0%)
Mean (SD)	6.33 (2.30)	-4.27 (7.40)
Median [25. 75th perc)	6.33 (4.71, 7.96)	-2.34 (-11.24, 1.83)
Table 6. mITT: Lean Mass % change from BL (patients who lost >2.5% body weight at Day 112)		
	S-pindolol (N= 2)	**Placebo (N=10)**
Number available	2 (100.0%)	10 (100.0%)
Mean (SD)	6.33 (2.30)	-4.88 (7.50)
Median [25. 75th perc)	6.33 (4.71, 7.96)	-4.82 (-11.24, 1.26)

Conclusion

The ACT-ONE study included patients who all had recent weight loss (≥5% documented weight loss in the previous 12 months, a subjective report of weight loss in the previous 12 months and a recorded body mass index (BMI) less than 20 kg/m^2, or ongoing documented weight loss of at least 1 kg in the week prior to Day 0, or 1.25 kg in the 2 weeks prior to Day 0, or 1.5 kg in the 3 to 6 weeks prior to Day 0 provided that BMI was not more than 25 kg/m2) all on the background of advanced cancer. Despite this uniform weight loss prior to enrolment during 112 days of double-blind treatment, some patients had ongoing weight loss and others showed weight gain.

There is interest in weight changes in other patient states with recent weight loss, particularly a desire to find treatments that relatively preserve muscle, both during ongoing weight loss, or during subsequent weight gain, once the initial weight loss has ceased. What this analysis shows is that the agent S-pindolol, at a randomised dose target of 10mg BID compared to placebo in patients who subsequently regain body weight led to an increase in lean mass change of 6.3 % on S-pindolol versus -4.9 % on placebo (mITT population), a change suggestive of muscle growth, thereby enhancing the muscle to fat ratio of the regained weight. In addition, in the patients who were documented to have ongoing weight loss S-pindolol lead to greater lean mass gain compared to placebo of 13.2 % compared to 3.5% (mITT population).

Example 3 - in vivo analysis of effect of beta-blockers on GLP1R agonist-induced muscle loss

The ability of beta-blockers to prevent or inhibit muscle loss and/or bone loss resulting from treatment with a GLP1R agonist is demonstrated in a murine model of diet induced obesity (DIO). Briefly, overweight mice are generated by feeding mice a high fat diet. A GLP1R agonist (or placebo control) is delivered to the overweight mice with or without concurrent treatment with S-oxprenolol dihydrogenphosphate (> 98% S-oxprenolol dihydrogenphosphate). The mice's body composition is monitored longitudinally for at least one month, including physical activity measurements, food consumption, and weight. Muscle function assessment is performed prior to sacrifice, and organ weights (e.g., heart, liver, spleen, lung, kidney) and muscle/fat weights (gastrocnemius, quadriceps, tibialis anterior, soleus, extensor digitorum longus, white adipose tissue, epididymal fat) are determined after sacrifice and used to determine fat-free mass (FFM), fat mass, and/or muscle mass and/or function. Additional endpoints may include: biomarkers; muscle function/quality as assessed by: in vivo muscle force and contractility (Plantar Flexion analysis), electromyography (EMG) of single motor unit potential, compound muscle action potential, and motor unit number estimation; ex vivo measurement of EDL contractility (specific force); and morphometry and immunohistochemistry of muscle fibers. It is expected that concurrent treatment with S-oxprenolol dihydrogenphosphate (> 98% S-oxprenolol dihydrogenphosphate) will result in decreased muscle loss as compared to treatment with only the GLP1R agonist.

Example 4 - Phase IIB study of treatment with GLP1R agonist and beta-blocker

The ability of beta-blockers to prevent or inhibit muscle loss and/or bone loss resulting from treatment with a GLP1R agonist is demonstrated in a human phase IIb clinical trial as diagramed in FIG. 5. Subjects are treated with the indicated increasing dosages of semaglutide for 16 weeks, in the presence or absence of S-oxprenolol dihydrogenphosphate (> 98% S-oxprenolol dihydrogenphosphate) at either a low dose, e.g., 120 mg daily, or a high dose, e.g., 240 mg daily. After cessation of semaglutide treatment at 16 weeks, subjects continue to be treated with S-oxprenolol dihydrogenphosphate (> 98% S-oxprenolol dihydrogenphosphate) for 24 weeks, 36 weeks or longer. At various time points before treatment, during treatment, and following cessation of treatment with semaglutide, subject characteristics are measured, including weight, lean body mass, fat mass, and bone density. It is expected that treatment with S-oxprenolol will result in subjects also treated with semaglutide having reduced loss of lean body mass, muscle mass and/or function, and/or bone density as compared to subjects treated only with semaglutide.

Example 5 - Phase IIB study of treatment of sarcopenic obesity with beta-blocker

The ability of beta-blockers to improve sarcopenic obesity is demonstrated in a human phase IIb clinical trial as diagramed in FIG. 6. Subjects having sarcopenic obesity are untreated or treated orally, twice a day, with S-oxprenolol at either a low dose or high dose for six months. Prior to treatment at time points of three months and six months, various markers and parameters related to muscle tissue function are examined, such as physical performance, lean body mass, fat mass, bone mass, bone density, muscle strength and function, PRO/QQL, and expression levels of leptin, adinopectin, sclerostin, osteocalrin, interleukin-6, etc. It is expected that treatment with S-oxprenolol will result in subjects having reduced loss of (or increased) lean body mass, muscle mass and/or function, and/or bone density, as well as superior physical performance, and as compared to untreated subjects.

Example 6 - effects of S-oxprenolol in murine model of cachexia

The ability of S-oxprenolol to prevent muscle wasting was shown in a murine model of KPC-induced cachexia. As shown in FIG. 7, treatment with S-oxprenolol resulted in a significantly less loss of body weight as compared to treatment with placebo. In addition, experiments conducted using a murine model of Lew Lung carcinoma (LLC)-induced cachexia demonstrated that treatment with S-oxprenolol preserved muscle and function (FIG. 8A and FIG, 8B). Moreover, further experiments conducted in a Yoshida AH-130 hepatoma model showed that S-oxprenolol is superior to R-oxprenolol in preserving lean body mass (FIG. 9). S-oxprenolol also significantly reduced atrophy in skeletal muscle in the Yoshida AH-130 hepatoma model, whereas R-oxprenolol did not (FIG. 10) These data provide evidence of reduced catabolism/increased anabolism resulting from treatment with S-oxprenolol.

Example 7 – Murine obesity models

Murine obesity models are conducted in a three phase approach which evaluates the effect of S-pindolol benzoate in preserving lean muscle mass during GLP-1 agonist therapy and improvements in the lean muscle mass:fat mass ratio of regained weight post-GLP-1 agonist therapy in diet-induced obese (DIO) mice.

Two metabolic phenotype DIO mice are evaluated in phase 1 (stable obese and weight-gaining).

The comparative agents include two other anabolic agents (DHEA and (S)-carvedilol) and placebo.

Schematics of the three phases are shown in FIGS. 11A, 11B and 11C.

Example 8 – Results of murine obesity models

The phase 1 and phase 2 studies described in Example 7 and FIGS. 11A and 11B were carried out.

Phase 1

In phase 1, the effect of 1 mg/kg po, 3 mg/kg po and 10 mg/kg po S-pindolol benzoate (doses corrected to free base equivalent) on body weight and composition over seven days was assessed in weight gain (WG) DIO mice and stable obese (SO) DIO mice.

Analysis of Day 7 body composition was by robust regression (bone mineral density (BMD), Bone %, Fat %, Lean %, bone mineral content (BMC)) or general linear model (total tissue mass (TTM), Fat g, Lean g) with treatment as a factor and Day 1 body weight as a covariate. Lean (g) data was log transformed for analysis. Data are adjusted means (n=10) and standard errors of the mean (SEM) were calculated from the residuals of the statistical models. Comparisons to vehicle were by Dunnett's test.

In the WG DIO mice, all doses of S-pindolol benzoate were found to significantly increase body weight at 7 days compared to vehicle, with a significant reduction in fat (%) and a significant increase in lean (%). In the SO DIO mice, increases in body weight at 7 days compared to vehicle were observed, as were small reductions in fat (%) and increases in lean (%). Based on the outcome of Phase 1, a dose of 2 mg/kg BID S-pindolol benzoate was selected for the Phase 2 mouse study.

Phase 2

The following treatment arms (n = 10/group) were assessed in Phase 2 of the DIO mouse model:

- Group 1: GLP-1 agonist (semaglutide 10 nmol/kg/day subcutaneous (sc))
- Group 2: GLP-1 agonist + S-pindolol benzoate (2 mg/kg BID po)

- Group 3: GLP-1 agonist + (S)-carvedilol (5 mg/kg/day po + sham 2nd dose po)
- Group 4: GLP-1 agonist + dehydroepiandrosterone (DHEA) (10mg/kg/day po + sham 2nd dose po)
- Group 5: Vehicle oral & vehicle sc

The change in baseline TTM (%), fat (%), lean (%) and BMC (%) at day 27 for each group is shown in FIG. 12. It was found that S-pindolol prevents muscle wasting in the context of GLP-1 receptor agonist therapy. In particular, S-pindolol prevented the reduction in lean mass (i.e. muscle mass) observed for semaglutide alone or for semaglutide in combination with (S)-carvedilol or DHEA. This was the case even though S-pindolol did not inhibit the reduction in TTM or fat % achieved with semaglutide. It was also observed that S-pindolol combined with semaglutide increased BMC compared with semaglutide alone or for semaglutide in combination with (S)-carvedilol or DHEA.

It was also found that S-pindolol increases total muscle in the context of GLP-1 receptor agonist therapy. This is shown in FIG. 13.

FIG. 14 shows the effect on cardiac muscle in each of the groups. It was found that S-pindolol protects against cardiac wasting induced by GLP-1 therapy.

As shown in FIG. 15, it was further found that grip strength (gF normalised to body weight) was improved when S-pindolol was combined with semaglutide, compared with semaglutide alone or in combination with DHEA or (S)-carvedilol.

Finally, as shown in FIG. 16, it was found that S-pindolol does not increase appetite in the context of GLP-1 receptor agonist therapy. S-pindolol in combination with semaglutide did not increase average daily food intake compared with semaglutide alone.

Conclusion

The DIO mouse model has confirmed that S-pindolol is effective at preventing muscle wasting during semaglutide treatment. Advantageous effects for S-pindolol were also observed on total muscle, cardiac muscle and grip strength, as well as on bone mineral content. S-pindolol generally outperformed the other beta-blocker (S-carvedilol) and the steroid DHEA. S-pindolol also did not counteract the ability of semaglutide to reduce appetite and cause fat mass loss.

Example 9 – Results of murine obesity models

The studies described in Example 3 were carried out.

S-oxprenolol phosphate (FDY-8801) was evaluated using a GLP-1 receptor agonist (GLP-1ra)-induced weight loss model in C57BL/6J DIO mice (JAX Stock #380050). Semaglutide, at a dose of 120 µg/kg administered subcutaneously once a day, was combined with three doses of FDY-8801 (10, 25, or 75 mg/kg) administered twice daily (BID) orally for 4 weeks. Treatments commenced at week twenty-five in a GLP-1ra-induced muscle loss model of C57BL/6J DIO mice, with body weight, food intake, and body composition measured via NMR and DEXA. Additional endpoints include oral glucose tolerance test (OGTT), muscle force assessments (e.g., force and force-frequency curve), and post-mortem collection of tissues such as gastrocnemius, soleus, tibialis, EDL, and diaphragm muscles. Blood and plasma were analyzed for ELISA markers (leptin, adiponectin, insulin) and clinical chemistry parameters (LDL, HDL, TC, NEFA, ALT, AST). Necropsy occurred after 4 weeks or upon reaching humane endpoints.

A diagram of the basic study design is shown in FIG. 17 and the treatment groups are shown in the table below (Table 6).

Table 6

Group	N	Treatment	Dosing Route	Dose	Dosing Frequency	Dosing Duration
1	12 (M)	Vehicle 0.9% Saline	PO	N/A	2XDaily	4 weeks
2	12 (M)	Semaglutide (S)	SC	120ug/kg	Once Daily	4 weeks
3	12 (M)	S+FDY-8801	SC+PO	120ug/kg (SC) + 10 mg/kg/day (PO)	SC: Once Daily PO: 2X daily	4 weeks
4	12 (M)	S+FDY-8801	SC+PO	120ug/kg (SC) + 25mg/kg/day (PO)	SC: Once Daily PO: 2X daily	4 weeks
5	12 (M)	S+FDY-8801	SC+PO	120ug/kg (SC) + 75 mg/kg/day (PO)	SC: Once Daily PO: 2X daily	4 weeks

FDY-8801 (75 mg/kg/day) in combination with semaglutide led to significantly greater body weight loss and significantly greater fat loss compared to semaglutide alone. There also appeared to be a dose response with FDY-8801 treatment. FIGS. 18A and 18B show the

body weight change from baseline as well as the statistical analysis. FIGS. 19A and 19B show change in fat based on NMR body composition analysis, as well as the statistical analysis. All animals receiving semaglutide had a decrease in food consumption; however, there was no significant difference in food intake between the semaglutide alone vs. semaglutide + FDY-8801 groups (data not shown), indicating that the observed changes in weight loss and fat loss do not appear to be due to the animals just eating less.

The combination of FDY-8801 + semaglutide showed trends in lean mass preservation compared to semaglutide alone. At the 4-week timepoint, the FDY-8801 high dose group had 15.2% less loss of lean mass compared to the semaglutide alone, as shown in the table below (Table 7).

Table 7			
	LS Mean Change from Baseline (g)	**Relative Difference**	**Interpretation**
High dose	-1.476	-15.2%	15.2% less loss
Mid Dose	-2.108	21.1%	21.1% more loss
Low Dose	-2.185	25.5%	25.5% more loss
Semaglutide	-1.741	NA	NA

When evaluating the fat and muscle compartments for total body weight (TBW) losses, the high dose of FDY-8801 + semaglutide showed increased TBW fat loss and decreased TBW muscle loss, as shown in the table below (Table 8).

Table 8			
Treatment Group	**TBW Loss Attributable to Fat (%)**	**TBW Loss Attributable to Lean Mass (%)**	**Other Loss (%)**
Semaglutide	80.76	13.42	5.82
Semaglutide + FDY-8801 (10 mg/kg)	82.81	16.67	0.52

Semaglutide + FDY-8801 (25 mg/kg)	81.84	16.69	1.47
Semaglutide + FDY-8801 (75 mg/kg)	85.27	8.92	5.81

The combination of FDY-8801 + semaglutide showed trends in bone mineral density (BMD) preservation compared to semaglutide alone. At the 4-week timepoint, the FDY-8801 mid and high dose groups had 150% and 92.9% less loss of BMD compared to semaglutide alone, respectively, as shown in the table below (Table 9).

Table 9

	LS Mean Change from Baseline (g/cm^2)	**Relative Difference**	**Interpretation**
High dose	-0.0001	-92.9%	92.9% less loss
Mid Dose	0.0007	-150.0%	150% less loss
Low Dose	-0.0020	42.9%	42.9% more loss
Semaglutide	-0.0014	NA	NA

The combination of FDY-8801 + semaglutide showed no significant difference in muscle weight at necropsy (compared to semaglutide alone), but there was perhaps some mild effect at muscle preservation with the mid dose (25 mg/kg/day). FIG. 20 shows the results as muscle weight normalized to body weight. There as potentially a greater impact on preservation of muscle composed of fast twitch muscle fibers.

The combination of FDY-8801 + semaglutide showed trends in increased muscle force compared to semaglutide alone, as the muscle force at 100 Hz for the semaglutide + FDY-8801 at 25 mg/kg and 75 mg/kg groups was higher than semaglutide alone. The normalized force curve as well as the 100 Hz data is shown in FIGS. 21A and 21B.

The combination of FDY-8801 (75 mg/kg) + semaglutide showed elevated levels of adiponectin compared to semaglutide alone, which is important in regulating energy balance

and inflammation (FIG. 22). There were no dramatic differences in insulin or leptin levels between semaglutide vs. semaglutide + FDY-8801 (data not shown).

Example 10 – FDY-8801 Mechanism

Cell-based assays were conducted to elucidate the mechanisms underlying the β3-mediated effects of FDY-8801.

FDY-8801 (in form of S-oxprenolol) was evaluated in vitro for its ability to increase cAMP production using the Hit Hunter® cAMP XS+ assay (Eurofins), which monitors the activation of a GPCR via Gi and Gs secondary messenger signaling. Compound activity was analyzed using the CBIS data analysis suite (ChemInnovation, CA). The results showed increased cAMP production upon treatment with FDY-8801 (in form of S-oxprenolol), thus confirming FDY-8801 activation of β3 receptors. The results obtained using ADRB3 as the assay target are shown in FIG. 23, which indicates an EC50 of 4.42 μM.

FDY-8801 (S-oxprenolol phosphate) was evaluated for its ability to induce nitric oxide (NO) release via the ß3 receptor in human umbilical vein endothelial cells (HUVECs) using a standard NO release assay kit with a fluorescence-based readout measuring relative fluorescence units (RFU). FDY-8801 was tested in triplicate at 4 different final concentrations, 0.1 to 100 μM, and at the highest concentration was also combined with an NO inhibitor, L-N^G-Nitroarginine (L-NNA). The data shown in FIG. 24 (expressed as mean ± SEM) indicates a dose dependent release of NO above background levels. The negative control (L-NNA) reduced NO release as expected.

Thus, the β3-mediated effects of FDY-8801 appear to be mediated by both activation of the cAMP/PKA pathway and the eNOS pathway. These dual effects of β3 receptor activation by FDY-8801 may have contributed to the greater reductions in total body weight and fat, preservation of bone density, and improved indicators of metabolic function (adiponectin) observed in the DIO mouse model with FDY-8801 + semaglutide vs. semaglutide alone (Example 9).

Example 11 – effect of S-pindolol after treatment with semaglutide

A study was conducted in accordance with phase 3 described in Example 7 and FIG. 11C in order to assess the effect of S-pindolol on muscle mass following treatment with

semaglutide. Mice were treated with semaglutide alone for a first period, before being treated with one of S-pindolol benzoate (ACM-001.1), (S)-Carvedilol and DHEA alone for a second period to assess the effect on those compounds during the weight gain following cessation of semaglutide treatment. The study involved six groups of mice, as set out in Table 10 below.

Table 10

Group	Period 1 Treatment (Day 1–28)	Period 2 Treatment (Day 29-56)	n
1	Control vehicle for semaglutide (5 ml/kg qd)	Vehicle (po, BID)	10
2	Semaglutide (10 nmol/kg, sc, qd)	Vehicle (po, BID)	10
3	Semaglutide (10 nmol/kg, sc, qd)	S-pindolol benzoate (3 mg/kg, BID, po)	10
4	Semaglutide (10 nmol/kg, sc, qd)	S-pindolol benzoate (4.5 mg/kg, BID, po)	10
5	Semaglutide (10 nmol/kg, sc, qd)	(S)-Carvedilol (5 mg/kg. qd VERUM, qd vehicle, po)	10
6	Semaglutide (10 nmol/kg, sc, qd)	DHEA (10 mg/kg, qd VERUM, qd vehicle, po)	10

The vehicle for the period 2 treatment in groups 1 and 2 was the vehicle used for the S-pindolol benzoate.

The body weights, food intakes and water intakes of the mice were measured daily. The body composition of the mice was monitored by DEXA at baseline, day 28 and day 56. Tissue weights were also measured at termination on day 57, including the total epididymal fat and retroperitoneal fat.

FIG. 25 shows the total muscle and gastrocnemius tissue weights at day 57 (normalised to tibia length) of the mice, with †† showing a significant difference from semaglutide followed by vehicle (group 2) with $p < 0.01$. Restoration of muscle was observed for the groups treated with S-pindolol after semaglutide treatment.

FIG. 26 shows total epididymal fat and total retroperitoneal fat of mice in each group at day 57, with † showing a significant difference from semaglutide followed by vehicle (group 2)

with $p < 0.05$. Mice treated with S-pindolol showed the lowest total epididymal fat and total retroperitoneal fat.

It was also found that S-pindolol caused an increase in bone mineral content (BMC) of the mice following cessation of treatment with semaglutide (i.e. an increase from day 28 to day 57, FIG. 27).

Conclusion

S-pindolol has been found to be effective in restoring muscle following cessation of semaglutide treatment. Epididymal and retroperitoneal fat were both decreased in mice treated with S-pindolol. BMC was restored in mice treated with S-pindolol following semaglutide treatment.

Example 12 – effect of S-pindolol during treatment with semaglutide

A further assessment was conducted to assess the effect of S-pindolol in diet-induced obese (DIO) mice during treatment with semaglutide. The follow groups of mice were assessed.

Table 11

Group No.	**Period 1 Treatment (Day 1 – 28)**	**n**
7	Control vehicle for semaglutide (5 ml/kg qd) Vehicle control for S-pindolol benzoate po BID	10
8	Semaglutide (10 nmol/kg, sc, qd) Vehicle control for S-pindolol benzoate po BID	10
9	Semaglutide (10 nmol/kg, sc, qd) + S-pindolol benzoate (3 mg/kg, BID, po)	10
10	Semaglutide (10 nmol/kg, sc, qd) + S-pindolol benzoate (4.5 mg/kg, BID, po)	10

The body weights, food intakes and water intakes of the mice were measured daily. The body composition of the mice was monitored by DEXA at baseline and day 28. Tissue weights were measured at termination, including the total epididymal fat and retroperitoneal fat. Heart rate and blood pressure was measured at days 7, 14, 21 and 28.

FIG. 28 shows (A) fat mass (%) change from baseline, (B) lean mass (%) change from baseline and (C) lean/fat ratio (%) change in baseline. Improvements in muscle during semaglutide therapy were observed for the mice treated with S-pindolol. Mice treated with S-pindolol and semaglutide lost at least as much fat as mice treated with semaglutide alone.

FIG. 29A shows that total muscle weight was increased in mice treated with S-pindolol. Total epididymal fat and total retroperitoneal fat were also more greatly reduced in mice treated with semaglutide and S-pindolol than mice treated with semaglutide alone. S-pindolol was also observed to protect cardiac mass during semaglutide treatment compared with semaglutide alone which was observed to reduce cardiac mass (FIG. 29B).

Hypotension observed with semaglutide alone was avoided in mice treated with semaglutide and S-pindolol (FIG. 30).

Conclusion

S-pindolol has been shown to reduce the loss of muscle mass during semaglutide treatment, leading to a greater increase in lean/fat ratio than semaglutide alone.

CLAIMS

1. A method of treating a subject in need thereof for diabetes and/or to induce weight loss, comprising providing to the subject an effective amount of a diabetes or weight loss drug in combination with an effective amount of S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

2. The method of claim 1, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a SGLT2 inhibitor.

3. The method of claim 2, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

4. The method of claim 2, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

5. The method of any one of claims 1-4, wherein the subject is provided oxprenolol or a pharmaceutically acceptable salt or salt thereof comprising at least 50% S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

6. The method of any one of claims 1-5, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

7. The method of any one of claims 1-6, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

8. The method of any one of claims 1-7, wherein the subject is treated for diabetes, optionally type 2 diabetes mellitus (T2DM).

9. The method of any one of claims 1-7, wherein the subject is treated to induce weight loss, optionally wherein the subject is overweight or obese or wherein the subject has sarcopenic obesity.

10. The method of any one of claims 1-9, wherein the diabetes or weight loss drug and the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof are administered during an overlapping time period.

11. The method of any one of claims 1-10, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

12. A method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density resulting from treatment of a subject with a therapeutic agent, comprising providing to the subject an effective amount of S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof in combination with the therapeutic agent, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to the subject without the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

13. The method of claim 12, wherein the therapeutic agent is a diabetes or weight loss drug.

14. The method of claim 13, wherein the therapeutic agent is a diabetes or weight loss drug selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

15. The method of claim 14, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

16. The method of claim 14, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

17. The method of any one of claims 12-16, wherein the subject is provided oxprenolol or a pharmaceutically acceptable salt or salt thereof comprising at least 50% S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

18. The method of any one of claims 12-17, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

19. The method of any one of claims 12-18, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;

b) S-oxprenolol dihydrogenphosphate and lixisenatide;

c) S-oxprenolol dihydrogenphosphate and liraglutide;

d) S-oxprenolol dihydrogenphosphate and dulaglutide;

e) S-oxprenolol dihydrogenphosphate and semaglutide;

f) S-oxprenolol dihydrogenphosphate and tirzepatide;

g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);

h) S-oxprenolol dihydrogenphosphate and empagliflozin;

i) S-oxprenolol dihydrogenphosphate and canagliflozin;

j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or

k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

20. The method of any one of claims 12-19, wherein the subject is treated for diabetes, optionally wherein the diabetes is type 2 diabetes mellitus (T2DM).

21. The method of any one of claims 12-19, wherein the subject is treated to induce weight loss, optionally wherein the subject is overweight or obese or wherein the subject has sarcopenic obesity.

22. The method of any one of claims 12-21, wherein the diabetes or weight loss drug and the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof are administered during an overlapping time period.

23. The method of any one of claims 12-22, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to treatment with the therapeutic agent in the absence of treatment with the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

24. A method for increasing, enhancing, or promoting weight loss resulting from treatment of a subject with a diabetes or weight loss drug, comprising providing to the subject an effective amount of S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof in combination with the diabetes or weight loss drug.

25. The method of claim 24, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

26. The method of claim 25, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

27. The method of claim 25, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

28. The method of any one of claims 24-27, wherein the subject is provided oxprenolol or a pharmaceutically acceptable salt or salt thereof comprising at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

29. The method of any one of claims 24-28, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

30. The method of any one of claims 24-29, wherein the subject is provided:

a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

31. The method of any one of claims 24-30, wherein the subject is treated for diabetes, optionally wherein the diabetes is type 2 diabetes mellitus (T2DM).

32. The method of any one of claims 24-30, wherein the subject is treated to induce weight loss, optionally wherein the subject is overweight or obese or wherein the subject has sarcopenic obesity.

33. The method of any one of claims 24-32, wherein the diabetes or weight loss drug and the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof are administered during an overlapping time period.

34. The method of any one of claims 24-33, wherein the method results in increased loss of weight as compared to treatment with the diabetes or weight loss drug in the absence of treatment with the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

35. A pharmaceutical composition comprising a therapeutic agent and S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient, diluent, or carrier, wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

36. The pharmaceutical composition of claim 35, wherein the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

37. The pharmaceutical composition of claim 36, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

38. The pharmaceutical composition of claim 36, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

39. The pharmaceutical composition of any one of claims 35-38, wherein the composition comprises oxprenolol or a pharmaceutically acceptable salt or solvate thereof comprising at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

40. The pharmaceutical composition of any one of claims 35-39, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

41. The pharmaceutical composition of any one of claims 35-40, comprising:
a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

42. A kit comprising:
a) a container comprising a pharmaceutical composition comprising a therapeutic agent and a pharmaceutically acceptable excipient, diluent, or carrier; and
b) a container comprising S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable excipient, diluent, or carrier,
wherein the therapeutic agent is not a beta-blocker, optionally where the therapeutic agent causes loss of muscle mass and/or function and/or bone density when provided to a subject in the absence of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

43. The kit of claim 42, wherein the therapeutic agent is a diabetes or weight loss drug, optionally selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor.

44. The kit of claim 43, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally selected from the group consisting of: exenatide (Byetta® and Bydureon BCise® (exenatide extended-release)), lixisenatide (Adlyxin®), liraglutide (Victoza®, Saxenda®), dulaglutide (Trulicity®), semaglutide (Wegovy®, Ozempic®, Rybelsus®), tirzepatide (Mounjaro®), survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a pharmaceutically acceptable salt or solvate of any of the foregoing.

45. The kit of claim 43, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

46. The kit of any one of claims 42-45, wherein the container comprising S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof comprises oxprenolol or a pharmaceutically acceptable salt or solvate thereof comprising at least 50% S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

47. The kit of any one of claims 42-46, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

48. The kit of any one of claims 42-47, comprising:
a) S-oxprenolol dihydrogenphosphate and exenatide;
b) S-oxprenolol dihydrogenphosphate and lixisenatide;
c) S-oxprenolol dihydrogenphosphate and liraglutide;
d) S-oxprenolol dihydrogenphosphate and dulaglutide;
e) S-oxprenolol dihydrogenphosphate and semaglutide;
f) S-oxprenolol dihydrogenphosphate and tirzepatide;
g) S-oxprenolol dihydrogenphosphate and Retatrutide (LY3437943);
h) S-oxprenolol dihydrogenphosphate and empagliflozin;
i) S-oxprenolol dihydrogenphosphate and canagliflozin;
j) S-oxprenolol dihydrogenphosphate and dapagliflozin; or
k) S-oxprenolol dihydrogenphosphate and ipragliflozin.

49. A method of treating a subject in need thereof for sarcopenic obesity, osteosarcopenia, osteoporosis, or osteosarcopenic adiposity syndrome (OSA), comprising providing to the subject an effective amount of S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof.

50. The method of claim 49, wherein the subject is provided oxprenolol or a pharmaceutically acceptable salt or salt thereof comprising at least 50% S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

51. The method of claim 49 or claim 50, wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises S-oxprenolol dihydrogenphosphate, optionally

wherein the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof comprises at least 50% S-oxprenolol dihydrogenphosphate.

52. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use in a method for preventing, inhibiting, or reducing loss of muscle mass and/or function and/or bone density in a subject resulting from a weight loss treatment, which method comprises providing to the subject an effective amount of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

53. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use in a method for protecting cardiac muscle and/or cardiac function in a subject during a weight loss treatment, or for protecting against hypotension and/or increased heartrate in a subject during a weight loss treatment, which method comprises providing to the subject an effective amount of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

54. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use in a method for increasing or restoring muscle mass and/or function and/or bone density in a subject following a weight loss treatment, which method comprises providing to the subject an effective amount of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

55. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-54, wherein the weight loss treatment comprises: (i) administration of a therapeutic agent which is a diabetes or weight loss drug; and/or (ii) bariatric surgery.

56. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to claim 55, wherein the diabetes or weight loss drug is selected from the group consisting of: a glucagon-like peptide-1 (GLP-1) receptor (GLP1R) agonist, a glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR) agonist, a glucagon receptor (GCGR) agonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor, or wherein the diabetes or weight loss drug is an amylin analogue.

57. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to claim 56, wherein the diabetes or weight loss drug is the GLP1R agonist, optionally wherein the GLP1R agonist is selected from the group consisting of: semaglutide, liraglutide, tirzepatide, exenatide, albiglutide, dulaglutide, lixisenatide, survodutide, orforglipron, danuglipron, and Retatrutide (LY3437943), or a salt or solvate of any of the foregoing,

optionally wherein the GLP1 agonist is selected from the group consisting of semaglutide, liraglutide and tirzepatide, or a salt or solvate of any of the foregoing.

58. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to claim 56, wherein the diabetes or weight loss drug is the SGLT2 inhibitor, optionally selected from the group consisting of: empagliflozin, canagliflozin, dapagliflozin, and ipragliflozin, or a pharmaceutically acceptable salt or solvate of any of the foregoing.

59. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-58, wherein the subject is overweight or obese, optionally wherein the subject has a body mass index of 30 or greater or wherein the subject has a body mass index of $\geq$ 27 kg/m^2 to < 30 kg/m^2 in the presence of at least one weight-related comorbidity.

60. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-59, wherein the subject has sarcopenic obesity.

61. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-60, wherein the method results in decreased loss of muscle mass and/or function and/or bone density as compared to the weight loss treatment in the absence of treatment with the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

62. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-61, wherein the method results in an increase in the proportion or amount of weight loss due to loss of adipose tissue and fat as compared to the amount of weight loss due to loss of muscle mass and/or function and/or bone density.

63. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-62, wherein the weight loss treatment and the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof are administered during an overlapping time period.

64. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use according to any one of claims 52-63, wherein the weight loss treatment comprises administration of a therapeutic agent which is a diabetes or weight loss drug, and wherein the method comprises administering the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof and the therapeutic agent simultaneously, concurrently, separately, concomitantly or sequentially.

65. S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof for use in a method of treating a subject in need thereof for sarcopenic obesity or osteosarcopenic adiposity syndrome (OSA), which method comprises providing to the subject an effective amount of the S-oxprenolol or pharmaceutically acceptable salt or solvate thereof.

66. A therapeutic agent for use in a method of treating a subject in need thereof for diabetes and/or to induce weight loss in combination with an effective amount of S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof, which method comprises providing to the subject an effective amount of the therapeutic agent, which therapeutic agent is a diabetes or weight loss drug.

67. A therapeutic agent for use according to claim 66, wherein the method or subject is as further defined in any one of claims 52-66.

68. A product comprising: (a) S-oxprenolol or a pharmaceutically acceptable salt or solvate thereof; and (b) a therapeutic agent which is a diabetes or weight loss drug, for simultaneous, concurrent, concomitant, separate or sequential use in a method as defined in any one of claims 52-67.