CLAIMS

1. Use of a myostatin-selective inhibitor in the manufacture of a medicament for the treatment of a metabolic disorder, wherein the medicament is to be used in conjunction with a GLP-1 receptor agonist;

wherein the metabolic disorder is overweight, obesity, type 2 diabetes mellitus (T2D), T2D associated with obesity, or metabolic syndrome;

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A; and

wherein the GLP-1 receptor agonist is capable of binding to and activating the GLP-1 receptor and comprises the amino acid sequence EGTFTSD (SEQ ID NO: 116) and/or the amino acid sequence HXXGXFTXD, wherein X is any amino acid residue (SEQ ID NO: 117).

2. Use of a GLP-1 receptor agonist in the manufacture of a medicament for the treatment of a metabolic disorder, wherein the medicament is to be used in conjunction with a myostatin-selective inhibitor;

wherein the metabolic disorder is overweight, obesity, type 2 diabetes mellitus (T2D), T2D associated with obesity, or metabolic syndrome;

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A; and

wherein the GLP-1 receptor agonist is capable of binding to and activating the GLP-1 receptor and comprises the amino acid sequence EGTFTSD (SEQ ID NO: 116) and/or the amino acid sequence HXXGXFTXD, wherein X is any amino acid residue (SEQ ID NO: 117).

3. Use of a myostatin-selective inhibitor and a GLP-1 receptor agonist in the manufacture of a medicament for the treatment of a metabolic disorder;

wherein the metabolic disorder is overweight, obesity, type 2 diabetes mellitus (T2D), T2D associated with obesity, or metabolic syndrome;

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A; and

wherein the GLP-1 receptor agonist is capable of binding to and activating the GLP-1 receptor and comprises the amino acid sequence EGTFTSD (SEQ ID NO: 116) and/or the amino acid sequence HXXGXFTXD, wherein X is any amino acid residue (SEQ ID NO: 117).

4. Use of a myostatin-selective inhibitor and a GLP-1 receptor agonist in the manufacture of a medicament for the treatment of a metabolic disorder;

wherein the metabolic disorder is overweight, obesity, type 2 diabetes mellitus (T2D), T2D associated with obesity, or metabolic syndrome;

wherein the GLP-1 receptor agonist is a GLP-1/GIP/glucagon receptor triple agonist; and

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A.

5. The use according to claim 4, wherein the GLP-1 receptor agonist is LY3437943.

6. The use according to any one of claims 3-5, wherein the myostatin-selective inhibitor and the GLP-1 receptor agonist are formulated in a single formulation.

7. The use according to any one of claims 3-5, wherein the myostatin-selective inhibitor and the GLP-1 receptor agonist are a single molecular construct.

8. The use according to any one of claims 1-3, 6, and 7, wherein the GLP receptor agonist is a GLP-1 analog, and wherein the GLP-1 analog is:

a. an Fc conjugate or multi-functional molecule comprising the GLP-1 analog; and/or

b. semaglutide, extended release exenatide, liraglutide, lixisenatide, tirzepatide, XW003, Noiiglutide, MEDI0382, dulaglutide, albiglutide, AMG 133, CT-388, cagrilintide/semaglutide combination, DD01, ALT-801, or IBI362.

9. The use according to any one of claims 1-8, wherein:

a. the myostatin-selective inhibitor is trevogrumab, GYM329, MST1032, or an antigen-binding fragment thereof, or an antibody or antigen-binding fragment that competes or cross-competes with trevogrumab, GYM329, MST1032, or apitegromab; and/or

b. the myostatin-selective inhibitor comprises at least one amino acid mutation that increases binding affinity for FcRn.

10. The use according to any one of claims 1-9, wherein the myostatin-selective inhibitor binds mature myostatin.

11. The use according to any one of claims 1-9, wherein the myostatin-selective inhibitor binds selectively to pro/latent myostatin.

12. The use according to any one of claims 1-11, wherein the myostatin-selective inhibitor is not apitegromab.

13. The use according to any one of claims 1-12, wherein:

a. the medicament is for the treatment of overweight or obesity in an adult subject with a body mass index (BMI) of 25 or greater or a child or adolescent subject aged 2-19 years with a BMI of at or above the 85th percentile on the CDC growth charts;

b. the medicament is for the treatment of overweight or obesity in a subject who has received at least one therapy for obesity, overweight, or a weight-related condition and failed to achieve an intended clinical outcome, wherein the intended clinical outcome is an increased ratio of lean mass to fat mass compared to the ratio prior to the start of the at least one therapy;

c. the medicament is for the treatment of overweight or obesity in a subject having one or more of: central adiposity, cardiovascular disease, kidney disease, fatty liver disease, sleep apnea, high blood pressure, high blood triglyceride levels, high blood cholesterol levels, low high-density lipoprotein (HDL) levels, and a hemoglobin A1c (HbA1c) level of 6% or greater; and/or

d. the medicament is for the treatment of overweight or obesity in a subject who is on a calorie restriction diet and/or an exercise regimen.

14. The use according to claim 13, wherein the subject failed to perform or continue with a diet regimen and/or an exercise regimen as part of weight management prior to receiving the at least one therapy for obesity, overweight, or a weight-related condition.

15. The use according to claim 13, wherein the subject has a BMI of between 28 and 40, inclusive of endpoints.

16. The use according to any one of claims 1-15, wherein:

a. the administration of the medicament reduces triglyceride, total cholesterol, LDL cholesterol, and/or non-fasted glucose levels relative to a baseline level as measured prior to starting the medicament; and/or

b. the administration of the medicament reduces fat mass, preserves lean mass, or improves insulin sensitivity and/or insulin secretion relative to a baseline level as measured prior to starting the medicament.

17. The use according to claim 16, wherein:

a. the administration of the medicament reduces triglyceride, total cholesterol, LDL cholesterol, and/or non-fasted glucose levels relative to treatment with a GLP-1 receptor agonist alone; and/or

b. the administration of the medicament improves insulin sensitivity and/or insulin secretion relative to treatment with a GLP-1 receptor agonist alone.

18. The use according to any one of claims 1-17, wherein the medicament is formulated for subcutaneous administration or intravenous administration.

19. The use according to any one of claims 1-18, wherein the medicament is provided as a kit.

20. A pharmaceutical composition comprising a myostatin-selective inhibitor and a GLP-1 receptor agonist;

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A; and

wherein the GLP-1 receptor agonist is capable of binding to and activating the GLP-1 receptor and comprises the amino acid sequence EGTFTSD (SEQ ID NO: 116) and/or the amino acid sequence HXXGXFTXD (SEQ ID NO: 117), wherein X is any amino acid residue.

21. The pharmaceutical composition of claim 20, wherein the GLP-1 receptor agonist is semaglutide, extended release exenatide, liraglutide, lixisenatide, tirzepatide, XW003, Noiiglutide, MEDI0382, dulaglutide, or albiglutide.

22. A pharmaceutical composition comprising a myostatin-selective inhibitor and a GLP-1 receptor agonist;

wherein the myostatin-selective inhibitor is a myostatin-selective antibody or antigen-binding fragment thereof that binds to myostatin and exhibits no detectable binding or potency towards GDF11 or Activin A; and

wherein the GLP-1 receptor agonist is a GLP-1/GIP/glucagon receptor triple agonist.

23. The pharmaceutical composition according to any one of claims 20-22, wherein the myostatin-selective inhibitor is trevogrumab, GYM329, MST1032, or an antigen-binding fragment thereof, or an antibody or antigen-binding fragment that competes or cross-competes with trevogrumab, GYM329, MST1032, or apitegromab.

24. The pharmaceutical composition according to any one of claims 20-23, wherein the myostatin-selective inhibitor and the GLP-1 receptor agonist are part of a single molecular construct.

25. A kit comprising the pharmaceutical composition of any one of claims 20-24.