CLAIMS

1. Use of a polypeptide comprising a fibronectin type III tenth (^{10}Fn3) domain which binds to myostatin in the manufacture of a medicament in:
(a) improving glycemic control in a human patient ; or

(b) treating, preventing, or reducing overweight or obesity and related comorbidities in a human patient; or

(c) treating or preventing type II diabetes in a human patient,
wherein the use comprises said polypeptide to be administered to the patient.

2. The use according to claim 1, wherein the patient has:
(a) a BMI >= 30 kg/m2; or

(b) a BMI >= 25 and < 30 kg/m2; or

(c) a BMI < 25.

3. The use according to any one of the preceding claims, wherein the polypeptide is to be administered as a formulation comprising
(i) at least 10 mg/mL of the polypeptide;
(ii) a disaccharide at a concentration of at least 5%;
(iii) a histidine buffer at a concentration of between about 20 to about 60 mM; and
(iv) a pharmaceutically acceptable aqueous carrier,
wherein the formulation has a pH range of about 6.5 to about 7.8,

optionally wherein:
(a) the polypeptide concentration in the formulation is between about 10 mg/mL and 200 mg/mL, between about 10 mg/mL and 150 mg/mL, or between about 10 mg/mL and 85 mg/mL; and/or.

(b) the disaccharide is present at weight (w/w) ratio of at least 5:1 protein to sugar; and/or

(c) the formulation comprises about 5% to about 30% of the disaccharide.

4. The use according to claim 3, wherein:

(a) the concentration of the disaccharide is about 150 mM to about 800 mM, or about 300 to about 700 mM; and/or

(b) the disaccharide is trehalose, and the formulation comprises about 5 to about 30% trehalose, about 15% to about 25% trehalose, or
about 20% to about 25% trehalose; and/or

(c) the disaccharide is trehalose dehydrate, and the concentration of trehalose dihydrate in the formulation is about 150 mM to about 800 mM, about 300 to about 700 mM, about 150 mM, about 200 mM, about 250 mM, about 300 mM, about 350 mM, about 400 mM, about 450 mM, about 500 mM, about 550 mM, about 575 mM, about 600, about 625 mM, about 650 mM, about 675 mM or about 700 mM; and/or

(d) the histidine is present at a concentration of at least 20 mM; and/or

(e) the viscosity of the formulation is from about 5 to 20 cps, from about 5 to 15 cps, or from about 7 to 12 cps; and/or

(f) the pH is about 6.6 to 7.6, about 6.8 to 7.4, or about 7.0 to 7.3; and/or

(g) the formulation comprises a surfactant at a concentration of between about 0.01% and 0.5%; and/or

(h) the formulation comprises a chelator, wherein the concentration of the chelator is between about 0.01 mM and about 0.5 mM or between about 0.05 mM and 0.2 mM, and wherein the chelator is selected from the group consisting of DPTA, EDTA and EGTA.

5. The use according to claim 3 or claim 4, wherein the formulation comprises:

(a) about 10-140 mg/mL of the polypeptide;
about 5-25% trehalose dihydrate;
about 20-30 mM histidine; and
a pharmaceutically acceptable aqueous carrier,
wherein the pH of the formulation is about 6.8 to 7.3;

(b) about 10-140 mg/mL of the polypeptide;
about 5-25% trehalose dihydrate;
about 20-30 mM histidine;
about 0.02-0.06 mM DTPA;
about 0.01-0.05% polysorbate 80; and
a pharmaceutically acceptable aqueous carrier,
wherein the pH of the formulation is about 6.8 to 7.3;

(c) about 10-140 mg/mL of the polypeptide;
about 600 mM trehalose dihydrate;
25-30 mM histidine; and
a pharmaceutically acceptable aqueous carrier,
wherein the pH of the formulation is about 7.0 to 7.3;

(d) about 10-140 mg/mL of the polypeptide;
about 600 mM trehalose dihydrate;
25-30 mM histidine;
about 0.02-0.06 mM DTPA;
about 0.01-0.05% polysorbate 80; and
a pharmaceutically acceptable aqueous carrier,
wherein the pH of the formulation is about 7.0 to 7.3;

(e) about 10-75 mg/mL of the polypeptide;
about 5-25% trehalose dihydrate;
about 20-30 mM histidine; and
a pharmaceutically acceptable aqueous carrier,
wherein the pH of the formulation is about 6.8 to 7.3;

(f) about 10-75 mg/mL of the polypeptide;

about 5-25% trehalose dihydrate;

about 20-30 mM histidine;

about 0.02-0.06 mM DTPA;

about 0.01-0.05% polysorbate 80; and

a pharmaceutically acceptable aqueous carrier,

wherein the pH of the formulation is about 6.8 to 7.3; or

(g) about 10-75 mg/mL of the polypeptide;

about 600 mM trehalose dihydrate;

about 30 mM histidine;

about 0.05 mM DTPA;

about 0.02% polysorbate 80;

a pharmaceutically acceptable aqueous carrier,

wherein the pH of the formulation is about 7.1.

6. The use according to claim 3, wherein the polypeptide is to be administered as a unit dosage form comprising about 1.0 mL or less of a formulation comprising,

(i) about 10-75 mg/mL of the polypeptide;

(ii) about 5-25% trehalose dihydrate;

(iii) about 20-30 mM histidine;

(iv) about 0.02-0.06 mM DTPA;

(v) about 0.01-0.05% polysorbate 80; and

(vi) a pharmaceutically acceptable aqueous carrier,

wherein the pH of the formulation is about 6.8 to 7.3.

7. The use according to any one of the preceding claims, wherein:

(a) the ^{10}Fn3 domain comprises BC, DE, and FG loops, and wherein at least one loop of the BC, DE, and FG loops has 0, 1, 2, or 3 amino acid substitutions relative to the respective BC, DE, and FG loops set forth in SEQ ID NOs: 5, 6 and 7**,** respectively;

and/or

(b) the ^{10}Fn3 domain comprises the amino acid sequence set forth in SEQ ID NO: 8; and/or

(c) the polypeptide comprises the amino acid sequence set forth SEQ ID NO: 11; and/or

(d) the polypeptide comprises the amino acid sequence set forth SEQ ID NO: 78; and/or

(e) the polypeptide is to be administered as a repeated subcutaneous injection; and/or

(f) the polypeptide is to be administered at a dosing interval of

(i) once a week; or

(ii) once every two weeks; or

(iii) once a month; and/or

(g) the polypeptide is to be administered at a dose of approximately 5 - 200mg; and/or

(h) central adiposity is reduced.

8. The use according to any one of claims 1(b) and 2 to 7, wherein the overweight or obesity related comorbidity is selected from the group consisting of type 2 diabetes, glucose intolerance, prediabetes, insulin resistance, hypertension, dyslipidemia, increased waist circumference, cardiovascular disease, non-alcoholic fatty liver disease, obstructive sleep apnea, physical impairment, osteoarthritis, osteoporosis, renal disease, sexual hormone(s) impairment, endocrine reproductive disorders such as polycystic ovary syndrome or male hypogonadism, stroke, and gallstones.

9. The use according to any one of claims 1(a) and 2 to 8, wherein an improvement in glycemic control is achieved by improving insulin sensitivity.

10. The use according to any one of claims 1(a), 1(b) and 2 to 9, wherein the patient has type II diabetes.

11. The use according to any one of claims 1(c) and 2 to 10, wherein the treatment results in an improvement in a Diabetes Treatment Satisfaction Questionnaire (DTSQ) score or Impact of Weight on Quality of Life (IWQOL) score.

12. The use according to any one of the preceding claims, wherein the treatment results in:

(a) a decrease in total body fat mass (FM) of at least 5 kg by week 48 compared to baseline, optionally wherein FM is assessed by dual-energy x-ray absorptiomery (DXA); and/or

(b) at least 5% decrease in total body fat mass (FM) by week 48 compared to baseline; optionally wherein FM is assessed by dual-energy x-ray absorptiomery (DXA); and/or.

(c) an at least 5% decrease in body weight by week 48 compared to baseline; and/or

(d) an at least 2% increase in body lean mass (LM) by week 48 compared to baseline, optionally

wherein LM is assessed by dual-energy x-ray absorptiometry (DXA); and/or

(e) a decrease in waist circumference (WC) and/or waist-to-hip ratio by week 48 compared to baseline; and/or

(f) a decrease in subcutaneous and abdominal visceral adipose tissue by week 48 compared to baseline; and/or

(g) an improvement in diabetes status by week 48 compared to baseline, optionally

wherein the improvement in diabetes status is assessed by HbA1c, Homeostatic Model Assessment (HOMA), quantitative insulin-sensitivity check index (QUICKI), and/or Matsuda Index; and/or

(h) a shift toward normal levels of one or more biomarkers selected from the group consisting of serum lipids, high-sensitivity C-reactive protein (hs-CRP), interleukin 6, leptin, and adiponectin, by week 48 compared to baseline; and/or

(i) an improvement in hand grip strength by week 48 compared to baseline, as assessed by dynamometry.

13. A kit for:

(a) improving glycemic control in a human patient; or

(b)

treating, preventing, or reducing obesity and related comorbidities in a human patient; or

(c) treating or preventing type II diabetes in a human patient, wherein the kit comprises:

(i) a dose of a polypeptide comprising a fibronectin type III tenth (^{10}Fn3) domain which binds to myostatin, wherein the ^{10}Fn3 domain comprises BC, DE, and FG loops, and wherein at least one loop of the BC, DE, and FG loops has 0, 1, 2, or 3 amino acid substitutions relative to the respective BC, DE, and FG loops set forth in SEQ ID NOs: 5, 6 and 7, respectively, and

(ii) instructions for using the polypeptide in the use of any one of the preceding claims.

14. The kit of claim13, wherein:

(a) the ^{10}Fn3 domain comprises the amino acid sequence set forth in SEQ ID NO:8; or

(b) the polypeptide comprises the amino acid sequence set forth SEQ ID NO:11; or

(c) the polypeptide comprises the amino acid sequence set forth SEQ ID NO: 78; or

the polypeptide is for to be administered as a unit dosage form comprising about 1.0 mL or less of a formulation comprising,

(i) about 10-75 mg/mL of the polypeptide;

(ii) about 5-25% trehalose dihydrate;

(iii) about 20-30 mM histidine;

(iv) about 0.02-0.06 mM DTPA;

(v) about 0.01-0.05% polysorbate 80; and

(vi) a pharmaceutically acceptable aqueous carrier,

wherein the pH of the formulation is about 6.8 to 7.3.

15. The use according to claim 2, or a formulation thereof, in combination with one or more additional therapeutic agents, optionally wherein:

(a) the polypeptide or formulation thereof:

(i) and one or more therapeutic agents are to be co-administered simultaneously; or

(ii) is to be administered prior to the one or more additional therapeutic agents that is to be administered.

(iii) is to be administered after the one or more additional therapeutic agents that is to be administered; and/or

(b) the additional therapeutic agent is an anti-obesity medication, optionally

wherein the anti-obesity medication is:

(i) semaglutide; or

(ii) tirzepatide; and/or

(c) (i) the ^{10}Fn3 domain comprises the amino acid sequence set forth in SEQ ID NO: 8; or

(ii) the polypeptide comprises the amino acid sequence set forth SEQ ID NO:11; or

(iii) the polypeptide comprises the amino acid sequence set forth SEQ ID NO: 78.