

COMBINATION THERAPIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application Nos. 63/238,068 filed August 27, 2021, 63/301,012 filed January 19, 2022, and 63/333,351 filed April 21, 2022, the contents of which are incorporated by reference in their entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[0002] The contents of the electronic sequence listing (VRNS_009_03WO_SeqList_ST26.xml; Size: 10,557 bytes; date of Creation: August 25, 2022) are herein incorporated by reference in their entirety.

BACKGROUND

[0003] Treatment of metabolic disorders such as obesity remains elusive as the regulation of metabolism and fat storage involves complex biological feedback systems. To date, drugs effective in regulating metabolic dysfunction often exhibit several side effects, which limit their usefulness in patient populations, and in particular, in obese patient populations, who may require long term treatment. Thus, there is a need for additional compositions and methods to treat metabolic disorders including obesity.

SUMMARY

[0004] The disclosure relates to the dual administration of ActRII pathway agents, *e.g.*, ActRII receptor antagonists, *e.g.*, ActRII receptor antibodies, and glucagon-like peptide-1 receptor (GLP-1) agonists for the treatment of metabolic disorders. The combination treatments of the disclosure comprising an ActRII pathway antibody and a GLP-1 agonist were found to reduce fat mass and maintain or increase lean mass. The combination treatments provided herein may improve metabolic dysfunction by reducing fat mass, increasing lean mass, improving glycemic control, and may also improve the tolerability and/or efficacy of one or both of these agents in subjects.

[0005] Provided herein are methods of treating a metabolic disorder in a subject, comprising administering to the subject in need thereof an ActRII receptor antibody and a glucagon-like peptide-1 receptor (GLP-1) agonist. In some examples, the metabolic disorder is selected from the group consisting of: obesity, diabetes, metabolic syndrome, anti-psychotic drug-associated obesity, glucocorticoid-induced obesity, hypothalamic obesity associated with craniopharyngioma, Prader-Willi syndrome, and a monogenetic disorder associated with obesity. In some examples, the diabetes is Type I diabetes or Type II diabetes.

[0005a] In an aspect, disclosed herein is the use of an ActRII receptor antibody in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the ActRII receptor antibody is to be administered

with a glucagon-like peptide-1 receptor (GLP-1) agonist.

[0005b] In another aspect, disclosed herein is the use of an ActRII receptor antibody in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the ActRII receptor antibody is to be administered with a GLP-1 agonist, wherein (i) the ActRII receptor antibody comprises: (a) the complementarity determining region (CDR) amino acid sequence of SEQ ID NOS: 1-6; and/or (b) the variable heavy chain amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and the variable light chain amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto; and wherein (ii) the GLP-1 agonist is a dual GLP-1 agonist and GIP agonist.

[0005c] In another aspect, disclosed herein is the use of an ActRII receptor antibody in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the ActRII receptor antibody is to be administered with a GLP-1 agonist, wherein: (i) the ActRII receptor antibody comprises: (a) the complementarity determining region (CDR) amino acid sequence of SEQ ID NOS: 1-6; and/or (b) the variable heavy chain amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and the variable light chain amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto; and wherein (ii) the GLP-1 agonist is semaglutide.

[0005d] In another aspect, disclosed herein is the use of a GLP-1 agonist in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the GLP-1 agonist is to be administered with an ActRII receptor antibody.

[0005e] In another aspect, disclosed herein is the use of a GLP-1 agonist in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the GLP-1 agonist is to be administered with an ActRII receptor antibody, wherein (i) the ActRII receptor antibody comprises: (a) the complementarity determining region (CDR) amino acid sequence of SEQ ID NOS: 1-6; and/or (b) the variable heavy chain amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and the variable light chain amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto; and wherein(ii) the GLP-1 agonist is a dual GLP-1 agonist and GIP agonist.

[0005f] In another aspect, disclosed herein is the use of a GLP-1 agonist in the manufacture of a medicament for treating a metabolic disorder in a subject, wherein the GLP-1 agonist is to be administered with an ActRII receptor antibody, wherein: (i) the ActRII receptor antibody comprises: (a) the complementarity determining region (CDR) amino acid sequence of SEQ ID NOS: 1-6; and/or (b) the variable heavy chain amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and the variable light chain amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto; and wherein (ii) the GLP-1 agonist is semaglutide.

[0006] In some examples, the monogenetic disorder associated with obesity, is one of Bardet-Biedl syndrome, or obesity resulting from mutations in one or more of the genes comprising: ADCY3, ALMS1, ARL6, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, BDNF, CCDC28B, CEP290,

CREBBP, EP300, GNAS, IER3IP1, MC3R, MKKS, MKS1, MRAP2, NTRK2, PCSK1, PHF6, POMC, SH2B1, SIM1, TMEM67, TRIM32, TTC8 and VPS13B.

[0007] In some examples, the treatment is useful for an obesity related co-morbidity, wherein the condition is selected from the group of: glucose intolerance, prediabetes, insulin resistance, high triglycerides, overweight associated physical impairment, osteoporosis, renal disease, obstructive sleep apnea, sexual hormones impairment, endocrine reproductive disorders, osteoarthritis, gastrointestinal cancers, dyslipidemia, hypertension, heart failure, coronary heart disease, stroke, and/or gallstones.

[0008] In some examples, the subject has a body mass index (BMI) of 30 or greater. In some examples, the subject has a BMI of 27 or greater and has one or more obesity-related co-morbidities. In some examples, the subject is overweight. In some examples, the subject is 18 years of age or older. In some examples, the subject is 45 years of age or older. In some examples, the subject is a child 0-17 years of age, inclusive.

[0009] In some examples, the treatment reduces body weight in the subject. In some examples, the treatment reduces fat mass in the subject. In some examples, the treatment increases lean mass in the subject. In some examples, the treatment reduces fat mass and increases lean mass in the subject. In some examples, the treatment reduces fat mass and maintains lean mass in the subject. In some examples, the treatment reduces central adiposity in the subject. In some examples, the treatment improves glycemic control in the subject.

[0010] In some examples, the treatment improves the safety, efficacy, and/or tolerability of the ActRII receptor antibody and/or the glucagon-like peptide-1 receptor (GLP-1) agonist.

[0011] In some examples, the efficacy of the treatment is measured by at least one of the following: body weight; bioelectrical impedance analysis (BIA); dual X-ray absorptiometry (DXA); waist circumference; decreased BMI; waist to hip ratio; wait to height ratio; blood lipids profile; leptin, adiponectin, and adipsin levels; urine biomarkers; hemoglobin A1c (HgbA1c) levels; hand dynamometry demonstrating muscle strength; glucose levels; insulin levels; short physical performance battery (SPPB); Impact of Weight on Quality of Life (IWQoL-Lite for CT) assessment; Short Form (36) Health Survey (SF-36) assessment; homeostasis model assessment 2 (HOMA2); and physical activity monitoring via actigraphy.

[0012] In some examples, the antibody comprises the amino acid sequence of SEQ ID NOS: 1-6. In some examples, the antibody comprises the amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and comprises the amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto. In some examples, the antibody comprises the amino acid sequence of SEQ ID NO: 9, or a sequence with sequence identity of at least 90% thereto; and comprises the amino acid sequence of SEQ ID NO: 10, or a sequence with sequence identity of at least 90% thereto.

[0013] In some examples, the antibody is specific for ActRIIA and ActRIIB.

[0014] In some examples, the GLP-1 agonist is an antibody, small molecule, peptide, or aptamer. In some examples, the GLP-1 agonist is selected from the group consisting of exenatide, exenatide extended-release, dulaglutide, liraglutide, lixisenatide, semaglutide, tirzepatide, cotadutide, noiiglutide, oxyntomodulin (e.g., mazdutide), retatrutide, albiglutide, beinaglutide and PEG-loxenate, pemvidutide, and danuglipron.

[0015] In some examples, the GLP-1 agonist is a dual GLP-1 agonist and GIP agonist. In some examples, the GLP-1 agonist is a dual GLP-1 agonist and GCG agonist. In some examples, the GLP-1 agonist is a triagonist of GIP/GLP-1/glucagon receptors.

[0016] In some examples, the ActRII receptor antibody is administered in a dose of about 3 mg/kg to about 50 mg/kg. In some examples, the ActRII receptor antibody is administered in a dose of about 10 mg/kg to about 30 mg/kg. In some examples, the ActRII receptor antibody is administered in a dose of about 10 mg/kg. In some examples, the ActRII receptor antibody is administered in a dose of about 30 mg/kg. In some examples, the ActRII receptor antibody is administered in a dose of about 200 mg to about 400 mg once weekly.

[0017] In some examples, the ActRII receptor antibody is administered in a dose of about 300 mg once weekly.

[0018] In some examples, the ActRII receptor antibody administration includes the administration of at least one loading dose of an ActRII receptor antibody at day 0 or week 0, prior to the administration of the ActRII receptor antibody and the GLP-1 agonist. In some examples, the loading dose of the ActRII receptor antibody is administered in a dose of about 10 mg/kg to about 30 mg/kg.

[0019] In some examples, the ActRII receptor antibody is administered at least once a day, at least once a week, at least twice a week, at least thrice a week, at least once every 2 weeks, at least once every 4 weeks, at least once every 6 weeks, or at least once every 12 weeks. In some examples, the ActRII receptor antibody is administered at week 0, at about week 4, and at least once every 12 weeks thereafter.

[0020] In some examples, the GLP-1 agonist is administered in a dose of about 0.005 mg to about 3.0 mg weekly. In some examples, the GLP-1 agonist dose is increased incrementally weekly from according to of the following regimens: from about 0.2 mg to about 3.0 mg, from about 0.1 to about 1.0 mg, from about 0.25 mg to about 2.4 mg, and from about 0.25 mg to about 0.5 mg. In some examples, the GLP-1 agonist dose is administered weekly in a dose of about 0.25 mg from about week 0 to about week 4, and in a dose of about 0.5 mg at week 5 and thereafter.

[0021] In some examples, the GLP-1 agonist dose is administered weekly in a dose of about 0.25 mg from about week 0 to about week 4, in a dose of about 0.5 mg from about week 5 to about week 8, in a dose of about 1.0 mg from about week 8 to about week 12, in a dose of about 1.7 mg from about week

12 to about week 15, in a dose of about 2.4 mg from about week 16 to about week 20, and a dose of about 2.4 mg from about week 20 and thereafter.

[0022] In some examples, the GLP-1 agonist dose is administered weekly in a dose of about 5.0 mg, about 10 mg, or about 15 mg.

[0023] In some examples, the ActRII receptor antibody and/or GLP-1 agonist are administered intravenously. In some examples, the ActRII receptor antibody and/or GLP-1 agonist are administered subcutaneously.

[0024] In some examples, the ActRII receptor antibody is administered prior to the GLP-1 agonist. In some examples, the ActRII receptor antibody is administered at least 12 weeks prior, at least 10 weeks prior, at least 8 weeks prior, at least 6 weeks prior, at least 4 weeks prior, at least 2 weeks prior, at least 1 week prior, at least 1 day prior, or at least 1 hour prior to the administration of the GLP-1 agonist.

[0025] In some examples, the GLP-1 agonist is administered prior to the ActRII receptor antibody. In some examples, the GLP-1 agonist is administered at least 2 weeks prior, at least 1 week prior, at least 5 days prior, at least 4 days prior, at least 2 days prior, at least 1 day prior, at least 6 hours prior, or at least 1 hour prior to the ActRII receptor antibody. In some examples, the ActRII receptor antibody and the GLP-1 agonist are co-administered.

[0026] Also provided herein is a combination comprising an ActRII receptor antibody and a GLP-1 agonist.

[0026a] In another aspect, disclosed herein is a combination comprising an ActRII receptor antibody and a GLP-1 agonist, wherein the ActRII receptor antibody comprises: (i) the complementarity determining regions (CDR) amino acid sequences of SEQ ID NOS: 1-6; and/or (ii) the variable heavy chain amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and the variable light chain amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto.

[0027] In some examples, the ActRII receptor antibody comprises the amino acid sequence of SEQ ID NOS: 1-6. In some examples, the ActRII receptor antibody comprises the amino acid sequence of SEQ ID NO: 7, or a sequence with sequence identity of at least 90% thereto; and comprises the amino acid sequence of SEQ ID NO: 8, or a sequence with sequence identity of at least 90% thereto. In some examples, the ActRII receptor antibody comprises the amino acid sequence of SEQ ID NO: 9, or a sequence with sequence identity of at least 90% thereto; and comprises the amino acid sequence of SEQ ID NO: 10, or a sequence with sequence identity of at least 90% thereto.

[0028] In some examples, the ActRII receptor antibody comprises a human IgG1 Fc domain with a modification selected from the group consisting of 259I, 252Y, 307Q, 308F, 428L, 434H, 434F, 434Y, 434A, 434M, and 434S, relative to a human IgG1 Fc domain according to the EU numbering scheme. In some examples, the ActRII receptor antibody comprises a human IgG1 Fc domain with a

modification selected from M428L and/or N434S relative to a human IgG1 Fc domain according to the EU numbering scheme.

[0029] Also provided herein is a pharmaceutical composition comprising the combination of an ActRII receptor antibody and a GLP-1 agonist, and a pharmaceutically acceptable excipient.

[0029a] In another aspect, disclosed herein is a pharmaceutical composition comprising the combination as defined herein and a pharmaceutically acceptable excipient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] **FIG. 1** is a schematic of a clinical study designed to compare the effects of an exemplary ActRII receptor antibody, bimagrumab, and a glucagon-like peptide-1 receptor (GLP-1) agonist, semaglutide, on fat loss, when given in combination or singly. The schematic includes a loading dose at week=0.

[0031] **FIG. 2** is an outline of the pre-clinical study of the effects of an ActRII receptor antibody and GLP1 agonists in diet-induced obese mice.

[0032] **FIG. 3** is a bar graph of the effects of the GLP1 agonist semaglutide and an ActRII receptor antibody, alone and in combination, on circulating Activin A in diet-induced obese mice.

[0033] **FIGS. 4A-4C** are bar graphs of the effects of the GLP1 agonist semaglutide and an ActRII receptor antibody, alone and in combination, on fat mass measured by MRI, inguinal fat weight measured post mortem at the end of the study, and circulating leptin levels in diet-induced obese mice.

[0034] **FIG. 5** is a bar graph of the effects of the GLP1 agonist semaglutide and an ActRII receptor antibody, alone and in combination, on lean muscle mass in diet-induced obese mice, assessed by weighing a gastrocnemius muscle post-mortem at the end of the study.

[0035] **FIG. 6** is a chart of mRNA transcript level changes, as assessed by RNAseq, in response to the combination of the GLP1 agonist semaglutide and an ActRII receptor antibody, in the inguinal fat of diet-induced obese mice.

[0036] **FIG. 7** is a line plot of the effects of the GLP1 agonists semaglutide, tirzepatide, and liraglutide, alone and in combination with an ActRII receptor antibody, on body weight over time, with a change in dose of tirzepatide at day 11 in both tirzepatide groups to induce better food intake, in diet-induced obese mice.

[0037] **FIG. 8** is a line plot of the effects of the GLP1 agonists semaglutide, tirzepatide, and liraglutide, alone and in combination with an ActRII receptor antibody, on body fat over time measured by MRI in diet-induced obese mice.