



(51) International Patent Classification:

C07K 16/46 (2006.01) A61K 47/68 (2017.01)

SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(21) International Application Number:

PCT/US2024/049607

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(22) International Filing Date:

02 October 2024 (02.10.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/587,503 03 October 2023 (03.10.2023) US

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))
- with sequence listing part of description (Rule 5.2(a))

(71) Applicant: **VETMAB BIOSCIENCES, INC.** [US/US];
3639 Midway Drive, Suite B #292, San Diego, California
92110 (US).

(72) Inventors: **ZHAN, Hangjun**; c/o Vetmab Biosciences, Inc., 3639 Midway Drive, Suite B #292, San Diego, California 92110 (US). **LONGPRE, Kristy**; c/o Vetmab Biosciences, Inc., 3639 Midway Drive, Suite B #292, San Diego, California 92110 (US). **BEVERS, Denise**; c/o Vetmab Biosciences, Inc., 3639 Midway Drive, Suite B #292, San Diego, California 92110 (US).

(74) Agent: **WHITING, Adam K.**; c/o FisherBroyles, LLP, 4100 Redwood Rd. 20A-203, Oakland, California 94619 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE,

(54) Title: LONG-ACTING GLUCAGON-LIKE PEPTIDE 1 RECEPTOR (GLP1R) AGONISTS FOR VETERINARY USE

(57) Abstract: Provided are various embodiments relating to a GLP1R agonist or a dual agonist that specifically binds canine, feline, and/or equine GLP1R, or Glucagon receptor/GIPR. Such agonists can be used alone or in combination in methods to treat canine, feline, and/or equine metabolic disorders, such as high glucose, obesity, osteoarthritis, improved cardiovascular outcomes, and for the extension of healthy aging.



LONG-ACTING GLUCAGON-LIKE PEPTIDE 1 RECEPTOR (GLP1R) AGONISTS FOR VETERINARY USE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority benefit of U.S. Provisional Patent Application No. 63/587,503, filed on October 3, 2023, the entirety of which is incorporated herein by reference.

FIELD

[0002] This disclosure relates to long-acting glucagon-like peptide one receptor (GLP1R) agonists, and their uses, for example, use for treating or regulating canine, feline, and equine metabolic disorders, such as high glucose, obesity, cardiovascular outcomes, osteoarthritis, and for the extension of healthy aging. The long-acting GLP1R agonists can also include long-acting oxyntomodulin (OXM), and/or dual receptor agonists of GLP1R/GIP or GLP1R/Glucagon.

REFERENCE TO SEQUENCE LISTING

[0003] The official copy of the Sequence Listing is submitted concurrently with the specification via USPTO Patent Center as an WIPO Standard ST.26 formatted XML file with file name "20136-002PV1.xml", a creation date of October 3, 2023, and a size of 31,959 bytes. This Sequence Listing filed via USPTO Patent Center is part of the specification and is incorporated in its entirety by reference herein.

BACKGROUND

[0004] Natural glucagon-like peptide one receptor (GLP1R) agonist is a polypeptide, with a short duration of action due to short *in vivo* half-life. GLP1R agonists mimic the hormone glucagon-like peptide 1 (GLP1) by stimulating the production of insulin when glucose levels rise and decreasing glucagon release (1). Because of this activity GLP1R agonists are prescribed for treatment of type 2 diabetes. There are at least six GLP1R agonists on the market with similar modes of action for the treatment of type 2 diabetes: exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide and semaglutide. The additional effects of GLP1R agonists including weight loss, slowing gastric emptying, satiation and reduction in calorie intake, have made GLP1R agonists like liraglutide and semaglutide some of the most efficacious weight loss drugs in clinical trials to date (1–3). In several meta-analysis studies, GLP1 agonists also showed improvement in cardiovascular outcomes (4–6). Further, in a recent study using a mouse OA model to evaluate liraglutide for the treatment of osteoarthritis (OA), found there was a dose dependent analgesic and anti-inflammatory effect (7).

[0005] Like humans, dogs suffer from weight gain, obesity, cardiovascular disease, and osteoarthritis. We propose that GLP1R agonists will be an effective treatment for these diseases. The mechanism of action for GLP1R agonists in dogs is slightly different than

humans as the main function of GLP1 in dogs is to stimulate glucose uptake rather than insulin release (8), to reduce blood glucose levels. Several studies in pre-diabetic/diabetic dog models with GLP-1/GLP-1 agonists have been completed as part of the development and understanding of diabetes treatments for humans, that confirm the mechanism of action for GLP1R agonists in the dog, safety of GLP1R agonists in the dog, and efficacy of GLP-1/GLP-1 agonists to reduce blood glucose levels in the dog (9–13). When aging, insulin resistance increase resulting in older individuals having higher rates of type 2 diabetes, however the impacts of GLP-1 on lowering blood sugar and increasing overall glycemic control suggests that GLP-1 may be able to suppress age-related metabolic problems which play a key role in the aging process. In combination with the linked neuroprotective properties, which suggests GLP-1 agonists may aid in age-related neurodegeneration, it has been suggested that GLP-1 agonists may be able to be given to aid in the extension of healthy aging (14).

[0006] Obesity is an increasing problem for our pets. Humans often share food or provide high calorie snacks resulting in approximately 59% of dogs classified as overweight in 2022 (15, 16). As GLP1R agonists are effective weight loss treatment for humans, data also suggests that they may be effective for overweight dogs. In a study evaluating the chronic effects of exenatide in a pre-diabetic canine model fed a high fat diet, body weight loss was observed in exenatide animals, in spite of no change on food consumption, fasting glycemia, and insulinemia (9). In another study evaluating an oral GLP1R agonist using a obesity and insulin resistance dog model, found that daily dosing with the GLP1R agonist resulted in decreased blood glucose excursions, body weight loss, and delayed gastric emptying in treated dogs (17). Although these studies utilize pre-diabetic/diabetic dogs, and it is not clear if the GLP1/GLP1R agonists used were caninized, these findings suggest that GLP1R agonists are able to reduce blood glucose and may be a treatment for obesity and weight gain in obese dogs.

[0007] Treatment with GLP-1/GLP-1 receptor agonists in canine cardiovascular disease models have shown improvement in cardiovascular outcomes. In multiple studies evaluating GLP1 amide (a cleavage product of GLP1 peptide) infusion treatment on dilated cardiomyopathy (DCM) found that GLP1 amide treatment was associated with improvements in myocardial glucose uptake, myocardial insulin responsiveness (MIR), improvements in contractility, ventricular performance in dogs with DCM (18, 19, 20). Treatment with liraglutide (GLP1 analog) in a atrial fibrillation canine model found that dogs treated with liraglutide was able to increase the conduction velocity, shorten the atrial effective refractory period, and suppress atrial fibrillation inducibility (21). These studies suggest that treatment with GLP1R agonists may be a beneficial treatment for DCM and/or other cardiovascular diseases.

[0008] GLP1R agonists may be an effective treatment for osteoarthritis (OA) in dogs. OA is a loss of function disease associated with pain. Currently there are no treatments for OA in dogs, however there are several medications to aid in the pain associated with the disease. Dogs with OA often become more sedentary, resulting in weight gain which, in turn, worsens OA and

associated joint pain. In a study evaluating the analgesic and anti-inflammatory properties of liraglutide found that in both mice and human OA patients, that GLP1R is expressed in cartilage and the synovial membrane (7). Treatment of chondrocytes and macrophage cells with liraglutide resulted in a dose-dependent anti-inflammatory effect. Additionally, using an OA mouse model where mice were treated with an intra-articular injection of liraglutide, results showed improved synovitis severity score. When the study was completed again for a longer duration and compared to dexamethasone, it was determined that liraglutide treatment was a more efficient analgesic than dexamethasone. In another study evaluating the protective effects of liraglutide on cartilage using an OA rat model, found that liraglutide treatment reduced cartilage degeneration (22). Like liraglutide, other GLP1R agonists may have similar anti-inflammatory effects that could make them an effective treatment for osteoarthritis. For obese humans and dogs, weight loss is seen as one of the most effective treatments for OA. As presented previously, GLP1R agonists have been shown to reduce weight in both humans and dogs, thus, a likely secondary outcome of weight loss will be reduction in OA pain.

SUMMARY

[0009] The present disclosure relates generally to GLP1R agonist molecules that are species-specific for canine, feline, or equine GLP1R, and the use of these agonists in compositions and methods for treating canine, feline, and equine subjects for high glucose, obesity, cardiovascular outcomes, and osteoarthritis. This summary is intended to introduce the subject matter of the present disclosure, but does not cover each and every embodiment, combination, or variation that is contemplated and described within the present disclosure. Further embodiments are contemplated and described by the disclosure of the detailed description, drawings, and claims.

[0010] In at least one embodiment, the present disclosure provides a GLP1R agonist of canine, feline, or equine GLP1R, wherein the agonist comprises a fusion comprising: (i) a species-specific IgG Fc region polypeptide, wherein the Fc region polypeptide comprises a Y at position 252 (Eu numbering); and (ii) a GLP1 polypeptide, an Extendin-4 polypeptide, or an OXM polypeptide.

[0011] In at least one embodiment of the GLP1R agonist of the present disclosure, the species-specific IgG Fc region polypeptide further comprises an A at positions 234 and 235 (Eu numbering).

[0012] In at least one embodiment of the GLP1R agonist of the present disclosure, the fusion comprises: (a) a wild-type GLP1 polypeptide of SEQ ID NO: 1; (b) a variant GLP1 polypeptide of SEQ ID NO: 2; (c) an OXM polypeptide of SEQ ID NO: 3, or a functional variant thereof; or (d) an Extendin-4 polypeptide of SEQ ID NO: 5, or a functional variant thereof.

[0013] In at least one embodiment of the GLP1R agonist of the present disclosure, the species-specific IgG Fc region polypeptide is attached to the GLP1 polypeptide, Extendin-4 polypeptide,

or OXM polypeptide via a first polypeptide linker; optionally, wherein the first polypeptide linker comprises an amino acid sequence selected from SEQ ID NO: 28 and 29

[0014] In at least one embodiment of the GLP1R agonist of the present disclosure, the agonist is a dual agonist and further comprises: (iii) a G1P polypeptide, or a Glucagon polypeptide.

[0015] In at least one embodiment of the GLP1R agonist of the present disclosure, the G1P polypeptide, or a Glucagon polypeptide is attached to the species-specific IgG Fc region polypeptide via a second polypeptide linker; optionally, wherein the second polypeptide linker comprises an amino acid sequence selected from SEQ ID NO: 28 and 29.

[0016] In at least one embodiment of the GLP1R agonist of the present disclosure, the agonist is: (a) a canine agonist or a canine dual agonist comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 8, 12, 16, 20, and 24; (b) a feline agonist or a feline dual agonist comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to a sequence selected from SEQ ID NO: 9, 13, 17, 21, and 25; the agonist is an equine agonist or an equine dual agonist comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 10, 11, 14, 15, 18, 19, 22, 23, 26, and 27.

[0017] In at least one embodiment, the present disclosure also provides an isolated nucleic acid or a vector encoding a GLP1R agonist of the present disclosure.

[0018] In at least one embodiment, the present disclosure also provides an isolated host cell comprising the nucleic acid or a vector encoding a GLP1R agonist of the present disclosure.

[0019] In at least one embodiment, the present disclosure also provides a method of producing a GLP1R agonist of the present disclosure, the method comprising culturing a host cell comprising the nucleic acid or a vector encoding a GLP1R agonist and isolating the agonist.

[0020] In at least one embodiment, the present disclosure also provides a pharmaceutical composition comprising a GLP1R agonist of the present disclosure and a pharmaceutically acceptable carrier.

[0021] In at least one embodiment, the present disclosure also provides a method of treating a canine, feline, or equine subject having a condition associated with GLP1, the method comprising administering to the canine, feline or equine subject a therapeutically effective amount of a species-specific GLP1R agonist of the present disclosure, or a pharmaceutical composition comprising a GLP1R agonist of the present disclosure.

[0022] In at least one embodiment, the present disclosure also provides a method of maintaining remission of a condition associated with GLP1 in a canine, feline, or equine subject, the method comprising administering to the canine a therapeutically effective amount

of a GLP1R agonist of the present disclosure, or a pharmaceutical composition comprising a GLP1R agonist of the present disclosure.

[0023] In at least one embodiment of the method, the condition associated with GLP1 is a metabolic disorder; optionally, wherein the metabolic disorder is associated with high glucose, obesity, poor cardiovascular outcome, and/or aging.

[0024] In at least one embodiment of the method, the condition associated with GLP1 is glucose dysregulation disease.

[0025] In at least one embodiment of the method, the condition associated with GLP1 is obesity or being overweight.

[0026] In at least one embodiment of the method, the condition associated with GLP1 is cardiovascular disease.

[0027] In at least one embodiment of the method, the condition associated with GLP1 is an age-related disorder; optionally, wherein the condition is age-related neurodegeneration.

[0028] In at least one embodiment, the present disclosure also provides a method of treating a canine, a feline, or an equine subject having a condition associated with GLP1R agonist activity, the method comprising administering to the canine, feline, or equine subject a therapeutically effective amount of the species-specific GLP1R agonist of the present disclosure, or the pharmaceutical composition comprising a GLP1R agonist of the present disclosure.

[0029] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or pharmaceutical composition is administered parenterally.

[0030] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition is administered by an intramuscular route, an intraperitoneal route, an intracerebrospinal route, a subcutaneous route, an intra-arterial route, an intrasynovial route, an intrathecal route, or an inhalation route.

[0031] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition is administered at an amount in the range of 0.0001 mg/kg body weight to 100 mg/kg body weight per dose.

[0032] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of the agonist or the pharmaceutical composition is administered in a per dose amount of at least about 0.025 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.075 mg/kg body weight, at least about 0.10 mg/kg body weight, at least about 0.125 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1.0 mg/kg body weight, at least about 1.25 mg/kg body weight, at least about 1.5 mg/kg body weight, at least about 1.75 mg/kg body weight, at least about 2.0 mg/kg body weight, or at least about 2.5 mg/kg body weight.

[0033] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount of about 0.025 mg/kg body weight to about 2.5 mg/kg body weight, about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

[0034] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount at an interval of: daily, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, weekly, semi-monthly, or monthly.

[0035] In at least one embodiment of the methods of the present disclosure, the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered weekly in a per dose amount of about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

[0036] Various other embodiments of the inventions provided by the present disclosure include, but are not limited to:

[0037] Embodiment 1. A long-acting GLP1R agonist of canine, feline, or equine GLP1R, wherein the agonist comprises a fusion comprising: (i) a species-specific IgG Fc region polypeptide, wherein the Fc region polypeptide comprises a Y at position 252 (Eu numbering); (ii) a first polypeptide linker; and (iii) a GLP1 polypeptide, an Extendin-4 polypeptide, or an OXM polypeptide.

[0038] Embodiment 2. A long-acting GLP1R agonist that specifically binds to feline GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) a GLP1 peptide of SEQ ID NO: 1 or a variant GLP1 polypeptide of SEQ ID NO: 2; (ii) a first polypeptide linker; and (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; optionally, wherein the GLP1R agonist comprises an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 9, 13, 17, 21, and 25.

[0039] Embodiment 3. A long-acting GLP1R agonist that specifically binds to equine GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) a GLP1 polypeptide of SEQ ID NO: 1 or a variant GLP1 polypeptide of SEQ ID NO: 2; (ii) a first polypeptide linker; and (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; optionally, wherein the GLP1R agonist comprises an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least

95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 10, 11, 14, 15, 18, 19, 22, 23, 26, and 27.

[0040] Embodiment 4. A long-acting GLP1R agonist that specifically binds to canine GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an extendin-4 polypeptide of SEQ ID NO: 5; (ii) a first polypeptide linker; and (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; optionally, wherein the GLP1R agonist comprises an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 8, 12, 16, 20, and 24.

[0041] Embodiment 5. A long-acting GLP1R agonist (e.g., SEQ ID NO: 17) that specifically binds to feline GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an Extendin-4 polypeptide of SEQ ID NO: 5; (ii) a first polypeptide linker; and (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0042] Embodiment 6. A long-acting GLP1R agonist (e.g., SEQ ID NO: 18 or SEQ ID NO: 19) that specifically binds to equine GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an extendin-4 polypeptide of SEQ ID NO: 5; (ii) a first polypeptide linker; and (iii) modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0043] Embodiment 7. A long-acting GLP1R_GCGR dual agonist (e.g., SEQ ID NO: 12) that specifically binds to canine GLP1R and canine GCGR, wherein the agonist is a polypeptide fusion comprising: (i) an OXM polypeptide of SEQ ID NO: 3; (ii) a polypeptide linker; and (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0044] Embodiment 8. A long-acting GLP1R_GCGR dual agonist (e.g., SEQ ID NO: 13) that specifically binds to feline GLP1R and GCGR, wherein the agonist is a polypeptide fusion comprising: (i) an OXM polypeptide of SEQ ID NO: 3; (ii) a polypeptide linker; and (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0045] Embodiment 9. A long-acting GLP1R_GCGR dual agonist (e.g., SEQ ID NO: 14 or SEQ ID NO: 15) that specifically binds to equine GLP1R and equine GCGR, wherein the agonist is a polypeptide fusion comprising: (i) an OXM peptide of SEQ ID NO: 3; (ii) a polypeptide linker; and (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0046] Embodiment 10. A long-acting GLP1R agonist (e.g., SEQ ID NO: 16) that specifically binds to canine GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an extendin-4 polypeptide of SEQ ID NO: 5; (ii) a polypeptide linker; and (iii) a modified canine IgG with

long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0047] Embodiment 11. A long-acting GLP1R agonist (e.g., SEQ ID NO: 17) that specifically binds to feline GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an extendin-4 polypeptide of SEQ ID NO: 5; (ii) a polypeptide linker; and (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0048] Embodiment 12. A long-acting GLP1R agonist (e.g., SEQ ID NO: 18 and SEQ ID NO: 19) that specifically binds to equine GLP1R, wherein the agonist is a polypeptide fusion comprising: (i) an extendin-4 polypeptide of SEQ ID NO: 5; (ii) a polypeptide linker; and (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0049] Embodiment 13. A long-acting GLP1R_Glucagon receptor dual agonist (e.g., SEQ ID NO: 20) that specifically binds to canine GLP1R and glucagon receptor, wherein the dual agonist is a polypeptide fusion comprising: (i) a GLP1 polypeptide of SEQ ID NO: 2; (ii) a first polypeptide linker; (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a glucagon peptide SEQ ID NO: 4.

[0050] Embodiment 14. A long-acting GLP1R_Glucagon receptor dual agonist (e.g., SEQ ID NO: 21) that specifically binds to feline GLP1R and glucagon receptor, wherein the dual agonist is a polypeptide fusion comprising: (i) a GLP1 polypeptide SEQ ID NO: 2; (ii) a first polypeptide linker; (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a glucagon peptide SEQ ID NO: 4.

[0051] Embodiment 15. A long-acting GLP1R_Glucagon receptor dual agonist (e.g., SEQ ID NO: 22 or SEQ ID NO: 23) that specifically binds to equine GLP1R and glucagon receptor, wherein the dual agonist is a polypeptide fusion comprising: (i) a GLP1 polypeptide of SEQ ID NO: 2; (ii) a first polypeptide linker; (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a glucagon polypeptide SEQ ID NO: 4.

[0052] Embodiment 16. A long-acting GLP1R_G1P receptor dual agonist (e.g., SEQ ID NO: 24) that specifically binds to canine GLP1R and G1P receptor, wherein the dual agonist is a polypeptide fusion comprising: (i) a GLP1 peptide SEQ ID NO: 2; (ii) a first polypeptide linker; (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0053] Embodiment 17. A long-acting GLP1R_G1P receptor dual agonist (e.g., SEQ ID NO: 25) that specifically binds to feline GLP1R and G1P receptor, wherein the dual agonist is a

polypeptide fusion comprising: (i) a GLP1 peptide SEQ ID NO: 2; (ii) a first polypeptide linker (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0054] Embodiment 18. A long-acting GLP1R_G1P receptor dual agonist (e.g., SEQ ID NO: 26 or 27) that specifically binds to equine GLP1R and G1P receptor, wherein the dual agonist is a polypeptide fusion comprising: (i) a GLP1 peptide SEQ ID NO: 2; (ii) a first polypeptide linker; (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions; and (iv) a second polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0055] Embodiment 19. An isolated nucleic acid or vector encoding a GLP1R agonist or dual agonist of any one of embodiments 1 to 18.

[0056] Embodiment 20. A host cell comprising the nucleic acid or vector of embodiment 19.

[0057] Embodiment 21. A method of producing a GLP1R agonist or dual agonist of any one of embodiments 1-18 comprising culturing a host cell of embodiment 20 and isolating the agonist.

[0058] Embodiment 22. A pharmaceutical composition comprising a GLP1R agonist or dual agonist of any one of embodiments 1 to 18 and a pharmaceutically acceptable carrier.

[0059] Embodiment 23. A method of treating a canine, feline and equine having a condition associated with GLP1, the method comprising administering to the canine, feline and equine a therapeutically effective amount of a GLP1R agonist or dual agonist of any one of embodiments 1 to 18 or the pharmaceutical composition of embodiment 22.

[0060] Embodiment 24. A method of maintaining remission of a condition associated with GLP1 in a canine, feline and equine, the method comprising administering to a therapeutically effective amount of a GLP1R agonist or dual agonist of any one of embodiments 1-18 or the pharmaceutical composition of embodiment 22.

[0061] Embodiment 25. The method of any one of embodiments 23-24, wherein the condition associated with GLP1 is a metabolic disorder; optionally, wherein the metabolic disorder is associated with high glucose, obesity, poor cardiovascular outcome, and/or aging.

[0062] Embodiment 26. The method of any one of embodiments 23-25, wherein the condition associated with GLP1 is a blood sugar dysregulation disease.

[0063] Embodiment 27. The method of any one of embodiments 23-26, wherein the condition associated with GLP1 is obesity, associated cardiovascular outcomes, osteoarthritis, and age-related disorders, such as age-related neurodegeneration.

[0064] Embodiment 28. The method of any one of embodiments 23-27, wherein the GLP1R agonist or dual agonist or the pharmaceutical composition is administered parenterally.

[0065] Embodiment 29. The method of any one of embodiments 23-28, wherein the GLP1R agonist or dual agonist or the pharmaceutical composition is administered by an intramuscular

route, an intraperitoneal route, an intracerebrospinal route, a subcutaneous route, an intra-arterial route, an intrasynovial route, an intrathecal route, or an inhalation route.

[0066] Embodiment 30. The method of any one of embodiments 23-29, wherein the GLP1R agonist or dual agonist is administered at an amount in the range of 0.0001 mg/kg body weight to 100 mg/kg body weight per dose.

[0067] Embodiment 31. The method of any one of embodiments 23-30, wherein the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of the agonist or the pharmaceutical composition is administered in a per dose amount of at least about 0.025 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.075 mg/kg body weight, at least about 0.10 mg/kg body weight, at least about 0.125 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1.0 mg/kg body weight, at least about 1.25 mg/kg body weight, at least about 1.5 mg/kg body weight, at least about 1.75 mg/kg body weight, at least about 2.0 mg/kg body weight, or at least about 2.5 mg/kg body weight.

[0068] Embodiment 32. The method of any one of embodiments 23-31, wherein the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount of about 0.025 mg/kg body weight to about 2.5 mg/kg body weight, about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

[0069] Embodiment 33. The method of any one of embodiments 23-32, wherein the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount at an interval of: daily, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, weekly, semi-monthly, or monthly.

[0070] Embodiment 34. The method of any one of embodiments 23-33, wherein the GLP1R agonist or the pharmaceutical composition, the therapeutically effective amount of agonist or the pharmaceutical composition is administered weekly in a per dose amount of about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0071] The present disclosure provides a detailed description, including examples, of GLP1R agonists that specifically bind to canine, feline, or equine GLP1R. The present disclosure also provides a detailed description, including examples, of GLP1R “dual agonists” that specifically bind to, and act as an agonist of, canine, feline, or equine GLP1R and also bind to, and act as an agonist of, either the canine, feline, or equine Glucagon receptor, or the canine, feline, or equine G1P receptor. The present disclosure provides various exemplary forms of these

agonists, including full-length sequences and uses of these agonists, including method of treatment of various diseases and disorders that are mediated or associated with the binding activity of GLP1R. Methods of designing, producing, or purifying agonists to canine, feline or equine GLP1R are also provided.

[0072] For the descriptions herein and the appended claims, the singular forms “a”, and “an” include plural referents unless the context clearly indicates otherwise. Thus, for example, reference to “a protein” includes more than one protein, and reference to “a compound” refers to more than one compound. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as “solely,” “only” and the like in connection with the recitation of claim elements, or use of a “negative” limitation. The use of “comprise,” “comprises,” “comprising” “include,” “includes,” and “including” are interchangeable and not intended to be limiting. It is to be further understood that where descriptions of various embodiments use the term “comprising,” those skilled in the art would understand that in some specific instances, an embodiment can be alternatively described using language “consisting essentially of” or “consisting of.”

[0073] Where a range of values is provided, unless the context clearly dictates otherwise, it is understood that each intervening integer of the value, and each tenth of each intervening integer of the value, unless the context clearly dictates otherwise, between the upper and lower limit of that range, and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of these limits, ranges excluding (i) either or (ii) both of those included limits are also included in the invention. For example, “1 to 50,” includes “2 to 25,” “5 to 20,” “25 to 50,” “1 to 10,” etc.

[0074] Generally, the nomenclature used herein and the techniques and procedures described herein include those that are well understood and commonly employed by those of ordinary skill in the art, such as the common techniques and methodologies described in e.g., Green and Sambrook, Molecular Cloning: A Laboratory Manual (Fourth Edition), Vols. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 2012 (hereinafter “Sambrook”); and Current Protocols in Molecular Biology, F. M. Ausubel et al., eds., originally published in 1987 in book form by Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., and regularly supplemented through 2011, and now available in journal format online as Current Protocols in Molecular Biology, Vols. 00 - 130, (1987-2020), published by Wiley & Sons, Inc. in the Wiley Online Library (hereinafter “Ausubel”).

[0075] All publications, patents, patent applications, and other documents referenced in this disclosure are hereby incorporated by reference in their entireties for all purposes to the same

extent as if each individual publication, patent, patent application or other document were individually indicated to be incorporated by reference herein for all purposes.

[0076] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the present invention pertains. It is to be understood that the terminology used herein is for describing particular embodiments only and is not intended to be limiting. For purposes of interpreting this disclosure, the following description of terms will apply and, where appropriate, a term used in the singular form will also include the plural form and vice versa.

[0077] “Full-length antibody,” “intact antibody,” or “whole antibody” are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0078] “Class” of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of human antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these are further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α , δ , ϵ , γ , and μ , respectively. Canine, feline, and equine species have different classes of antibodies that are shared by many other mammalian species. For example, canine species have antibody classes, IgGA, IgGB, IgGC, IgGD; feline species have antibody classes, IgGA1, IgGA2, IgGB; Equine IgG1, IgG2, IgG3, IgG4, IgG5, IgG6 and IgG7.

[0079] “Fc region,” refers to a dimer complex comprising the C-terminal polypeptide sequences of an immunoglobulin heavy chain, wherein a C-terminal polypeptide sequence is that which is obtainable by papain digestion of an intact antibody. The Fc region may comprise native or variant Fc sequences. The Fc sequence of an immunoglobulin generally comprises two constant domains, a CH2 domain and a CH3 domain, and optionally comprises a CH4 domain. The boundaries of the Fc sequence of an immunoglobulin heavy chain may vary depending on immunoglobulin class and species.

[0080] The term “IgX Fc” means the Fc region is derived from a particular antibody isotype (e.g., IgG, IgA, IgD, IgE, IgM, etc.), where “X” denotes the antibody isotype. Thus, “IgG Fc” denotes the Fc region of a γ chain, “IgA Fc” denotes the Fc region of an α chain, “IgD Fc” denotes the Fc region of a δ chain, “IgE Fc” denotes the Fc region of an ϵ chain, “IgM Fc” denotes the Fc region of a μ chain, etc. In some embodiments, the IgG Fc region comprises CH1, hinge, CH2, CH3, and CL1. “IgX-N-Fc” denotes that the Fc region is derived from a particular subclass of antibody isotype (such as canine IgG subclass A, B, C, or D; or feline IgG subclass 1, 2a, or 2b), where “N” denotes the subclass. In some embodiments, IgX Fc or IgX-N-Fc regions are derived from a companion animal, such as a dog. In some embodiments, IgG Fc regions are isolated from canine γ heavy chains, such as IgG-A, IgG-B, IgG-C, or IgG-D. Antibodies comprising an Fc region of IgG-A, IgG-B, IgG-C, or IgG-D may provide for higher

expression levels in recombination production systems. "IgX Fc" and "IgX Fc polypeptide" are intended to include wild-type IgX Fc polypeptides and variant IgX Fc polypeptides.

[0081] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: Clq binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

[0082] "Fusion polypeptide" as used herein, refers to two or more polypeptide molecules that are linked (or "fused") in a configuration that does not occur naturally. An exemplary fusion polypeptide of the present disclosure includes a "GLP1R agonists" which are a fusion comprising an GLP1 polypeptide covalently linked through a polypeptide linker at its C-terminus to the N-terminus of an IgG Fc region polypeptide.

[0083] "Polypeptide linker" or "polypeptide linker" as used herein refers to a chain of two or more amino acids with each end of the chain covalently attached to a different polypeptide molecule, thereby functioning to conjugate or fuse the different polypeptides.

[0084] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (e.g., an antibody) and its binding partner (e.g., an antigen).

"Binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (e.g., antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the equilibrium dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0085] "Binds specifically" or "specific binding" refers to binding of an antibody to an antigen with an affinity value of no more than about 1×10^{-7} M. In some embodiments, an antibody may have a secondary affinity for an antigen other than the antigen to which it binds specifically, where "secondary affinity" will generally refer to binding of an antibody to a secondary antigen with an affinity value of more than about 10 nM as described elsewhere herein. Where an antibody may have a secondary affinity for a secondary antigen, such an antibody will nevertheless bind specifically to the primary antigen.

[0086] As used herein, "percent (%) amino acid sequence identity" and "homology" with respect to a polypeptide, or antibody sequence are defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as

BLAST, BLAST-2, ALIGN, or MEGALINE™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of sequences being compared.

[0087] An “amino acid substitution” refers to the replacement of one amino acid in a polypeptide with another amino acid. In some embodiments, an amino acid substitution is a conservative substitution. Amino acid substitutions may be introduced into a molecule of interest and the products screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC or enhanced pharmacokinetics.

[0088] The term “vector” is used to describe a polynucleotide that can be engineered to contain a cloned polynucleotide or polynucleotides that can be propagated in a host cell. A vector can include one or more of the following elements: an origin of replication, one or more regulatory sequences (such as, for example, promoters or enhancers) that regulate the expression of the polypeptide of interest, or one or more selectable marker genes (such as, for example, antibiotic resistance genes and genes that can be used in colorimetric assays, for example, β -galactosidase). The term “expression vector” refers to a vector that is used to express a polypeptide of interest in a host cell.

[0089] A “host cell” refers to a cell that may be or has been a recipient of a vector or isolated polynucleotide. Host cells may be prokaryotic cells or eukaryotic cells. Exemplary eukaryotic cells include mammalian cells, such as primate or non-primate animal cells; fungal cells, such as yeast; plant cells; and insect cells. Nonlimiting exemplary mammalian cells include, but are not limited to, NS0 cells, PER.C6® cells (Crucell), 293 cells, and CHO cells, and their derivatives, such as 293-6E, DG44, CHO-S, and CHO-K cells. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) encoding an amino acid sequence(s) provided herein.

[0090] The term “companion animal species” refers to an animal suitable to be a companion to humans. In some embodiments, a companion animal species is a small mammal, such as a canine, feline, dog, cat, horse, rabbit, ferret, guinea pig, rodent, etc. In some embodiments, a companion animal species is a large animal like camel or farm animal, such as a horse, cow, pig, etc.

[0091] To “reduce” or “inhibit” means to decrease, reduce, or arrest an activity, function, or amount as compared to a reference. In some embodiments, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 20% or greater. In some embodiments, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 50% or greater. In some embodiments, by “reduce” or “inhibit” is meant the ability to cause an overall decrease of 75%, 85%, 90%, 95%, or greater. In some embodiments, the amount noted above is inhibited or

decreased over a period of time, relative to a control dose (such as a placebo) over the same period of time. A “reference” as used herein, refers to any sample, standard, or level that is used for comparison purposes. A reference may be obtained from a healthy or non-diseased sample. In some examples, a reference is obtained from a non-diseased or non-treated sample of a companion animal. In some examples, a reference is obtained from one or more healthy animals of a particular species, which are not the animal being tested or treated.

[0092] “Substantially similar” or “substantially the same,” as used herein, refers to a sufficiently high degree of similarity between two numeric values (for example, one associated with a test antibody and the other associated with a reference antibody), such that one of skill in the art would consider the difference between the two values to be of little or no biological and/or statistical significance within the context of the biological characteristic measured by said values (e.g., K_D values).

[0093] “Substantially different,” as used herein, refers to a sufficiently high degree of difference between two numeric values (generally one associated with a molecule and the other associated with a reference molecule) such that one of skill in the art would consider the difference between the two values to be of statistical significance within the context of the biological characteristic measured by said values (e.g., K_D values).

[0094] “Treatment,” “treat” or “treating” refers to intervention in an attempt to alter the natural course of a disorder in the individual being treated and can be performed either for prophylaxis or during the course of clinical pathology. Desired results of treatment can include, but are not limited to, preventing occurrence or recurrence of the disorder, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disorder, preventing metastasis, decreasing the rate of progression, amelioration or palliation of a disease state, and remission or improved prognosis. For example, treatment can include administration of a therapeutically effective amount of pharmaceutical formulation comprising a GLP1R agonist to a subject to delay development or slow progression of a disease or condition mediated by GLP1 or disease or condition in which GLP1 may play a role in reducing the pathogenesis and/or progression. Treatment does not require one-hundred percent removal of all aspects of the disorder.

[0095] “Pharmaceutical formulation” refers to a preparation in a form that allows the biological activity of the active ingredient(s) to be effective, and which contain no additional components which are toxic to the subjects to which the formulation is administered. A pharmaceutical formulation may include one or more active agents. For example, a pharmaceutical formulation may include a GLP1R agonist as the sole active agent of the formulation or may include a GLP1R agonist and one or more additional active agents.

[0096] “Pharmaceutically acceptable carrier” refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to the subject to whom it is

administered. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0097] “Therapeutically effective amount” refers to the amount of an active ingredient or agent (e.g., a pharmaceutical formulation) to achieve a desired therapeutic or prophylactic result, e.g., to treat or prevent a disease, disorder, or condition in a subject. In the case of a GLP1 mediated disease or condition, the therapeutically effective amount of the therapeutic agent is an amount that reduces, prevents, inhibits, and/or relieves to some extent one or more of the symptoms associated with the disease, disorder, or condition.

[0098] “Individual” or “subject” refers to a mammal, including but not limited to, domesticated or companion animals (e.g., cows, sheep, cats, dogs, and horses), primates (e.g., humans and non-human primates such as monkeys), rabbits, and rodents (e.g., mice and rats).

[0099] “Amino acid sequence,” means a sequence of amino acids residues in a peptide or protein. The terms “polypeptide” and “protein” are used interchangeably to refer to a polymer of amino acid residues and are not limited to a minimum length. Such polymers of amino acid residues may contain natural or non-natural amino acid residues, and include, but are not limited to, peptides, oligopeptides, dimers, trimers, and multimers of amino acid residues. Both full-length proteins and fragments thereof are encompassed by the definition. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. Furthermore, for purposes of the present disclosure, a “polypeptide” refers to a protein which includes modifications, such as deletions, additions, and substitutions (generally conservative in nature), to the native sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

[0100] The terms “heavy chain constant region” or “constant heavy chain” are used interchangeably to refer to a region comprising at least three heavy chain constant domains, CH1, CH2, and CH3. Nonlimiting exemplary heavy chain constant regions include γ , δ , α , ϵ , and μ . Each heavy chain constant region corresponds to an antibody isotype. For example, an antibody comprising a γ constant region is an IgG antibody, an antibody comprising a δ constant region is an IgD antibody, an antibody comprising an α constant region is an IgA antibody, an antibody comprising a μ constant region is an IgM antibody, and an antibody comprising an ϵ constant region is an IgE antibody. Certain isotypes can be further subdivided into subclasses. For example, IgG antibodies include, but are not limited to, IgG1 (comprising a γ_1 constant region), IgG2 (comprising a γ_2 constant region), IgG3 (comprising a γ_3 constant region), and IgG4 (comprising a γ_4 constant region) antibodies; IgA antibodies include, but are not limited to, IgA1 (comprising an α_1 constant region) and IgA2 (comprising an α_2 constant region) antibodies; and IgM antibodies include but are not limited to IgM1 and IgM2.

[0101] The terms “light chain constant region” or “constant light chain” are used interchangeably to refer to a region comprising a light chain constant domain, CL. Nonlimiting exemplary light chain constant regions include λ and κ . Non-function-altering deletions and alterations within the domains are encompassed within the scope of the term “constant region” unless designated otherwise. Canine, feline, and equine have antibody classes such as IgG, IgA, IgD, IgE, and IgM. Within the canine IgG antibody class are IgG-A, IgG-B, IgG-C, and IgG-D.

[0102] In some embodiments, a biological activity of an Fc polypeptide is the ability to bind FcRn. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind C1q. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind CD16. In some embodiments, a biological activity of an Fc polypeptide is the ability to bind protein A.

[0103] In some embodiments, a variant IgG Fc polypeptide comprises a variant IgG Fc polypeptide of a companion animal species. In some embodiments, a variant IgG Fc polypeptide comprises a variant canine IgG Fc polypeptide. In some embodiments, a variant IgG Fc polypeptide (e.g., a variant canine IgG-A Fc polypeptide, a variant canine IgG-C Fc polypeptide, or a variant canine IgG-D Fc polypeptide, variant feline IgG1a Fc polypeptide) has an activity that the reference (e.g., wild-type) polypeptide substantially lacks.

[0104] An IgG Fc region polypeptide, or fusion comprising an IgG Fc region polypeptide, may be modified to extend or shorten its half-life. In some embodiments involving a higher dose of antibody, a shorter half-life may be desirable for acute treatment. In some embodiments involving a lower dose of antibody, a longer half-life may be desirable for prolonged treatment. For example, as discussed below, mutations in IgG Fc that affect FcRn interactions may be introduced.

[0105] In some embodiments, a variant IgG Fc (e.g., a variant canine IgG Fc polypeptide) has modified FcRn binding affinity compared to a reference polypeptide. In some embodiments, a variant IgG Fc has increased FcRn binding affinity at an acidic pH (e.g., at a pH in the range of from about 5.0 to about 6.5, such as at a pH of about 5.0, a pH of about 5.5, a pH of about 6.0, or a pH of about 6.5) compared to a reference polypeptide.

[0106] In some embodiments, a variant has at least 1, 2, 3, 4, 5, or 6 amino acids substituted by a different amino acid.

[0107] In some embodiments, a variant has at least about 50% sequence identity with the reference nucleic acid molecule or polypeptide after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Such variants include, for instance, polypeptides wherein one or more amino acid residues are added, deleted, at the N- or C-terminus of the polypeptide. In some embodiments, a variant has at least about 50% sequence identity, at least about 60% sequence identity, at least about 65% sequence identity, at least about 70% sequence identity, at least about 75% sequence identity, at least about 80%

sequence identity, at least about 85% sequence identity, at least about 90% sequence identity, at least about 95% sequence identity, at least about 97% sequence identity, at least about 98% sequence identity, or at least about 99% sequence identity with the sequence of the reference nucleic acid or polypeptide.

[0108] In some embodiments, a GLP1R agonist may activate GLP1R signaling function in a companion animal species by at least 5%, 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%.

[0109] Long-Acting GLP1R Agonists

[0110] The present disclosure provides agonists of GLP1R that are species-specific for the canine, feline, or equine GLP1R protein. The GLP1R agonists have a novel fusion polypeptide structure, wherein the fusion comprises the following component polypeptides: (i) a species-specific IgG Fc region polypeptide, wherein the Fc region polypeptide comprises a Y at position 252 (Eu numbering); (ii) a first polypeptide linker; and (iii) a GLP1 polypeptide, an Extendin-4 polypeptide, or an OXM polypeptide.

[0111] The present disclosure also contemplates that this fusion polypeptide structure can further comprise as a component: (iv) a G1P polypeptide, or a Glucagon polypeptide. In such an embodiment with an additional G1P or Glucagon polypeptide, the "GLP1R agonist" is effectively a "dual agonist" as the additional polypeptides allow the fusion to bind specifically to G1P or Glucagon in addition to GLP1R.

[0112] The various polypeptide components can be varied to provide as described in greater detail below to provide a range of species-specific GLP1R agonists. In various embodiments of the GLP1R agonists of the present disclosure, IgG Fc region polypeptide can be a species-specific Fc region variant that is long-acting, that is provides increased *in vivo* pharmacokinetic half-life to the agonist. A range of IgG Fc region variants that provide increased half-life are well known in the art and can be used in the agonists of the present disclosure. For example, in some embodiments, in addition to the Y at position 252 (Eu numbering), the species-specific IgG Fc region polypeptide can be a Fc region variant comprising an A at positions 234 and 235 (Eu numbering).

[0113] In various embodiments of the GLP1R agonists of the present disclosure the GLP1 polypeptide component of the fusion can comprise the wild-type GLP1 polypeptide, a truncated version of the wild-type GLP1 polypeptide, or a functional variant of the wild-type GLP1 polypeptide. For example, the present disclosure provides a GLP1R agonist comprising a GLP1 polypeptide of SEQ ID NO: 1, which comprises amino acids 7-37 of the wild-type GLP1. In another embodiment, the GLP1R agonist comprises a GLP1 polypeptide component that comprises a variant of the wild-type sequence of SEQ ID NO: 1. In such an embodiment, the

GLP1 polypeptide comprises SEQ ID NO: 2, which is a variant of SEQ ID NO: 1 comprising either a G or S amino acid at position 2 of the SEQ ID NO: 1.

[0114] It is also contemplated that the GLP1R agonist polypeptide fusions of the present disclosure can comprise a range of alternative polypeptides rather than GLP1. For example, in various embodiments, the GLP1R agonist can comprise an OXM polypeptide (SEQ ID NO: 3), or a functional variant thereof; or an Extendin-4 polypeptide of SEQ ID NO: 5, or a functional variant thereof.

[0115] Table 1 below provides a summary description of the exemplary GLP1R agonist sequences referenced in the present disclosure, including canine GLP1R agonists and dual agonists, feline GLP1R agonists and dual agonists, and equine GLP1R agonists and dual agonists. The sequences also are included in the accompanying Sequence Listing.

[0116] **TABLE 1:** Exemplary sequences of GLP1R agonists, GLP1, OXM, Gluc, Extendin-4, G1P, and related molecules

SEQ ID NO:	SEQUENCE	DESCRIPTION
1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGAG	Wild-type GLP1 (7-37)
2	H X EGTFTSDVSSYLEGQAAKEFIAWLVKGAG	Variant GLP1 (7-37) X: G or S
3	HSQGTFTSDYSKYLDSSRAQDFVQWLMNTRKNNIA	Oxyntomodulin (OXM)
4	HSQGTFTSDYSKYLDSSRAQDFVQWLMNT	Glucagon (Gluc)
5	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS	Extendin-4
6	YAEGTFISDYSIAMDKIRQQDFVNWLLAQKGGKNDWKHNITQ	Wild-type Gastric inhibitory polypeptide (G1P)
7	Y X EGTFISDYSIAMDKIRQQDFVNWLLAQKGGK	Variant Gastric inhibitory polypeptide (G1P) X: A; G; S
8	H G EGTFTSDVSSYLEGQAAKEFIAWLVKG GGGS GGGG GGGG SGGG ENGRVPRPPDCPKCPAPEAAGGPSVFIFPPKPKDTLYI ARTPEVTCVVVDLDPEDPEVQISWFVDGKQM Q TAKTQPREEQ FNGTYRVVSVLP I GHQDWLKGKQFTCKVNNKALPSPIERTIS KARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDV EWQSNQQEPESKYRTTPPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSPGK	Canine long-acting GLP1R agonist GLP1 + IgG-B Fc with LALA
9	H G EGTFTSDVSSYLEGQAAKEFIAWLVKG GGGS GGGG GGGG SGGG GKTDHPPGPKPCDCPKCPPPEAAGGPSIFIFPPKPKDT LYISRTPEVTCVVVDLGPDDSDVQITWFDNTQVYTAKTSPR EEQFNSTYRVVSVLP I LHQDWLKGKEFKCKVNSKSLPSPIER TISKAKGQPHQPQVYVLP P AQEELSRNKVSVTCLIKSFHPPD IAVEWEITGQPEPENNYRTTPPQLDSDGTYFVYSKLSVDRSH WQRGNTYTCSVSHEALHSHHTQKSLTQSPGK	Feline long-acting GLP1R agonist GLP1 + IgG1 Fc with LALA
10	H G EGTFTSDVSSYLEGQAAKEFIAWLVKG GAG GGGS GGGG SG GGSGGG SEPIPDNHQKVSDMSKCPKCPAPEAAGGPSVFIFPP NPKDTLYITRTPEVTCVVVDVSQENPDVKNWYMDGVEVRTA TTRPK E EQFNSTYRVVSVLRIHQDWLSGKEFKCKVNNQALP QPIERTITKTKGRSQEPQVYVLAHPDEL S SKSVSVTCLVKD FYPPEINIEWQSNQQELETKYSTTQAQQDSDGSYFLYSKLS	Equine long-acting GLP1R agonist GLP1 + IgG1 Fc with LALA

	VDRNRWQQGTTFTTCGVMHEALHNHYTQKNVSKNPGK	
11	HGEFTFTSDVSSYLEGQAAKEFIAWLVKGGAGGGGGSGGGSGGGSSVPPKQCPYPYTHSKAAGGPSVFIFPPNPKDTLYISRTPVVTCVVVNLSDQYPDVQFSWYVDNTEVHSAITKQREAQFNSTYRVVSVLPIQHODWLSGKEFKCSVTNVGVPQPISRRAISRGKGPSRVPQVYVLPHPDELAKSKVSVTCLVKDFYPPDISVEWQSNRWPELEGKYSTTPAQLDGDGSYFLYSKLSLETSRWQQVESFTCAVMHEALHNHYTKTDISESLGK	Equine long-acting GLP1R agonist GLP1 + IgG2 Fc with LALA
12	HSQGTFTSDYSKYLDSRRRAQDFVQWLMNTRKNKNNIAGGGGGSGGGSGGGSGGGSENGRVPRPPDCPKCPAPEAAGGPSVFIFPPKPKDTLYIARTPEVTCVVVDLDPEDPEVQISWFVDGKQMOTAKTQPREEQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTISKARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFPPDIDVEWQSNQQEPESKYRTTPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK	Canine long-acting GLP1R agonist OXM + IgGB LALA
13	HSQGTFTSDYSKYLDSRRRAQDFVQWLMNTRKNKNNIAGGGGGSGGGSGGGSGGGGKTDHPPGPKPCDCPKCPPEAAGGPSIFIFPPKPKDTLYISRTPEVTCLVVDLGPDDSDVQITWFVDNTQVYTAKTSPREEQFNSTYRVVSVLPILHQDWLKGKEFKCKVNSKSLPSPIERTISKAKGQPHEPQVYVLPQAQEELSRNKVSVTCLIKSFHPPDIAVEWEITGQPEPENNYRTTPQLDSDGTYFVYSKLSVDRSHWQRGNTYTCSVSHEALSHHTQKSLTQSPGK	Feline long-acting GLP1R agonist OXM + IgG1 LALA
14	HSQGTFTSDYSKYLDSRRRAQDFVQWLMNTRKNKNNIAGGGGGSGGGSGGGSGGGSEPIPDNHQKVSDMSKCPKCPAPEAAGGPSVFIFPPNPKDTLYITRTPEVTCVVVDVSQENPDVKFNWYMDGVEVRTATTRPKEEQFNSTYRVVSVLRIQHODWLSGKEFKCKVNNQALPQPIERTITKTKGRSQEPQVYVLAPHPDELAKSKVSVTCLVKDFYPPEINIEWQSNQQPELETKYSTTQAQQDSYFLYSKLSVDRNRWQQGTTFTTCGVMHEALHNHYTQKNVSKNPGK	Equine long-acting GLP1R agonist OXM + GLP1-IgG1
15	HSQGTFTSDYSKYLDSRRRAQDFVQWLMNTRKNKNNIAGGGGGSGGGSGGGSGGGSSVPPKQCPYPYTHSKAAGGPSVFIFPPNPKDTLYISRTPVVTCVVVNLSDQYPDVQFSWYVDNTEVHSAITKQREAQFNSTYRVVSVLPIQHODWLSGKEFKCSVTNVGVPQPISRRAISRGKGPSRVPQVYVLPHPDELAKSKVSVTCLVKDFYPPDISVEWQSNRWPELEGKYSTTPAQLDGDGSYFLYSKLSLETSRWQQVESFTCAVMHEALHNHYTKTDISESLGK	Equine long-acting GLP1R agonist OXM + IgG2 Fc with LALA
16	HGEFTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGSGGGSGGGSENGRVPRPPDCPKCPAPEAAGGPSVFIFPPKPKDTLYIARTPEVTCVVVDLDPEDPEVQISWFVDGKQMOTAKTQPREEQFNGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTISKARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFPPDIDVEWQSNQQEPESKYRTTPQLDEDGSYFLYSKLSVDKSRWQRGDTFICAVMHEALHNHYTQESLSHSPGK	Canine long-acting GLP1R agonist Extendin-4 + IgG-B LALA
17	HGEFTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGSGGGSGGGGKTDHPPGPKPCDCPKCPPEAAGGPSIFIFPPKPKDTLYISRTPEVTCLVVDLGPDDSDVQITWFVDNTQVYTAKTSPREEQFNSTYRVVSVLPIHQDWLKGKEFKCKVNSKSLPSPIERTISKAKGQPHEPQVYVLPQAQEELSRNKVSVTCLIKSFHPPDIAVEWEITGQPEPENNYRTTPQLDSDGTYFVYSKLSVDRSHWQRGNTYTCSVSHEALSHHTQKSLTQSPGK	Feline long-acting GLP1R agonist Extendin-4 + IgG1 LALA
18	HGEFTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSGGGGGSGGGSGGGSGGGSEPIPDNHQKVSDMSKCPKCPAPEAAGGPSVFIFPPNPKDTLYITRTPEVTCVVVDVSQENPDVKFNWYMDGVEVRTATTRPKEEQFNSTYRVVSVLRIQHODWLSGKEFKCKVNNQALPQPIERTITKTKGRSQEPQVYVLAPHPDELAKSKVSVTCLVKDFYPPEINIEWQSNQQPELETKYSTTQAQQDSYFLYSKLSVDRNRWQQGTTFTTCGVMHEALHNHYTQKNVSKNPGK	Equine long-acting GLP1R agonist Extendin-4 + IgG1 LALA

19	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS GGGGGSGGGSGGGSGGGSS VPKPQCAPPYTHSKAAGGPSVFIF PPNPKDTLYISRTPVVTCVVVNLSDQYPDVQFSWYVDNTEVH SAITKQREAQFNSTYRVVSVLPIQHQDWLSGKEFKCSVTNVG VPQPISRRAISRKGKPSRVPQVYVLPHPDELAKSKVSVTCLV KDFYPPDISVEWQSNRWPELEGKYSTTPAQLDGDGSYFLYSK LSLETSRWQQVESFTCAVMHEALHNHYTKTDISESLGK	Equine long-acting GLP1R agonist Extending-4 + IgG2 LALA
20	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGG GGGSGGGSGGGG SGGGG ENGRVPRPPDCPKCPAPEAAGGPSVFIFPPPKPDTLYI ARTPEVTCVVVDLDPEDPEVQISWFVDGKQMOTAKTQPREEQ FNGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTIS KARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDV EWQSNQQEPESKYRTTPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSP GGGGSGGG HSQGTFTS DYSKYLDSRRAQDFVQWLMNT	Canine GLP1 + Gluc Dual agonist GLP1 + Canine IgG-B Fc with LALA + Gluc
21	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGG GGGSGGGSGGGG SGGGG KTDHPPGPKPCDCPKCPPPEAAGGPSIFIFPPPKPDT LYISRTPEVTCVVVDLGPDDSDVQITWFVDNTQVYTAKTSPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVNSKSLPSPIER TISKAKGPHEPQVYVLPPEAEELSRNKVSVTCLIKSFHPPD IAVEWEITGQPEPENNYRTTPQLDSDGTYFVYSKLSVDRSH WQRGNTYTCSVSHEALSHHTQKSLTQSPG GGGGSGGG HSQG TFTSDYSKYLDSRRAQDFVQWLMNT	Feline GLP1 + Gluc Dual agonist GLP1 + Feline IgG1 with LALA + Gluc
22	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGGAG GGGGSGGGSG GGSGGGG SEPIPDNHQKVSDMSKCPKCPAPEAAGGPSVFIFPP NPKDTLYITRTPEVTCVVVDVSQENPDVKFNWYMDGVEVRTA TTRPKEEQFNSTYRVVSVLRIQHQDWLSGKEFKCKVNNQALP QPIERTITKTGRSQEPQVYVLPAPHPDELSSKSKVSVTCLVKD FYPPEINIEWQSNQPELETKYSTTQAQDSDGSYFLYSKLS VDRNRWQQGTTFTCGVMHEALHNHYTQKNVSKNPG GGGGSGG GHS QGTFTSDYSKYLDSRRAQDFVQWLMNT	Equine GLP1 + Gluc Dual agonist GLP1 + Equine IgG1 with LALA + Gluc
23	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGGAG GGGGSGGGSG GGSGGGG SVPKPQCAPPYTHSKAAGGPSVFIFPPNPKDTLYIS RTPVVTCVVVNLSDQYPDVQFSWYVDNTEVHSAITKQREAQF NSTYRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPISRRAISR GKGPSRVPQVYVLPHPDELAKSKVSVTCLVKDFFYPPDISVE WQSNRWPELEGKYSTTPAQLDGDGSYFLYSKLSLETSRWQQV ESFTCAVMHEALHNHYTKTDISESLG GGGGSGGG HSQGTFTS DYSKYLDSRRAQDFVQWLMNT	Equine GLP1 + Gluc Dual agonist GLP1 + Equine IgG2 with LALA + Gluc
24	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGG GGGSGGGSGGGG SGGGG ENGRVPRPPDCPKCPAPEAAGGPSVFIFPPPKPDTLYI ARTPEVTCVVVDLDPEDPEVQISWFVDGKQMOTAKTQPREEQ FNGTYRVVSVLPIGHQDWLKGKQFTCKVNNKALPSPIERTIS KARGQAHQPSVYVLPSPREELSKNTVSLTCLIKDFFPPDIDV EWQSNQQEPESKYRTTPQLDEDGSYFLYSKLSVDKSRWQR GDTFICAVMHEALHNHYTQESLSHSP GGGGSGGG YAEGTFIS DYSIAMDKIRQQDFVNWLLAQKKG	Canine GLP1 + G1P Dual agonist GLP1 + Canine IgG-B Fc with LALA + G1P
25	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGG GGGSGGGSGGGG SGGGG KTDHPPGPKPCDCPKCPPPEAAGGPSIFIFPPPKPDT LYISRTPEVTCVVVDLGPDDSDVQITWFVDNTQVYTAKTSPR EEQFNSTYRVVSVLPILHQDWLKGKEFKCKVNSKSLPSPIER TISKAKGPHEPQVYVLPPEAEELSRNKVSVTCLIKSFHPPD IAVEWEITGQPEPENNYRTTPQLDSDGTYFVYSKLSVDRSH WQRGNTYTCSVSHEALSHHTQKSLTQSPG GGGGSGGG YAEG TFISDIAMDKIRQQDFVNWLLAQKKG	Feline GLP1 + G1P Dual agonist GLP1 + Feline IgG1 Fc with LALA + G1P
26	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGGAG GGGGSGGGSG	Equine GLP1 + G1P

	GGSGGGSEPIPDNHQKVSMSKCPKCPAPEAAGGPSVFIFPP NPKDTLYITRTPEVTCVVVDVSDQENPDVKNWYMDGVEVRTA TTRPKEEQFNSTYRVVSVLRIQHQDWLSGKEFKCKVNNQALP QPIERTITKTGRSQEPQVYVLAPHPDELSKSKSVTCLVKD FYPPEINIEWQSNGQPELETKYSTTQAQQDSGYSFLYSKLS VDRNRWQQGTTFTCGVMHEALHNHYTQKNVSKNPGGGGSGG GYAEGTFISDYSIAMDKIRQQDFVNWLLAQKGK	<u>Dual agonist</u> GLP1 + Equine IgG1 Fc with LALA + G1P
27	HGEGTFTSDVSSYLEGQAAKEFIAWLVKGGAGGGGSGGGSG GGSGGGSSVPKPQCAPPYTHSKAAGGPSVFIFPPNPKDTLYIS RTPVVTCTVVNLSQYDPDVQFSWYVDNTEVHSAITKQREAF NSTYRVVSVLPIQHQDWLSGKEFKCSVTNVGVPQPISRISR GKGPSRVPQVYVLPHPDELAKSKSVTCLVKDFYPPDISVE WQSNRWPELEGKYSTTPAQLDGDGSYFLYSKLSLETSRWQQV ESFTCAVMHEALHNHYTKTDISESLGGGGSGGGGYAEGTFIS DYSIAMDKIRQQDFVNWLLAQKGK	<u>Equine GLP1 + G1P</u> <u>Dual agonist</u> GLP1 + Equine IgG2 Fc with LALA + G1P

[0117] As shown by the exemplary GLP1R agonist molecules in Table 1, the present disclosure contemplates a canine agonist or a canine dual agonist comprising an amino acid sequence selected from SEQ ID NO: 8, 12, 16, 20, and 24, or a functional variant thereof comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 8, 12, 16, 20, and 24.

[0118] The present disclosure also contemplates a feline specific GLP1R agonist or feline dual agonist comprising an amino acid sequence selected from SEQ ID NO: 9, 13, 17, 21, and 25, or a functional variant thereof comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 9, 13, 17, 21, and 25.

[0119] Additionally, the present disclosure contemplates an equine specific GLP1R agonist or an equine dual agonist comprising an amino acid sequence selected from SEQ ID NO: 10, 11, 14, 15, 18, 19, 22, 23, 26, and 27, or a functional variant thereof comprising an amino acid sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity to a sequence selected from SEQ ID NO: 10, 11, 14, 15, 18, 19, 22, 23, 26, and 27.

[0120] Generally, the GLP1R agonists comprise a polypeptide fusion of (i) a species-specific IgG Fc region polypeptide, wherein the Fc region polypeptide comprises a Y at position 252 (Eu numbering); and (ii) a GLP1 polypeptide, an Extendin-4 polypeptide, or an OXM polypeptide. Typically, the polypeptide fusion comprises at least a first polypeptide linker between the IgG Fc region polypeptide and the GLP1 polypeptide, Extendin-4 polypeptide, or OXM polypeptide. The exemplary GLP1R agonists of Table 1 use a first polypeptide linker of amino acid sequence GGGSGGGSGGGSGGG (SEQ ID NO: 28) to attach (or fuse) the C-terminus of the GLP1 (or related) polypeptide component to the N-terminus of the IgG Fc region polypeptide component. This general GLP1R agonist fusion polypeptide structure of the

present disclosure is exemplified by the Table 1 agonists of SEQ ID NO: 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19.

[0121] Although the polypeptide of SEQ ID NO: 28 is exemplified as the first polypeptide linker in the GLP1R agonists of Table 1, one of ordinary skill in the art will understand a wide range of polypeptide linkers are known in the art and can be used in the GLP1R agonist fusions, compositions, and methods of the present disclosure. Generally, polypeptides comprising polypeptide chains of 5 to 30 amino acids can be used to fuse the polypeptide components of the GLP1R agonists of the present disclosure. Other exemplary polypeptide linkers useful in the compositions and methods of the present disclosure can include but are not limited to: (GGGGS)_n, (SSSSG)_n, (GGGG)(SGGGG)_n, (EAAAK)_n, (XP)_n, ENLYFQ(-G/S), typically, where n is 2 to 6.

[0122] As described elsewhere herein, it is contemplated that any of the GLP1R agonists fusions of the present disclosure can further include a second agonist polypeptide component that allows them to function as a dual agonist. In these dual agonist embodiments, the second agonist polypeptide is attached via a linker to the other terminus of the species-specific IgG Fc region polypeptide. For example, a GLP1R dual agonist of the present disclosure can comprise a second agonist polypeptide such as a G1P polypeptide, or a Glucagon polypeptide. Typically, the second agonist polypeptide (e.g., G1P or Glucagon) is attached to the other terminus of the species-specific IgG Fc region polypeptide via a second polypeptide linker. The second polypeptide linker can comprise a polypeptide chain of 5 to 30 amino acids, such as sequence selected from SEQ ID NO: 28 and 29. Such GLP1R dual-agonists are exemplified by the Table 1 GLP1R agonists of SEQ ID NO: 20, 21, 22, 23, 24, 25, 26, and 27.

[0123] One of ordinary skill in the art will recognize that a wide range of alternative polypeptide fusion structures capable of acting as GLP1R agonists or dual agonist can be prepared based on the various combination of polypeptide components disclosed in the exemplary agonists of Table 1. For example, the present disclosure contemplates GLP1R agonists wherein the order of the polypeptide components in the fusion is switched with little or no effect on the agonist activity of the fusion. A wide range of polypeptide fusion structures and polypeptide linkers are known in the art and can be used in the GLP1R agonist fusions, compositions, and methods of the present disclosure. The exemplary GLP1R agonists and dual agonists of Table 1 use the linker GGGSGGGSGGGSGGG (SEQ ID NO: 28) to link the C-terminus of the GLP1 (or related) polypeptide component to the N-terminus of the IgG Fc region polypeptide component. They also use the shorter linker GGGGSGGG (SEQ ID NO: 29), to link the C-terminus of the IgG Fc region polypeptide component to the N-terminus of the second agonist polypeptide component (e.g., G1P) in the dual-agonist embodiments. One of ordinary skill, however, will immediately recognize that these polypeptide linkers could be switched in order or substituted with other polypeptide linkers.

[0124] Pharmaceutical Compositions of GLP1R Agonists

[0125] The present disclosure also provides pharmaceutical compositions and pharmaceutical formulations comprising a GLP1R agonist. Generally, “pharmaceutical formulation” and “pharmaceutical composition” refer to a preparation which is in such form as to permit the biological activity of the active ingredient(s) to be effective, and which contains no additional components that are unacceptably toxic to a subject to which the formulation would be administered. Accordingly, in some embodiments, the present disclosure provides a pharmaceutical formulation comprising a GLP1R agonist as described herein and a pharmaceutically acceptable carrier. In some embodiments, the GLP1R agonist is the sole active agent of the pharmaceutical composition. Such pharmaceutical formulations can be prepared by mixing a GLP1R agonist, having the desired degree of purity, with one or more pharmaceutically acceptable carriers. Typically, such formulations can be prepared as an aqueous solution (see e.g., US Pat. No. 6,171,586, and WO2006/044908) or as a lyophilized formulation (see e.g., US Pat. No. 6,267,958).

[0126] Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed. A wide range of such pharmaceutically acceptable carriers are well-known in the art (see e.g., Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)). Exemplary pharmaceutically acceptable carriers include alumina; aluminum stearate; lecithin; serum proteins, such as human serum albumin, canine or other animal albumin; buffers such as phosphate, citrate, tromethamine or HEPES buffers; glycine; 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, or magnesium trisilicate; polyvinyl pyrrolidone, cellulose-based substances; polyethylene glycol; sucrose; mannitol; or amino acids including, but not limited to, arginine.

[0127] The pharmaceutical composition can be stored in lyophilized form. Thus, in some embodiments, the preparation process includes a lyophilization step. The lyophilized composition may then be reformulated, typically as an aqueous composition suitable for parenteral administration, prior to administration to the dog. In other embodiments, particularly where the antibody is highly stable to thermal and oxidative denaturation, the pharmaceutical composition can be stored as a liquid, i.e., as an aqueous composition, which may be administered directly, or with appropriate dilution, to the dog. A lyophilized composition can be reconstituted with sterile Water for Injection (WFI). Bacteriostatic reagents, such as benzyl alcohol, may be included. Thus, the invention provides pharmaceutical compositions in solid or liquid form.

[0128] The pH of the pharmaceutical compositions may be in the range of from about pH 5 to about pH 8, when administered. The compositions of the invention are sterile if they are to be used for therapeutic purposes. Sterility can be achieved by any of several means known in the

art, including by filtration through sterile filtration membranes (e.g., 0.2-micron membranes). Sterility may be maintained with or without anti-bacterial agents.

[0129] It is also contemplated that the formulations disclosed herein may contain active ingredients in addition to the GLP1R agonist, as necessary for the particular indication being treated in the subject to whom the formulation is administered. Preferably, any additional active ingredient has activity complementary to that of the GLP1R agonist activity and the activities do not adversely affect each other.

[0130] Exemplary Uses of Long-Acting GLP1R Agonists and Pharmaceutical Compositions

[0131] The GLP1R agonists and pharmaceutical compositions comprising them of the present disclosure may be useful for treating a GLP1 mediated condition, disorder, or disease, in a subject, wherein the subject may be in a companion animal, including, but not limited to, a canine or a feline or an equine.

[0132] In some embodiments, GLP1R agonist or pharmaceutical compositions comprising the same can be utilized in accordance with the methods herein to treat conditions associated with GLP1. In some embodiments, a GLP1R agonist or pharmaceutical composition is administered to a companion animal, such as a canine or a feline or an equine, to treat a condition associated with GLP1. In some embodiments, a GLP1R agonist or pharmaceutical composition is administered to a companion animal, such as a canine or a feline or an equine, to maintain remission of a condition associated with GLP1 and/or G1P, OXM, glucagon.

[0133] In at least one embodiment, the present disclosure also provides a method of treating a canine, a feline, or an equine subject having a condition associated with GLP1R agonist activity, the method comprising administering to the canine, feline, or equine subject a therapeutically effective amount of the species-specific GLP1R agonist of the present disclosure, or the pharmaceutical composition comprising a GLP1R agonist of the present disclosure.

[0134] In at least one embodiment, the methods of the present disclosure can be used in maintaining remission of a condition associated with GLP1 in a canine, feline, or equine subject. In such an embodiment, the method comprises administering to the canine a therapeutically effective amount of a GLP1R agonist of the present disclosure, or a pharmaceutical composition comprising a GLP1R agonist of the present disclosure.

[0135] Exemplary conditions associated with GLP1 that can be treated using the methods and GLP1R agonists or dual agonists of the present disclosure include metabolic disorders, such as metabolic disorders associated with high glucose, obesity, poor cardiovascular outcome, and/or aging. In at least one embodiment, the condition associated with GLP1 that can be treated is glucose dysregulation disease. In at least one embodiment, the condition associated with GLP1 that can be treated is obesity or being overweight. In at least one embodiment, the

condition associated with GLP1 that can be treated is cardiovascular disease. In at least one embodiment, the condition associated with GLP1 that can be treated is an age-related disorder, such as age-related neurodegeneration.

[0136] The therapeutically effective amount can be an amount one in which any toxic or detrimental effects of the substance/molecule, agonist or antagonist are outweighed by the therapeutically beneficial effects. A therapeutically effective amount may be delivered in one or more administrations. A therapeutically effective amount refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0137] A GLP1R agonist alone, or dual agonist, as described herein, may be administered in a therapeutically effective amount in the range of 0.0001 mg/kg body weight to 100 mg/kg body weight per dose. In at least one embodiment, the therapeutically effective amount of the GLP1R agonist alone, dual agonist, or the pharmaceutical composition comprising it, is administered in a per dose amount of at least about 0.025 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.075 mg/kg body weight, at least about 0.10 mg/kg body weight, at least about 0.125 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1.0 mg/kg body weight, at least about 1.25 mg/kg body weight, at least about 1.5 mg/kg body weight, at least about 1.75 mg/kg body weight, at least about 2.0 mg/kg body weight, or at least about 2.5 mg/kg body weight.

[0138] In at least one embodiment, the therapeutically effective amount of the GLP1R agonist alone, dual agonist, or the pharmaceutical composition comprising it is administered in a per dose amount of about 0.025 mg/kg body weight to about 2.5 mg/kg body weight, about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

[0139] The timing of dose administration can depend on a number of factors, including the amount of the dosage, the particular condition or disorder being treated, and the pharmacokinetic (PK) parameters of the pharmaceutical composition in the subject being treated. PK parameters for an GLP1R agonist of the present disclosure can be determined using techniques known in the art, and as exemplified in the Examples of the present disclosure. In at least one embodiment, the therapeutically effective amount of the GLP1R agonist alone, dual agonist, or the pharmaceutical composition comprising it, can be administered in a per dose amount at an interval of: daily, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, weekly, semi-monthly, or monthly. In at least one embodiment, the GLP1R agonist alone, dual agonist, or the pharmaceutical composition is administered weekly in a per dose amount of about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

[0140] A GLP1R agonist alone, a dual agonist or a pharmaceutical composition comprising a GLP1R agonist alone, or dual agonist can be administered to a companion animal at one time or over a series of treatments. For example, a GLP1R agonist alone, or dual agonist or a pharmaceutical composition comprising a GLP1R agonist alone, or dual agonist may be administered at least once, more than once, at least twice, at least three times, at least four times, or at least five times.

[0141] In some embodiments, the dose is administered once per week for at least two or three consecutive weeks, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more weeks of no treatment. In other embodiments, the therapeutically effective dose is administered once per day for two to five consecutive days, and in some embodiments, this cycle of treatment is repeated two or more times, optionally interspersed with one or more days or weeks of no treatment.

[0142] Administration can be “in combination with” one or more further therapeutic agents includes simultaneous (concurrent) and consecutive or sequential administration in any order. The term “concurrently” is used herein to refer to administration of two or more therapeutic agents, where at least part of the administration overlaps in time or where the administration of one therapeutic agent falls within a short period of time relative to administration of the other therapeutic agent. For example, the two or more therapeutic agents are administered with a time separation of no more than about a specified number of minutes. The term “sequentially” is used herein to refer to administration of two or more therapeutic agents where the administration of one or more agent(s) continues after discontinuing the administration of one or more other agent(s), or wherein administration of one or more agent(s) begins before the administration of one or more other agent(s). For example, administration of the two or more therapeutic agents are administered with a time separation of more than about a specified number of minutes. As used herein, “in conjunction with” refers to administration of one treatment modality in addition to another treatment modality. As such, “in conjunction with” refers to administration of one treatment modality before, during or after administration of the other treatment modality to the animal.

[0143] In some embodiments, a GLP1R agonist or pharmaceutical composition comprising a GLP1R agonist and/or dual agonist is administered parenterally, by subcutaneous administration, intravenous infusion, or intramuscular injection. In some embodiments, a GLP1R agonist and/or dual agonist or pharmaceutical composition comprising a GLP1R agonist and/or dual agonist is administered as a bolus injection or by continuous infusion over a period of time. In some embodiments, a GLP1R agonist and/or dual agonist or pharmaceutical composition comprising a GLP1R agonist and/or dual agonist is administered by an intramuscular, an intraperitoneal, an intracerebrospinal, a subcutaneous, an intra-arterial, an intrasynovial, an intrathecal, or an inhalation route.

[0144] Provided herein are methods of exposing to a cell a GLP1R agonist alone, or dual agonist or a pharmaceutical composition comprising a GLP1R agonist alone, or dual agonist under conditions permissive for binding of the antibody to a GLP1R agonist alone, or dual agonist. In some embodiments, the cell is exposed to the antibody or pharmaceutical composition *ex vivo*. In some embodiments, the cell is exposed to the antibody or pharmaceutical composition *in vivo*. In some embodiments, a cell is exposed to the GLP1R agonist alone, or dual agonist or the pharmaceutical composition under conditions permissive for binding of a GLP1R agonist alone or binding of a dual agonist to GLP1R.

[0145] In some embodiments, a cell may be exposed *in vivo* to the GLP1R agonist alone, or dual agonist or the pharmaceutical composition by any one or more of the administration methods described herein, including but not limited to, intraperitoneal, intramuscular, intravenous injection into the subject. In some embodiments, a cell may be exposed *ex vivo* to a GLP1R agonist alone, or dual agonist or the pharmaceutical composition by exposing the cell to a culture medium comprising the antibody or the pharmaceutical composition. In some embodiments, the permeability of the cell membrane may be affected by the use of any number of methods understood by those of skill in the art (such as electroporating the cells or exposing the cells to a solution containing calcium chloride) before exposing the cell to a culture medium comprising the antibody or the pharmaceutical composition.

[0146] Provided herein are methods of using the GLP1R agonist alone, or dual agonist, polypeptides and polynucleotides for detection, diagnosis and monitoring of a condition associated with GLP1R. Provided herein are methods of determining whether a companion animal will respond to a GLP1R agonist alone, or dual agonist therapy. In some embodiments, the method comprises detecting whether the animal has cells that express GLP1R. In some embodiments, the method of detection comprises contacting the sample with an antibody, polypeptide, or polynucleotide and determining whether the level of binding differs from that of a reference or comparison sample (such as a control). In some embodiments, the method may be useful to determine whether the antibodies or polypeptides described herein are an appropriate treatment for the subject animal.

[0147] In some embodiments, the sample is a biological sample. The term “biological sample” means a quantity of a substance from a living thing or formerly living thing. In some embodiments, the biological sample is a cell or cell/tissue lysate. In some embodiments, the biological sample includes, but is not limited to, blood, (for example, whole blood), plasma, serum, urine, synovial fluid, and epithelial cells.

[0148] In some embodiments, the cells or cell/tissue lysate are contacted with a GLP1R agonist alone, or dual agonist and the binding between the antibody and the cell is determined. When the test cells show binding activity as compared to a reference cell of the same tissue type, it may indicate that the subject would benefit from treatment with a GLP1R agonist alone, or dual agonist. In some embodiments, the test cells are from tissue of a companion animal.

[0149] Various methods known in the art for detecting specific antibody-antigen binding can be used. Exemplary immunoassays which can be conducted include fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), nephelometric inhibition immunoassay (NIA), enzyme linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). An indicator moiety, or label group, can be attached to the subject antibodies and is selected so as to meet the needs of various uses of the method which are often dictated by the availability of assay equipment and compatible immunoassay procedures. Appropriate labels include, without limitation, radionuclides (for example ^{125}I , ^{131}I , ^{35}S , ^3H , or ^{32}P), enzymes (for example, alkaline phosphatase, horseradish peroxidase, luciferase, or p-galactosidase), fluorescent moieties or proteins (for example, fluorescein, rhodamine, phycoerythrin, GFP, or BFP), or luminescent moieties (for example, Qdot™ nanoparticles supplied by the Quantum Dot Corporation, Palo Alto, Calif.). General techniques to be used in performing the various immunoassays noted above are known to those of ordinary skill in the art.

EXAMPLES

[0150] Various features and embodiments of the disclosure are illustrated in the following representative examples, which are intended to be illustrative, and not limiting. Those skilled in the art will readily appreciate that the specific examples are only illustrative of the invention as described more fully in the claims which follow thereafter. Every embodiment and feature described in the application should be understood to be interchangeable and combinable with every embodiment contained within.

[0151] Example 1: Identification of canine, feline and equine GLP1, OXM, Glucagon, G1P sequences

[0152] The canine, feline and equine GLP1 sequences were identified from the Uniprot database. The amino acid sequence of GLP1 (SEQ ID NO: 1) is 100% conserved among the three species.

[0153] The canine, feline, and equine oxyntomodulin (OXM) sequences were identified from the UniProt database. The OXM amino acid sequence (SEQ ID NO: 3) is 100% conserved among the three species.

[0154] The canine, feline and equine Glucagon sequences were identified from the Uniprot database. The glucagon amino acid sequence (SEQ ID NO: 4) is 100% conserved among the three species.

[0155] The canine, feline and equine gastric inhibitory polypeptide (G1P) sequences were identified from the Uniprot database. The G1P amino acid sequence (SEQ ID NO: 5) is 100% conserved among the three species.

[0156] Example 2: Modifications of canine, feline, and equine IgG molecules

[0157] The “YTE” mutations are well known to extend the *in vivo* half-life of human IgG molecules. We introduced the YTE “Y” mutation at position 252 (Eu Numbering) in canine, feline and equine IgG molecules, including: canine IgGA, IgGB, IgGC, and IgGD; feline IgG1, IgG1A, IgG1B, and IgGB; and equine IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, and IgG7.

[0158] The “LALA” mutations are well known to reduce Fcγ and C1Q related activity when introduced into human IgG molecules. We introduced the LALA “A” mutations at positions 234 and 235 (Eu Numbering) in canine, feline and equine IgG molecules, including: canine IgGA, IgGB, IgGC, and IgGD; feline IgG1, IgG1A, IgG1B, IgGB; and equine IgG1, IgG2, IgG3, IgG4, IgG5, IgG6, and IgG7.

[0159] Example 3: Design of canine, feline and equine GLP1R agonists

[0160] Here is an exemplified sequence of canine long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 8). The agonist molecule of SEQ ID NO: 8 comprises a fusion of (i) a GLP1 polypeptide of SEQ ID NO: 1 with modification of SEQ ID NO: 2; (ii) a polypeptide linker of SEQ ID NO: 28; and (iii) a modified canine IgG molecule with a long-acting YTE “Y” mutation at position 252 and the LALA “A” mutations at positions 234 and 235 that reduce complement activation or Fcγ receptor function.

[0161] Here is an exemplified sequence of feline long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 9). A long-acting GLP1R agonist SEQ ID NO: 9 that binds to feline GLP1R, wherein the agonist is a feline Fc fusion comprising (i) a GLP1 peptide of SEQ ID NO: 1 with modification of SEQ ID NO: 2; (ii) a polypeptide linker of SEQ ID NO: 28; and (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0162] Here is an exemplified sequence of equine long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 10 and 11). Long-acting GLP1R agonist SEQ ID NO: 10 or SEQ ID NO: 11 that binds to equine GLP1R, wherein the agonist is an equine Fc fusion comprising (i) a GLP1 peptide SEQ ID NO: 1 with modification SEQ ID NO: 2; (ii) a polypeptide linker of SEQ ID NO: 28; and (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0163] Here is an exemplified sequence of canine long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 16). A long-acting GLP1R agonist SEQ ID NO: 16 that binds to canine GLP1R, wherein the agonist is a canine Fc fusion comprising (i) extendin-4 peptide SEQ ID NO: 5 with modification of SEQ ID NO: 2; (ii) a polypeptide linker of SEQ ID NO: 28; and (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0164] Here is an exemplified sequence of feline long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 17). A long-acting GLP1R agonist SEQ ID NO: 17 that binds to feline

GLP1R, wherein the agonist is a feline Fc fusion comprising (i) extendin-4 peptide SEQ ID NO: 5; (ii) a polypeptide linker of SEQ ID NO: 28; and (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0165] Here is an exemplified sequence of equine long-acting GLP1R agonist with reduced Fcγ function (SEQ ID NO: 18 and 19). Long-acting GLP1R agonist SEQ ID NO: 18 or SEQ ID NO: 19 that binds to equine GLP1R, wherein the agonist is an equine Fc fusion comprising (i) extendin-4 peptide SEQ ID NO: 5 (ii) a polypeptide linker (iii) modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0166] Example 4: Design of canine, feline and equine GLP1R dual agonists

[0167] Here is an exemplified sequence of canine long-acting GLP1R_GCGR dual agonist with reduced Fcγ function (SEQ ID NO: 12). A long-acting GLP1R_GCGR dual agonist SEQ ID NO: 12 that binds to feline GLP1R and GCGR, wherein the agonist is a canine Fc fusion comprising (i) a canine OXM peptide SEQ ID NO: 3 (ii) a polypeptide linker (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0168] Here is an exemplified sequence of feline long-acting GLP1R_GCGR dual agonist with reduced Fcγ function (SEQ ID NO: 13). A long-acting GLP1R_GCGR dual agonist SEQ ID NO: 13 that binds to feline GLP1R and GCGR, wherein the agonist is a canine Fc fusion comprising (i) a canine OXM peptide SEQ ID NO: 3 (ii) a polypeptide linker (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0169] Here is an exemplified sequence of equine long-acting GLP1R_GCGR dual agonist with reduced Fcγ function (SEQ ID NO: 14 and 15). Long-acting GLP1R_GCGR dual agonist SEQ ID NO: 14 or SEQ ID NO: 15 that binds to equine GLP1R and GCGR, wherein the agonist is an equine Fc fusion comprising (i) an equine OXM peptide SEQ ID NO: 3 (ii) a polypeptide linker (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions.

[0170] Here is an exemplified sequence of canine long-acting GLP1R_glucagon receptor dual agonist with reduced Fcγ function (SEQ ID NO: 20). A long-acting GLP1R_Glucagon receptor dual agonist SEQ ID NO: 20 that binds to canine GLP1R and glucagon receptor, wherein the dual agonist is a canine Fc fusion comprising (i) a canine GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a glucagon peptide SEQ ID NO: 4.

[0171] Here is an exemplified sequence of feline long-acting GLP1R_glucagon receptor dual agonist with reduced Fcγ function (SEQ ID NO: 21). A long-acting GLP1R_Glucagon receptor

dual agonist SEQ ID NO: 21 that binds to feline GLP1R and glucagon receptor, wherein the dual agonist is a feline Fc fusion comprising (i) a feline GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a glucagon peptide SEQ ID NO: 4.

[0172] Here is an exemplified sequence of equine long-acting GLP1R_glucagon receptor dual agonist with reduced Fcγ function (SEQ ID NO: 22 and 23). A long-acting GLP1R_Glucagon receptor dual agonist SEQ ID NO: 22 or SEQ ID NO: 23 that binds to equine GLP1R and glucagon receptor, wherein the dual agonist is an equine Fc fusion comprising (i) a feline GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a glucagon peptide SEQ ID NO: 4.

[0173] Here is an exemplified sequence of canine long-acting GLP1R_G1P receptor dual agonist with reduced Fcγ function (SEQ ID NO: 24). A long-acting GLP1R_G1P receptor dual agonist SEQ ID NO: 24 that binds to canine GLP1R and G1P receptor, wherein the dual agonist is a canine Fc fusion comprising (i) a canine GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified canine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0174] Here is an exemplified sequence of feline long-acting GLP1R_G1P receptor dual agonist with reduced Fcγ function (SEQ ID NO: 25). A long-acting GLP1R_G1P receptor dual agonist SEQ ID NO: 25 that binds to feline GLP1R and G1P receptor, wherein the dual agonist is a feline Fc fusion comprising (i) a feline GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified feline IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0175] Here is an exemplified sequence of equine long-acting GLP1R_G1P receptor dual agonist with reduced Fcγ function (SEQ ID NO: 26 and 27). A long-acting GLP1R_G1P receptor dual agonist SEQ ID NO: 26 or SEQ ID NO: 27 that binds to equine GLP1R and G1P receptor, wherein the dual agonist is an equine Fc fusion comprising (i) an equine GLP1 peptide SEQ ID NO: 2 (ii) a polypeptide linker (iii) a modified equine IgG with long-acting mutation and LALA mutations that reducing complement activation or Fcγ receptor functions. (iv) a polypeptide linker fused to a G1P peptide SEQ ID NO: 6 with modification SEQ ID NO: 7.

[0176] Example 5: Recombinant expression of canine long-acting GLP1R agonist fusion protein

[0177] The long-acting canine GLP1R agonist fusion protein sequence of SEQ ID NO: 8 (referred to Examples 6 and 7 as “VMB-C005”) was designed for recombinant expression. This

fusion was expressed using in CHO cells and the expressed protein was purified using a protein A affinity column. The VMB-C005 fusion protein of SEQ ID NO: 8 was found to be well expressed with a transient expression from 27 mL producing 24.3 mg of protein. The fusion protein was over 96% monomeric after one step of protein A purification, as determined by electrophoresis analysis of reduced and non-reduced forms samples.

[0178] Example 6: Pharmacokinetic study of canine long-acting GLP1R agonist fusion protein

[0179] This example illustrates a pharmacokinetic (PK) study in two dogs over a 28-day period of a long-acting canine GLP1R agonist fusion protein of SEQ ID NO: 8 test article (also referred to in this study as "VMB-C005"). Safety and tolerability were evaluated via physical exams, clinical pathology, and observations of serious adverse events (SAEs) and adverse events (AEs).

[0180] Materials and methods

[0181] Test Article and Vehicle Identification: the identity, characteristics, and stability of the VMB-C005 test article are provided in Table 2.

[0182] TABLE 2

Identification:	VMB-C005
Batch (Lot) No.:	20231221_VMBC005
Formulation	1x PBS + 6% Sucrose, pH 7.4
Concentration	4.64 mg/mL
LAL Endotoxin	0.2 EU/mg
Monomer Content (SE-HPLC)	95.66%

[0183] Dogs are the target species for VMB-C005. Beagle dogs were utilized as the test system for the study as summarized in Table 3.

[0184] TABLE 3

Species:	Dog
Breed:	Beagle
Number of Animals (by Study Number):	Acclimated: 3 Randomized: 2
Gender:	Male and Female
Physiological Status	Intact or neutered, non-pregnant, non-lactating
Source:	High Quality Research colony
Age:	The approximate age of the dogs at the initiation of dosing (Day 0) was 35 months for the female and 33 months for the male
Body Weight:	Body weight at the initiation of dosing (Day 0) was 11.2 (F) and 13.2 (M) kgs.

[0185] This study did not duplicate previous research and was intended to evaluate PK and safety in dogs under laboratory conditions. This study was designed to use the fewest number of dogs anticipated to provide meaningful data consistent with the objectives of the study. Procedures avoided or minimized discomfort, distress, and pain to the dogs. Approximately 5 days of acclimation was given to accustom the dogs to housing in study cages.

[0186] Veterinary care was available throughout the course of each study. Dogs were examined by veterinary staff as warranted by clinical signs or other changes. The dogs were observed daily with respect to general health and signs of disease. Physical exams, heart rate, rectal temperature, respiratory rate, and clinical pathology were collected at the first day of acclimation (Day -5) and prior to dosing on Day 0. There was no need for animal replacements during the study.

[0187] Environmental conditions were monitored, recorded, and maintained, according to Testing Facility SOPs. The targeted conditions for the animal room environment were: Temperature of 65°F to 68°F; Humidity of 30% to 57%; and a light cycle of 12 hours light and 12 hours dark. Diet consisted of once daily feeding of commercially available Exclusive Red Flannel Prime Formula dry kibble manufactured for PMI nutrition, LLC. A high-protein dog food that meets AAFCO nutritional requirements. Water was Fort Collins tap water and was available *ad libitum* to each animal via automatic waterers.

[0188] Experimental design of the PK study of VMB-C005 is summarized in Table 4. All procedures, methods, activities, and analysis were performed by qualified personnel with appropriate training and experience.

[0189] **TABLE 4:** Experimental Design

Treatment Group	Route	Dose Frequency	Dose Level (mg/kg)	Number of Dogs	Study Duration (days)
1	IV	1x	0.025	2	28

[0190] The route of administration of VMB-C005 test article is summarized in Table 5.

[0191] **TABLE 5**

Dose Route:	Bolus IV injection into the front forearm.
Frequency:	Once on Day 0.
Dose Level(s):	0.025 mg/kg
Dose Volume:	Day 0 dose volume was 0.5 (F) and 0.7 (M) ml.
Method:	Test article was removed from frozen storage and allowed to acclimate to room temperature prior to dosing. Group 1 was dosed via bolus IV injection. The area over the cephalic vein was raised by occluding the vein manually. The needle was attached to the syringe containing the appropriate volume of test article was be inserted into the vein. After verifying accurate needle

	placement, the occlusion is removed, and the contents of the syringe injected slowly. Each animal was then returned to the home cage and monitored following dose administration. A separate sterile needle and syringe were used for each individual animal. Individual doses were based on the most recent body weights.
--	--

[0192] General in-life assessments of the test systems are described in Table 6.

[0193] **TABLE 6:** General in-life assessments

Assessment	Frequency	Comments
Daily Health Observations	Daily, beginning at acclimation start through Day 28.	Lab technicians or designee completed observations.
Physical Exams	Days -5, 0, and 28. In the event of an adverse event, a physical exam will also be completed.	The Investigator or Examining Veterinarian completed the physical exams for each dog. Physical exams included evaluation of body weight, heart rate, rectal temperature, respiratory rate. Physical exams included a subjective assessment of general appearance and attitude, otic, ocular/mucous membranes, respiratory, cardiovascular, gastrointestinal, neurologic, musculoskeletal, integumentary and genitourinary.
Daily Food Weight	Daily beginning on Day -5 to Day 28	The Investigator or designee weighed the food bowl and food prior to and after feeding. If the food bowl was knocked over during the meal, or if the dog defecates/contaminants the food bowl, this was noted.

[0194] The clinical pathology sample collection was at Days -5 and 28, The bioanalysis sample collection schedule was: Day 0 (pre-dose, 0.5, 4, 8hrs post-dose); Day 1 (24 and 36 hrs post-dose); Day 2 (48 hrs post-dose); Day 3, 4, 7, 14, 21, and 28. The animals were fasted prior to blood collection for the clinical pathology. Fasting was not required for the Bioanalysis collections. All blood samples were 1 mL and were collected from the jugular veins of the animals. Aseptic technique was used, the blood collection needle was attached to a needle holder. The needle was placed into the vein and a vacuum blood collection tube was inserted into the needle holder. The tube was allowed to fill and then removed. It was not documented

if blood was collected from the right or left jugular vein. Only EDTA anticoagulant was used. Samples were placed on ice until centrifuged.

[0195] For the clinical chemistry analysis, whole blood was centrifuged at 3,350×g for 10 min. The resulting serum was aliquoted into collection tubes. Serum for Bioanalysis was stored at the test facility and sent to BioAgilytix on dry ice for analysis.

[0196] Whole blood with EDTA was collected and shipped at 4°C to Heska for CBC analysis on the same day of collection.

[0197] Results

[0198] Individual body weight data are presented in TABLE . There were no significant changes to body weight over the course of a 28-day study.

[0199] **TABLE 7** Body Weight (kg) of dogs following dosing of VMB-C005 for 28-day Study

Dog No.	Acclimation	Day 0	Day 7	Day 14	Day 21	Day 28	Body Weight Change (Day 0-Day 28)
KQB1 (F)	10.8	11.2	10.7	10.4	10.6	10.8	0.0
4595841 (M)	13.1	13.2	13.3	13.4	13.6	13.5	0.2
Mean ±SEM	12.0 ± 1.2	12.2 ±1.0	12.0 ±1.3	11.9 ±1.5	12.1 ±1.5	12.2 ±1.4	0.2 ±0.2

[0200] Daily food weight data were recorded (not shown) and there were no remarkable changes in food consumption during the study.

[0201] Complete blood count (CBC) data are summarized in Table 8.

[0202] **TABLE 8:** Individual Clinical Chemistry and CBC Values on Day -5 and Day 28

Lab Parameter	Reference Range-Lower	Reference Range-Higher	Units	Day -5		Day 28	
				KQB1	4595841	KQB1	4595841
Plasma protein	6.0	7.5	g/dl	5.5 ^a	6.7	6.0	6.7
Hematocrit	33	56	%	53.8	49.4	48.9	50.6
MCV	60	76	fl	64.4	62.9	64.4	63.7
Reticulocytes	0	60	x10 ³ /μl	34	31	68 ^a	64 ^a
Red blood cells	5.1	8.5	x10 ⁶ /μl	8.36	7.85	7.59	7.95
Hemoglobin	11	19	g/dl	19.2 ^a	16.9	18.0	18.0
MCHC	30	38	g/dl	35.7	34.2	36.8	35.5
White blood cells	6.0	17.0	x10 ³ /μl	10.37	5.96 ^a	9.37	5.46 ^a
Seg neutrophils	3.0	11.5	x10 ³ /μl	6.22	3.99	5.43	4.04
Lymphocytes	1.0	4.8	x10 ³ /μl	3.21	1.49	2.44	1.04
Monocytes	0.2	1.4	x10 ³ /μl	0.62	0.30	0.09 ^a	0.11 ^a
Eosinophils	0.2	1.4	x10 ³ /μl	0.21	0.18	1.41 ^a	0.27
Basophils	0	0.1	x10 ³ /μl	0.10			

NRBC / 100 WBC			/ 100 WBC	1	2		1
Platelets	150	500	x10 ³ /μl	453	313	438	304
BUN	7	28	mg/dl	12.7	12.9	12.3	15.8
Creatinine	0.6	1.5	mg/dl	0.5 ^a	0.6	0.5 ^a	0.6
Phosphorus	2.8	6.1	mg/dl	3.8	3.3	3.9	3.4
Calcium	9.0	12.1	mg/dl	10.5	10.9	10.2	10.9
Total protein	5.4	7.4	g/dl	5.6	6.0	5.5	6.1
Albumin	2.7	4.5	g/dl	3.6	3.8	3.6	3.8
Globulin	1.9	3.4	g/dl	2	2	2	2
ALT	10	120	U/l	25	20	23	28
AST	16	40	U/l	37	26	39	26
ALP	18	141	U/l	43	56	43	47
GGT	0	6	U/l	1	3	1	3
Total bilirubin	0	0.4	mg/dl	0.1	0.1	0.1	0.1
Cholesterol	130	300	mg/dl	141	244	147	257
Glucose	65	122	mg/dl	83	88	87	85
Sodium	145	158	mmol/l	149	148	147	146
Potassium	4.1	5.5	mmol/l	4.7	4.1	4.2	4.5
Chloride	106	127	mmol/l	113	112	112	115
Na/K ratio				32	36	35	32
Bicarbonate	14	27	mmol/l	23	23	22	19
Anion gap	8	25		18	17	17	17
Triglycerides	30	130	mg/dl	29	36	38	49
^a Out of range parameter.							

[0203] Dog KQB1 and dog 4595841 both had elevated reticulocytes and monocytes at Day 28. The Study Veterinarian deemed these not clinically significant, but noted they were higher than Day -5. Due to the small samples size and no control group, additional investigation is needed to determine if there are any trends in these parameters.

[0204] There were no adverse events reported during the study. There were no injection site reactions observed during the study.

[0205] VMB-C005 serum concentrations

[0206] A summary of individual VMB-C005 serum concentrations collected across all timepoints following a single 0.025 mg/kg dose is provided in Table 9.

[0207] **TABLE 9: Serum VMB-C005 concentration following single dose**

Subject ID	Timepoint	Dilution Factor	Concentration (ng/mL)
KQB1	predose	1	2.83
	0.5h	100	571
	4h	100	277
	8h	100	141
	24h	50	18.5
	36h	50	6.18

	48h	50	4.30
	Day 3	50	3.17
	Day 4	50	3.00
	Day 7	100	2.96
	Day 14	50	2.72
	Day 21	10	2.92
	Day 28	10	3.02
4595841	predose	1	2.91
	0.5h	100	487
	4h	100	222
	8h	100	100
	24h	50	14
	36h	50	5.35
	48h	50	3.92
	Day 3	50	5.53
	Day 4	50	4.66
	Day 7	50	4.09
	Day 14	50	2.77
	Day 21	10	4.11
	Day 28	10	3.63

[0208] The PK data in Table 9 suggest that the dose was too low or the dose route was not appropriate as GLP-1 was minimally evident following Day 0 dosing.

[0209] **Conclusions**

[0210] Administration to two beagle dogs of the long-acting canine GLP1R agonist of SEQ ID NO: 8 in test article VMB-C005 was well tolerated. PK data analysis showed that a single IV dose of VMB-C005 is measurable for less than 24 hours. The clinical pathology dataset noted a few out of range parameters. Both dogs had elevated reticulocytes and monocytes at Day 28. There were no effects on body weight or food consumption. No AEs were reported for the duration of the study.

[0211] **Example 7: Three dose level study of a canine long-acting GLP1R agonist**

[0212] This example illustrates a pharmacokinetic (PK) study in eight dogs over a 28-day period of three dose levels of the canine long-acting GLP1R agonist test article, VMB-C005 (described in Example 6). Safety and tolerability were evaluated via physical exams, clinical pathology, and observations of serious adverse events (SAEs) and adverse events (AEs).

[0213] **Materials and methods**

[0214] Test Article and Vehicle Identification: the identity, characteristics, and stability of the VMB-C005 test article are provided in : the identity, characteristics, and stability of the VMB-C005 test article are provided in Table 2.

[0215] **TABLE TABLE 10**

Identification:	VMB-C005
-----------------	----------

Batch (Lot) No.:	20231221_VMBC005
Formulation	1x PBS + 6% Sucrose, pH 7.4
Concentration	4.64 mg/mL
LAL Endotoxin	0.1 EU/mg
Monomer Content (SE-HPLC)	97.09%

[0216] Dogs are the target species for VMB-C005. Beagle dogs were utilized as the test system for the study as summarized in Table 11.

[0217] TABLE 11

Species:	Dog
Breed:	Beagle
Number of Animals (by Study Number):	Acclimated: 8 Randomized: 6
Gender:	Male and Female
Physiological Status	Intact or neutered, non-pregnant, non-lactating
Source:	High Quality Research colony
Age:	The approximate age of the dogs at the initiation of dosing (Day 0) was 35 months
Body Weight:	Body weight at the initiation of dosing (Day 0) was between 8.6 and 13.1 kgs.

[0218] This study did not duplicate previous research and was intended to evaluate PK and safety in dogs under laboratory conditions. This study was designed to use the fewest number of dogs anticipated to provide meaningful data consistent with the objectives of the study. Procedures avoided or minimized discomfort, distress, and pain to the dogs. Approximately 3 days of acclimation was given to accustom the dogs to housing in study cages.

[0219] Veterinary care was available throughout the course of each study. Dogs were examined by veterinary staff as warranted by clinical signs or other changes. The dogs were observed daily with respect to general health and signs of disease. Physical exams, heart rate, rectal temperature, respiratory rate, and clinical pathology were collected at the first day of acclimation (Day -3) and prior to dosing on Day 0. There was no need for animal replacements during the study.

[0220] Environmental conditions were monitored, recorded, and maintained, according to Testing Facility SOPs. The targeted conditions for the animal room environment were: Temperature of 65°F to 68°F; Humidity of 30% to 57%; and a light cycle of 12 hours light and 12 hours dark. Diet consisted of once daily feeding of commercially available Exclusive Red Flannel Prime Formula dry kibble manufactured for PMI nutrition, LLC. A high-protein dog food that meets AAFCO nutritional requirements. Water was Fort Collins tap water and was available *ad libitum* to each animal via automatic waterers.

[0221] Experimental design of the PK study of VMB-C005 is summarized in Table 12. All procedures, methods, activities, and analysis were performed by qualified personnel with appropriate training and experience.

[0222] **TABLE 12:** Experimental Design

Treatment Group	Route	Dose Frequency	Dose Level (mg/kg)	Number of Dogs	Study Duration (days)
1	IV	1x	0.25	2	14
2			0.75	2	14
3			0.125	2	14

[0223] The route of administration of VMB-C005 test article is summarized in Table 13.

[0224] **TABLE 13**

Dose Route:	Bolus IV injection into the front forearm.
Frequency:	Once on Day 0.
Dose Level(s):	0.125, 0.25, or 0.75 mg/kg
Dose Volume:	Day 0 dose volume was 0.2-2.1 mLs.
Method:	Test article was removed from frozen storage and allowed to acclimate to room temperature prior to dosing. Group 1 was dosed via bolus IV injection. The area over the cephalic vein was raised by occluding the vein manually. The needle was attached to the syringe containing the appropriate volume of test article was be inserted into the vein. After verifying accurate needle placement, the occlusion is removed, and the contents of the syringe injected slowly. Each animal was then returned to the home cage and monitored following dose administration. A separate sterile needle and syringe were used for each individual animal. Individual doses were based on the most recent body weights.

[0225] General in-life assessments of the test systems are described in Table 14.

[0226] **TABLE 14:** General in-life assessments

Assessment	Frequency	Comments
Daily Health Observations	Daily, beginning at acclimation start through Day 14.	Lab technicians or designee completed observations.

Physical Exams	Days -3, 0, and 14. In the event of an adverse event, a physical exam will also be completed.	The Investigator or Examining Veterinarian completed the physical exams for each dog. Physical exams included evaluation of body weight, heart rate, rectal temperature, respiratory rate. Physical exams included a subjective assessment of general appearance and attitude, otic, ocular/mucous membranes, respiratory, cardiovascular, gastrointestinal, neurologic, musculoskeletal, integumentary and genitourinary.
Daily Food Weight	Daily beginning on Day -3 to Day 14	The Investigator or designee weighed the food bowl and food prior to and after feeding. If the food bowl was knocked over during the meal, or if the dog defecates/contaminants the food bowl, this was noted.

[0227] The clinical pathology sample collection was at Days -3 and 14. The bioanalysis sample collection schedule was: Day 0 (pre-dose, 0.5, 4, 8 hrs post-dose); Day 1 (24 and 36 hrs post-dose); Day 2 (48 hrs post-dose); Day 3, 4, 7, and 14. The animals were fasted prior to blood collection for the clinical pathology. Fasting was not required for the Bioanalysis collections. All blood samples were 1 mL and were collected from the jugular veins of the animals. Aseptic technique was used, the blood collection needle was attached to a needle holder. The needle was placed into the vein and a vacuum blood collection tube was inserted into the needle holder. The tube was allowed to fill and then removed. It was not documented if blood was collected from the right or left jugular vein. Only EDTA anticoagulant was used. Samples were placed on ice until centrifuged.

[0228] For the clinical chemistry analysis, whole blood was centrifuged at 3,350×g for 10 min. The resulting serum was aliquoted into collection tubes. Serum for Bioanalysis was stored at the test facility and sent to BioAgilytix on dry ice for analysis.

[0229] Whole blood with EDTA was collected and shipped at 4°C to Heska for CBC analysis on the same day of collection.

[0230] Results

[0231] Individual body weight data are presented in TABLE . There were no significant changes to body weight over the course of the 28-day study.

[0232] TABLE 15 Body Weight (kg) of dogs following dosing of VMB-C005 for 28-day Study

Dog No.	Acclimation	Day 0	Day 7	Day 14	Body Weight Change (Day 0-Day 28)
0.125 mg/kg VMB-C005 (Group 3)					

4579560	13.2	12.9	12.8	12.6	-0.6
RLO8	8.7	8.6	8.8	8.6	-0.1
Mean ±SEM	11.0 ±2.3	10.8 ±4.3	10.8 ±2.0	10.6 ±2.0	-0.4 ±0.3
0.25 mg/kg VMB-C005 (Group 1)					
YOP1	12.3	12.5	12.2	11.8	-0.5
RJ08	9.5	9.4	9.2	9.2	-0.3
Mean ±SEM	10.9 ±1.4	11.0 ±1.6	10.7 ±1.5	10.5 ±1.3	-0.4 ±0.1
0.75 mg/kg VMB-C005 (Group 2)					
4576790	12.8	13.1	13.2	13.5	0.7
ARK8	8.9	8.8	8.8	8.8	0.1
Mean ±SEM	10.9 ±2.0	11.0 ±2.2	11.0 ±2.2	11.2 ±2.4	0.4 ±0.3

[0233] Daily food weight data were recorded (not shown) and there were no remarkable changes in food consumption during the study.

[0234] Complete blood count (CBC) data are summarized in Tables 16, 17, and 18, below.

[0235] **TABLE 16:** Individual Clinical Chemistry and CBC Values Collected in Acclimation and Day 14 for dogs dosed with 0.125 mg/kg VMB-C005

Lab Parameter	Reference Range-Lower	Reference Range-Higher	Units	Acclimation		Day 14	
				4579560	RLO8	4579560	RLO8
Plasma protein	6.0	7.5	g/dl	6.7	6.7	6.6	6.9
Hematocrit	33	56	%	53.9	53.8	53.3	45.7
MCV	60	76	fl	67.8	67.7	68.5	68.4
Reticulocytes	0	60	x10 ³ /μl	56	40	70 H	20
Red blood cells	5.1	8.5	x10 ⁶ /μl	7.95	7.95 H	7.77	6.69
Hemoglobin	11	19	g/dl	19.6 H	19.1	19.5 H	17.0
MCHC	30	38	g/dl	36.3	35.5	36.7	37.2
White blood cells	6.0	17.0	x10 ³ /μl	8.16	7.29	7.35	7.19
Seg neutrophils	3.0	11.5	x10 ³ /μl	5.22	4.16	5.07	4.75
Lymphocytes	1.0	4.8	x10 ³ /μl	2.04	1.60	1.62	1.94
Monocytes	0.2	1.4	x10 ³ /μl	0.41	0.73	0.29	0.14 L
Eosinophils	0.2	1.4	x10 ³ /μl	0.49	0.73	0.37	0.36
Basophils	0	0.1	x10 ³ /μl		0.07		
NRBC / 100 WBC			/ 100 WBC	4		3	
Platelets	150	500	x10 ³ /μl	187	363	167	508 H
BUN	7	28	mg/dl	11.6	9.3	12.9	9.6
Creatinine	0.6	1.5	mg/dl	0.7	0.5 L	0.9	0.4 H
Phosphorus	2.8	6.1	mg/dl	4.3	3.6	4.4	4.3
Calcium	9.0	12.1	mg/dl	10.4	10.3	10.6	10.4
Total protein	5.4	7.4	g/dl	6.2	5.9	6.2	6.1
Albumin	2.7	4.5	g/dl	3.9	3.7	3.9	3.8
Globulin	1.9	3.4	g/dl	2	2	2	2
ALT	10	120	U/l	27	43	28	27

AST	16	40	U/l	26	15 L	26	17
ALP	18	141	U/l	45	45	36	37
GGT	0	6	U/l	3	3	2	3
Total bilirubin	0	0.4	mg/dl	0.0	0.0	0.1	0.1
Cholesterol	130	300	mg/dl	193	275	195	351 H
Glucose	65	122	mg/dl	90	95	88	93
Sodium	145	158	mmol/l	147	146	148	145
Potassium	4.1	5.5	mmol/l	4.3	4.5	4.4	4.9
Chloride	106	127	mmol/l	111	109	112	109
Na/K ratio				34	32	34	30
Bicarbonate	14	27	mmol/l	18	21	19	21
Anion gap	8	25		22	21	21	20
Triglycerides	30	130	mg/dl	36	54	29	51

H, parameter is above reference range; L, parameter is below reference range.

[0236] TABLE 17: Individual Clinical Chemistry and CBC Values Collected in Acclimation and Day 14 for dogs dosed with 0.25 mg/kg VMB-C005

Lab Parameter	Reference Range-Lower	Reference Range-Higher	Units	Acclimation		Day 14	
				YOP1	RJ08	YOP1	RJ08
Plasma protein	6.0	7.5	g/dl	6.8	6.3	6.5	6.9
Hematocrit	33	56	%	52.0	53.6	49.3	48.9
MCV	60	76	fl	67.1	66.8	68.1	68.3
Reticulocytes	0	60	$\times 10^3/\mu\text{l}$	8	40	22	21
Red blood cells	5.1	8.5	$\times 10^6/\mu\text{l}$	7.75	8.02	7.24	7.16
Hemoglobin	11	19	g/dl	18.8	19.0	18.4	18.2
MCHC	30	38	g/dl	36.2	35.5	37.3	37.2
White blood cells	6.0	17.0	$\times 10^3/\mu\text{l}$	7.96	14.63	6.88	13.65
Seg neutrophils	3.0	11.5	$\times 10^3/\mu\text{l}$	5.33	10.39	4.33	10.65
Lymphocytes	1.0	4.8	$\times 10^3/\mu\text{l}$	2.15	3.07	2.13	2.05
Monocytes	0.2	1.4	$\times 10^3/\mu\text{l}$	0.32	0.73	0.21	0.27
Eosinophils	0.2	1.4	$\times 10^3/\mu\text{l}$	0.16	0.44	0.21	0.68
Basophils	0	0.1	$\times 10^3/\mu\text{l}$				
NRBC / 100 WBC			/ 100 WBC			1	
Platelets	150	500	$\times 10^3/\mu\text{l}$	315	406	323	393
BUN	7	28	mg/dl	9.1	7.5	7.2	9.9
Creatinine	0.6	1.5	mg/dl	0.6	0.4 L	0.6	0.4 L
Phosphorus	2.8	6.1	mg/dl	4.3	3.4	4.6	3.3
Calcium	9.0	12.1	mg/dl	10.7	10.4	10.7	10.6
Total protein	5.4	7.4	g/dl	6.2	5.7	6.3	6.1
Albumin	2.7	4.5	g/dl	4.1	3.6	4.1	3.7
Globulin	1.9	3.4	g/dl	2	2	2	2
ALT	10	120	U/l	27	25	38	23
AST	16	40	U/l	22	19	20	18
ALP	18	141	U/l	18	61	16 L	49

GGT	0	6	U/l	4	4	5	3
Total bilirubin	0	0.4	mg/dl	0.0	0.0	0.1	0.1
Cholesterol	130	300	mg/dl	206	221	192	265
Glucose	65	122	mg/dl	93	84	87	88
Sodium	145	158	mmol/l	147	150	148	148
Potassium	4.1	5.5	mmol/l	4.3	3.9 L	4.7	4.4
Chloride	106	127	mmol/l	111	111	111	112
Na/K ratio				34	38	31	34
Bicarbonate	14	27	mmol/l	24	23	22	19
Anion gap	8	25		16	20	20	21
Triglycerides	30	130	mg/dl	35	33	15	34
H, parameter is above reference range; L, parameter is below reference range.							

[0237] TABLE 18: Individual Clinical Chemistry and CBC Values Collected in Acclimation and Day 14 for dogs dosed with 0.75 mg/kg VMB-C005

Lab Parameter	Reference Range-Lower	Reference Range-Higher	Units	Acclimation		Day 14	
				4576790	ARK8	4576790	ARK8
Plasma protein	6.0	7.5	g/dl	6.2	7.4	6.2	7.0
Hematocrit	33	56	%	54.0	45.6	54.1	44.5
MCV	60	76	fl	69.2	65.2	69.4	66.0
Reticulocytes	0	60	x10 ³ /μl	23	49	31	47
Red blood cells	5.1	8.5	x10 ⁶ /μl	7.80	7.00	7.79	6.74
Hemoglobin	11	19	g/dl	19.6 H	16.4	20.0 H	16.5
MCHC	30	38	g/dl	36.3	36.0	36.9	37.2
White blood cells	6.0	17.0	x10 ³ /μl	6.98	8.10	7.73	8.46
Seg neutrophils	3.0	11.5	x10 ³ /μl	4.89	5.10	5.10	5.41
Lymphocytes	1.0	4.8	x10 ³ /μl	1.19	1.70	1.86	2.28
Monocytes	0.2	1.4	x10 ³ /μl	0.21	0.24	0.08 L	0.17 L
Eosinophils	0.2	1.4	x10 ³ /μl	0.70	1.05	0.70	0.59
Basophils	0	0.1	x10 ³ /μl				
NRBC / 100 WBC			/ 100 WBC		1		
Platelets	150	500	x10 ³ /μl	252	567 H	283	530 H
BUN	7	28	mg/dl	14.1	10.3	14.1	11.4
Creatinine	0.6	1.5	mg/dl	0.8	0.5 L	0.8	0.6
Phosphorus	2.8	6.1	mg/dl	4.1	3.5	4.4	3.1
Calcium	9.0	12.1	mg/dl	10.3	10.6	10.4	10.3
Total protein	5.4	7.4	g/dl	5.7	6.7	5.9	6.4
Albumin	2.7	4.5	g/dl	3.7	4.0	3.7	3.8
Globulin	1.9	3.4	g/dl	2	3	2	3
ALT	10	120	U/l	24	77	24	25
AST	16	40	U/l	27	18	32	20
ALP	18	141	U/l	53	49	59	31
GGT	0	6	U/l	3	6	1	5
Total bilirubin	0	0.4	mg/dl	0.1	0.1	0.1	0.1

Cholesterol	130	300	mg/dl	173	313 H	192	291
Glucose	65	122	mg/dl	86	94	97	96
Sodium	145	158	mmol/l	149	148	149	145
Potassium	4.1	5.5	mmol/l	4.2	4.4	4.4	4.8
Chloride	106	127	mmol/l	112	110	113	110
Na/K ratio				35	34	34	30
Bicarbonate	14	27	mmol/l	23	22	21	20
Anion gap	8	25		18	20	19	20
Triglycerides	30	130	mg/dl	16	32	23	34
H, parameter is above reference range; L, parameter is below reference range.							

[0238] There were no remarkable trends or consistent out of range clinical chemistry or CBC values noted for any animals throughout the study. There were no adverse events reported during the study. There were no injection site reactions observed during the study.

[0239] VMB-C005 serum concentrations

[0240] A summary of individual VMB-C005 serum concentrations collected across all timepoints following a single dose of 0.125, 0.25, or 0.75 mg/kg are provided in Tables 19, 20, and 21, respectively.

[0241] **TABLE 19:** Serum VMB-C005 concentration following single 0.125 mg/kg dose

Subject ID	Timepoint	Concentration (ng/mL)
4579560	predose	BLQ
	0.5h	1696
	4h	754
	8h	218
	24h	109
	36h	50.4
	48h	10.00
	Day 3	5.95
	Day 4	BLQ
	Day 7	BLQ
	Day 14	BLQ
RLO8	predose	BLQ
	0.5h	2945
	4h	1678
	8h	941
	24h	141
	36h	48.9
	48h	55.7
	Day 3	12.0
	Day 4	9.79
	Day 7	4.74
	Day 14	BLQ
"BLQ" = below the level of quantification		

[0242] TABLE 20: Serum VMB-C005 concentration following single 0.25 mg/kg dose

Subject ID	Timepoint	Concentration (ng/mL)
YOP1	predose	4.43
	0.5h	4888
	4h	2476
	8h	1460
	24h	205
	36h	66.0
	48h	37.7
	Day 3	13.0
	Day 4	6.07
	Day 7	BLQ
	Day 14	BLQ
RJ08	predose	BLQ
	0.5h	5303
	4h	1411
	8h	1655
	24h	270
	36h	84.0
	48h	44.2
	Day 3	16.5
	Day 4	8.23
	Day 7	BLQ
	Day 14	BLQ

"BLQ" = below the level of quantification

[0243] TABLE 21: Serum VMB-C005 concentration following single 0.75 mg/kg dose

Subject ID	Timepoint	Concentration (ng/mL)
4576790	predose	BLQ
	0.5h	15149
	4h	7931
	8h	4556
	24h	796
	36h	321
	48h	98.3
	Day 3	40.7
	Day 4	20.4
	Day 7	BLQ
	Day 14	BLQ
ARK8	predose	BLQ
	0.5h	13688
	4h	8832
	8h	5677
	24h	1171

	36h	480
	48h	135
	Day 3	60.7
	Day 4	34.3
	Day 7	9.72
	Day 14	BLQ
"BLQ" = below the level of quantification		

[0244] Area Under the Curve (AUC)

[0245] Mean AUC values following dosing of VMB-C005 at the three dosing levels as described above are listed in Table 22. AUC values increased in a dose dependent manner.

[0246] TABLE 22

	Dose VMB-C005		
	0.125 mg/kg	0.25 mg/kg	0.75 mg/kg
AUC ±SE	830.9	1748	5859
95% Confidence Interval	406.8-12.55	1532-1964	5221-6497

[0247] Conclusions

[0248] Administration of VMB-C005 at 0.125, 0.25 and 0.75 to beagle dogs was well tolerated. Review of the clinical pathology dataset noted that there were a few out of range parameters, but there were no consistent out of range parameters nor trends identified. There were no effects on body weight or food consumption. No AEs were reported for the duration of the study. There was a dose dependent increase in AUC values, however overall PK analysis suggest that VMB-C005 is only measurable for a maximum of 7 days (0.75 mg/kg dose), likely suggesting that at any of the doses evaluated that dogs would likely need to be dosed weekly.

[0249] References

1. Trapp S, Brierley DI. Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. Br J Pharmacol. 2022;179(4):557–70.
2. O'Neil PM, Birkenfeld AL, McGowan B, Mosenzon O, Pedersen SD, Wharton S, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. The Lancet. 2018;392(10148):637–49.
3. Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002.

4. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. *Circulation*. 2017;136(9):849–70.
5. Pulipati VP, Ravi V, Pulipati P. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2020 Dec 1;27(18):1922–30.
6. Bethel MA, Patel RA, Merrill P, Lokhnygina Y, Buse JB, Mentz RJ, et al. Cardiovascular outcomes with glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(2):105–13.
7. Meurot C, Martin C, Sudre L, Breton J, Bougault C, Rattenbach R, et al. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. *Sci Rep*. 2022;12(1):1567.
8. Model JF, Rocha DS, da C Fagundes A, Vinagre AS. Physiological and pharmacological actions of glucagon like peptide-1 (GLP-1) in domestic animals. *Vet Anim Sci*. 2022;16:100245.
9. Ionut V, Woolcott OO, Mkrtchyan HJ, Stefanovski D, Kabir M, Iyer MS, et al. Exenatide treatment alone improves β -cell function in a canine model of pre-diabetes. *PLoS One*. 2016;11(7):e0158703.
10. Elahi D, Angeli FS, Vakili-pour A, Carlson OD, Tomas E, Egan JM, et al. GLP-1 (32–36) amide, a novel pentapeptide cleavage product of GLP-1, modulates whole body glucose metabolism in dogs. *Peptides*. 2014;59:20–4.
11. Ionut V, Liberty IF, Hucking K, Lottati M, Stefanovski D, Zheng D, et al. Exogenously imposed postprandial-like rises in systemic glucose and GLP-1 do not produce an incretin effect, suggesting an indirect mechanism of GLP-1 action. *Am J Physiol-Endocrinol Metab*. 2006;291(4):E779–85.
12. Moore MC, Werner U, Smith MS, Farmer TD, Cherrington AD. Effect of the glucagon-like peptide-1 receptor agonist lixisenatide on postprandial hepatic glucose metabolism in the conscious dog. *Am J Physiol-Endocrinol Metab*. 2013;305(12):E1473–82.
13. Nishizawa M, Moore MC, Shiota M, Gustavson SM, Snead WL, Neal DW, et al. Effect of intraportal glucagon-like peptide-1 on glucose metabolism in conscious dogs. *Am J Physiol-Endocrinol Metab*. 2003;284(5):E1027–36.

14. Chavda VP, Balar PC, Vaghela DA, Dodiya P. Unlocking longevity with GLP-1: A key to turn back the clock? *Maturitas*. 2024;108028.
15. APOP. <https://www.petobesityprevention.org/>. Association for Pet Obesity Prevention. Available from: <https://www.petobesityprevention.org/>
16. State of U.S. Pet Obesity [Internet]. The Association for Pet Obesity Prevention, LLC; p. 1–27. Report No.: 2022. Available from: <https://static1.squarespace.com/static/6425ec5d33eaaa634113b2d4/t/6454f61c0cad164860799c8f/1683289630779/2022+State+of+US+Pet+Obesity+Report.pdf>
17. Pechenov S, Revell J, Will S, Naylor J, Tyagi P, Patel C, et al. Development of an orally delivered GLP-1 receptor agonist through peptide engineering and drug delivery to treat chronic disease. *Sci Rep*. 2021;11(1):22521.
18. Chen M, Angeli FS, Shen Y tang, Shannon RP. GLP-1 (7–36) amide restores myocardial insulin sensitivity and prevents the progression of heart failure in senescent beagles. *Cardiovasc Diabetol*. 2014;13(1):1–12.
19. Nikolaidis LA, Elahi D, Shen YT, Shannon RP. Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. *Am J Physiol-Heart Circ Physiol*. 2005;289(6):H2401–8.
20. Nikolaidis LA, Elahi D, Hentosz T, Doverspike A, Huerbin R, Zourelas L, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation*. 2004;110(8):955–61.
21. Nakamura H, Niwano S, Niwano H, Fukaya H, Murakami M, Kishihara J, et al. Liraglutide suppresses atrial electrophysiological changes. *Heart Vessels*. 2019;34:1389–93.
22. Chen J, Xie JJ, Shi KS, Gu YT, Wu CC, Xuan J, et al. Glucagon-like peptide-1 receptor regulates endoplasmic reticulum stress-induced apoptosis and the associated inflammatory response in chondrocytes and the progression of osteoarthritis in rat. *Cell Death Dis*. 2018;9(2):212.

[0250] While the foregoing disclosure of the present invention has been described in some detail by way of example and illustration for purposes of clarity and understanding, this disclosure including the examples, descriptions, and embodiments described herein are for illustrative purposes, are intended to be exemplary, and should not be construed as limiting the

present disclosure. It will be clear to one skilled in the art that various modifications or changes to the examples, descriptions, and embodiments described herein can be made and are to be included within the spirit and purview of this disclosure and the appended claims. Further, one of skill in the art will recognize a number of equivalent methods and procedure to those described herein. All such equivalents are to be understood to be within the scope of the present disclosure and are covered by the appended claims.

[0251] Additional embodiments of the invention are set forth in the following claims.

[0252] The disclosures of all publications, patent applications, patents, or other documents mentioned herein are expressly incorporated by reference in their entirety for all purposes to the same extent as if each such individual publication, patent, patent application or other document were individually specifically indicated to be incorporated by reference herein in its entirety for all purposes and were set forth in its entirety herein. In case of conflict, the present specification, including specified terms, will control.

CLAIMS

What is claimed is:

1. A GLP1R agonist of canine, feline, or equine GLP1R, wherein the agonist comprises a fusion comprising:
 - (i) a species-specific IgG Fc region polypeptide, wherein the Fc region polypeptide comprises a Y at position 252 (Eu numbering); optionally, wherein the Fc region polypeptide comprises an A at positions 234 and 235 (Eu numbering); and
 - (ii) a GLP1 polypeptide, an Extendin-4 polypeptide, or an OXM polypeptide.
2. The agonist of claim 1, wherein the fusion comprises:
 - (a) a wild-type GLP1 polypeptide of SEQ ID NO: 1;
 - (b) a variant GLP1 polypeptide of SEQ ID NO: 2;
 - (c) an OXM polypeptide of SEQ ID NO: 3, or a functional variant thereof; or
 - (d) an Extendin-4 polypeptide of SEQ ID NO: 5, or a functional variant thereof.
3. The agonist of any one of claims 1-2, wherein the species-specific IgG Fc region polypeptide is attached to the GLP1 polypeptide, Extendin-4 polypeptide, or OXM polypeptide via a first polypeptide linker; optionally, wherein the first polypeptide linker comprises an amino acid sequence selected from SEQ ID NO: 28 and 29.
4. The agonist of any one of claims 1-2, wherein the agonist is a dual agonist and further comprises:
 - (iii) a G1P polypeptide, or a Glucagon polypeptide.
5. The agonist of claim 5, wherein the G1P polypeptide, or a Glucagon polypeptide is attached to the species-specific IgG Fc region polypeptide via a second polypeptide linker; optionally, wherein the second polypeptide linker comprises an amino acid sequence selected from SEQ ID NO: 28 and 29.
6. The agonist of any one of claims 1-2, wherein the agonist is:
 - (a) a canine agonist or a canine dual agonist comprising an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 8, 12, 16, 20, and 24;
 - (b) a feline agonist or a feline dual agonist comprising an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 9, 13, 17, 21, and 25; or
 - (c) an equine agonist or an equine dual agonist comprising an amino acid sequence having at least 90% identity to a sequence selected from SEQ ID NO: 10, 11, 14, 15, 18, 19, 22, 23, 26, and 27.
7. An isolated nucleic acid or vector encoding the agonist of any one of claims 1-6.

8. An isolated host cell comprising the nucleic acid or vector of claim 7.
9. A method of producing an agonist of any one of claims 1-6, comprising culturing the host cell of claim 8 and isolating the agonist.
10. A pharmaceutical composition comprising the agonist of any one of claims 1-6 and a pharmaceutically acceptable carrier.
11. A method of treating a canine, feline or equine having a condition associated with GLP1, the method comprising administering to the canine, feline or equine a therapeutically effective amount of the agonist of any one of claims 1-6 or the pharmaceutical composition of claim 10.
12. A method of maintaining remission of a condition associated with GLP1 in a canine, feline, or equine, the method comprising administering to the canine a therapeutically effective amount of the GLP1R agonist of any one of claims 1-6 or the pharmaceutical composition of claim 10.
13. The method of any one of claims 11-12, wherein the condition associated with GLP1 is a metabolic disorder; optionally, wherein the metabolic disorder is associated with high glucose, obesity, poor cardiovascular outcome, and/or aging.
14. The method of any one of claims 11-12, wherein the condition associated with GLP1 is glucose dysregulation disease.
15. The method of any one of claims 11-12, wherein the condition associated with GLP1 is being overweight and/or obesity.
16. The method of any one of claims 11-12, wherein the condition associated with GLP1 is cardiovascular disease.
17. The method of any one of claims 11-12, wherein the condition associated with GLP1 is an age-related disorder; optionally, wherein the condition is age-related neurodegeneration.
18. A method of treating a canine, a feline, or an equine subject having a condition associated with GLP1R agonist activity, the method comprising administering to the canine, feline, or equine subject a therapeutically effective amount of the species-specific agonist or dual agonist of any one of claims 1-6, or the pharmaceutical composition of claim 10.
19. The method of claim 18, wherein the agonist or the pharmaceutical composition is administered parenterally.
20. The method of any one of claims 11-18, wherein the agonist or the pharmaceutical composition is administered by an intramuscular route, an intraperitoneal route, an

intracerebrospinal route, a subcutaneous route, an intra-arterial route, an intrasynovial route, an intrathecal route, or an inhalation route.

21. The method of any one of claims 11-20, wherein the therapeutically effective amount of the agonist or the pharmaceutical composition is administered at an amount in the range of about 0.0001 mg/kg body weight to about 100 mg/kg body weight per dose.

22. The method of any one of claims 11-21, wherein therapeutically effective amount of the agonist or the pharmaceutical composition is administered in a per dose amount of at least about 0.025 mg/kg body weight, at least about 0.05 mg/kg body weight, at least about 0.075 mg/kg body weight, at least about 0.10 mg/kg body weight, at least about 0.125 mg/kg body weight, at least about 0.25 mg/kg body weight, at least about 0.5 mg/kg body weight, at least about 0.75 mg/kg body weight, at least about 1.0 mg/kg body weight, at least about 1.25 mg/kg body weight, at least about 1.5 mg/kg body weight, at least about 1.75 mg/kg body weight, at least about 2.0 mg/kg body weight, or at least about 2.5 mg/kg body weight.

23. The method of any one of claims 11-22, wherein the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount of about 0.025 mg/kg body weight to about 2.5 mg/kg body weight, about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.

24. The method of any one of claims 11-23, wherein the therapeutically effective amount of agonist or the pharmaceutical composition is administered in a per dose amount at an interval of: daily, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, weekly, semi-monthly, or monthly.

25. The method of any one of claims 11-24, wherein the therapeutically effective amount of agonist or the pharmaceutical composition is administered weekly in a per dose amount of about 0.05 mg/kg body weight to about 1.5 mg/kg body weight, about 0.10 mg/kg body weight to about 1.0 mg/kg body weight, about 0.25 mg/kg body weight to about 0.75 mg/kg body weight.