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(71) Demandeur/Applicant:
AMGEN INC., US

(72) Inventeurs/Inventors:
XIONG, YUMEI, US;
VENIANT ELLISON, MURIELLE MARIE, US

(74) Agent: SMART & BIGGAR LLP

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(54) Title: GROWTH DIFFERENTIATION FACTOR 15 COMBINATION THERAPY

(57) Abrégé/Abstract:
The present disclosure provides combination therapy with GDF15 molecules. In some embodiments, the GDF15 molecule is a GDF15-Fc fusion, in which a GDF15 region is fused to an Fc region, optionally via a linker. In one embodiment, combination therapy comprises administration of a GDF15 molecule with a GLP-1R agonist. In another embodiment, combination therapy comprises administration of a GDF15 molecule with a GIPR antagonist.

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(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **XIONG, YuMei**; c/o Amgen Inc., Law Department – Patent Operations, One Amgen Center Drive, M/S 28-5-A, Thousand Oaks, California 91320-1799 (US). **VENIANT ELLISON, Murielle Marie**; c/o Amgen Inc., Law Department – Patent Operations, One Amgen Center Drive, M/S 28-5-A, Thousand Oaks, California 91320-1799 (US).

(74) Agent: **MAH, Angie S.**; AMGEN INC., Law Department - Patent Operations M/S 28-5-A, One Amgen Center Drive, Thousand Oaks, California 91320-1799 (US).

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(54) Title: GROWTH DIFFERENTIATION FACTOR 15 COMBINATION THERAPY

(57) Abstract: The present disclosure provides combination therapy with GDF15 molecules. In some embodiments, the GDF15 molecule is a GDF15-Fc fusion, in which a GDF15 region is fused to an Fc region, optionally via a linker. In one embodiment, combination therapy comprises administration of a GDF15 molecule with a GLP-1R agonist. In another embodiment, combination therapy comprises administration of a GDF15 molecule with a GIPR antagonist.

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GROWTH DIFFERENTIATION FACTOR 15 COMBINATION THERAPY

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/815,866, filed on March 8, 2019, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled A-2298-WO-PCT_SeqList.txt, created March 2, 2020, which is 166 kb in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The instant disclosure relates to GDF15 molecules, such as GDF15 fusion proteins, compositions thereof, and methods for making and using such proteins, such as its use in combination therapy.

BACKGROUND

Growth differentiation factor 15 (GDF15), also referred to as macrophage inhibitory cytokine 1 (MIC1) (Bootcov MR, 1997, *Proc Natl Acad Sci* 94:11514-9), placental bone morphogenetic factor (PLAB) (Hromas R 1997, *Biochim Biophys Acta.* 1354:40-4), placental transforming growth factor beta (PTGFB) (Lawton LN 1997, *Gene.* 203:17-26), prostate derived factor (PDF) (Paralkar VM 1998, *J Biol Chem.* 273:13760-7), and nonsteroidal anti-inflammatory drug-activated gene (NAG-1) (Baek SJ 2001, *J Biol Chem.* 276: 33384-92), is a secreted protein that circulates in plasma as an ~25 kDa homodimer. GDF15 binds to GDNF family receptor α-like (GFRAL) with high affinity. GDF15-induced cell signaling is believed to require the interaction of GFRAL with the coreceptor RET.

GDF15 has been linked to multiple biological activities. Elevated GDF15 has been shown to be correlated with weight loss and administration of GDF15 has been shown to reduce food intake and body weight.

Glucose-dependent insulinotropic polypeptide (GIP, formerly called gastric inhibitory polypeptide) and glucagon like polypeptide-1 (GLP-1) are known insulinotropic factors ("incretins"). GIP is a single 42-amino acid peptide and human GIP is derived from the processing of proGIP, a 153-amino acid precursor. GIP secretion is induced by food ingestion and has a number of physiological effects, including promotion of fat storage in adipocytes and promotion of pancreatic islet β-cell function and glucose-dependent insulin secretion. Intact GIP is rapidly degraded by DPPIV to an inactive form. The receptor for GIP, GIP

receptor (GIPR), is a member of the secretin-glucagon family of G-protein coupled receptors (GPCRs). Human GIPR comprises 466 amino acids.

Glucagon-like peptide-1 (GLP-1) is a 31-amino acid peptide derived from the proglucagon gene. It is secreted by intestinal L-cells and released in response to food ingestion to induce insulin secretion from pancreatic β-cells. In addition to the incretin effects, GLP-1 also decreases glucagon secretion, delays gastric emptying and reduces caloric intake. GLP-1 exerts its effects by activation of the GLP-1 receptor (GLP-1R), which belongs to a class B G-protein-coupled receptor. The function of GLP-1 is limited by rapid degradation by the DPP-IV enzyme. Longer lasting GLP-1R agonists such as exenatide, liraglutide, dulaglutide have been developed and are being used clinically to improve glycemic control in patients with type 2 diabetes. Furthermore, GLP-1R agonists can promote body weight reduction as well as reduction in blood pressure and plasma cholesterol levels in patients.

Accordingly, there is a need for combination therapy comprising a GDF15 molecule with one or more other therapeutic agent(s), such as a GLP-1R agonist (e.g., a GLP-1 analog), and/or a GIPR antagonist (e.g., a GIPR antibody). The present disclosure meets this need and provide related advantages.

SUMMARY

Provided herein is combination therapy comprising a GDF15 molecule, including methods of treating a condition comprising administering a GDF15 molecule and another therapeutic agent. In one embodiment, the other therapeutic agent is a GIPR antagonist, such as a GIPR antigen binding protein. In one embodiment, the GIPR antigen binding protein is an antibody. In another embodiment, the other therapeutic agent is a GLP-1R agonist, such as dulaglutide.

Also provided herein is a method of treating a metabolic condition in a subject comprising administering a GDF15 molecule and a GIPR antagonist, wherein administration of the GDF15 molecule and the GIPR antagonist has a synergistic effect as compared to administration of the GDF15 molecule or GIPR antagonist alone.

The present disclose also provides a method of treating a metabolic condition in a subject comprising administering a GDF15 molecule and dulaglutide, wherein administration of the GDF15 molecule and dulaglutide has a synergistic effect as compared to administration of the GDF15 molecule or dulaglutide alone.

In one embodiment, combination therapy comprises administering a GDF15 molecule with a corresponding Fc molecule, such as described herein and in Table 6.

In one embodiment, the GDF15 molecule and the other therapeutic agent are administered concurrently. In another embodiment, the GDF15 molecule and the other therapeutic agent are administered sequentially.

Also provided herein is a pharmaceutical composition comprising a GDF15 molecule and the other therapeutic agent, such as a pharmaceutical composition comprising a GDF15 molecule a GIPR antagonist, wherein administration of the composition has a synergistic effect as compared to administration of the GDF15 molecule or GIPR antagonist alone. In some embodiments, the GIPR antagonist is an antibody. In some embodiments, the synergistic effect is in decreasing body weight. The GIPR antagonist of the composition may comprise a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, wherein the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprises the amino acid sequences of SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively. In some embodiments, the GIPR antagonist of the composition comprises a light chain variable region and a heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90; 91 and 92; 93 and 94; or 95 and 96, respectively. In some embodiments, the GIPR antagonist of the composition comprises a light chain and a heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98; 99 and 100; 101 and 102; 103 and 104, or 105 and 106, respectively. In some embodiments, the GDF15 molecule of the composition is a fusion protein comprising a GDF15 region joined to an Fc region. In some embodiments, the GDF15 region is joined to the Fc region via a linker. In some embodiments, the GDF15 region comprises the amino acid sequence of SEQ ID NO: 6 and at least one mutation. In some embodiments, at least one of the mutations is of the aspartate at position 5. In some embodiments, the aspartate at position 5 is mutated to glutamate. In some embodiments, the GDF15 region further comprises a mutation of the asparagine at position 3. In some embodiments, the asparagine at position 3 mutated to glutamine. In some embodiments, the linker of the GDF molecule joined to the Fc region is a (G4S)n or (G4Q)n linker, wherein n is greater than 0 (e.g., n is 1 or 2). The Fc region may comprise a charged pair mutation or a truncated hinge region, or both. In some embodiments, the Fc region is selected from Table 3. In yet other embodiments, the composition further comprises a corresponding Fc molecule to the GDF15 molecule, e.g., as described herein and in Table 6.

Also provided herein is a pharmaceutical composition comprising a GDF15 molecule and dulaglutide, wherein administration of the composition has a synergistic effect as compared to administration of the GDF15 molecule or dulaglutide alone. A pharmaceutical composition comprising a GDF15 molecule and dulaglutide, wherein administration of the composition has a synergistic effect as compared to administration of the GDF15 molecule or dulaglutide alone. In some embodiments, the synergistic effect is in decreasing body weight. In some embodiments, the GDF15 molecule of the composition is a fusion protein comprising a GDF15 region joined to an Fc region. In some embodiments, the GDF15 region is joined to the Fc region via a linker. In some embodiments, the GDF15 region comprises the amino

acid sequence of SEQ ID NO: 6 and at least one mutation. In some embodiments, at least one of the mutations is of the aspartate at position 5. In some embodiments, the aspartate at position 5 is mutated to glutamate. In some embodiments, the GDF15 region further comprises a mutation of the asparagine at position 3. In some embodiments, the asparagine at position 3 mutated to glutamine. In some embodiments, the linker of the GDF molecule joined to the Fc region is a (G4S)n or (G4Q)n linker, wherein n is greater than 0 (e.g., n is 1 or 2). The Fc region may comprise a charged pair mutation or a truncated hinge region, or both. In some embodiments, the Fc region is selected from Table 3. In yet other embodiments, the composition further comprises a corresponding Fc molecule to the GDF15 molecule, e.g., as described herein and in Table 6.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows the body weight change in grams in mice administered vehicle weekly (Group A); dulaglutide twice per week (Group B); GIPR antibody 2.63.1 weekly and vehicle weekly, the latter being on the alternate dulaglutide dosing day (Group C); FcΔ10(-)-(G4S)4-GDF15 (SEQ ID NO: 39) (along with its heterodimerization partner, FcΔ10(+,K) (SEQ ID NO: 32)) weekly and vehicle weekly, the latter on the alternate dulaglutide dosing day (Group D); FcΔ10(-)-(G4S)4-GDF15) (along with its heterodimerization partner, FcΔ10(+,K)) weekly and dulaglutide twice per week (Group E); FcΔ10(-)-(G4S)4-GDF15 (along with its heterodimerization partner, FcΔ10(+,K)) weekly and GIPR antibody 2.63.1 weekly (Group F).

Figure 1B shows the percent body weight change of the mice in Groups A-F.

Figure 2A shows the percent body weight change of the mice in Groups A-F 2 weeks after treatment started.

Figure 2B shows the percent body weight change of the mice in Groups A-F 5 weeks after treatment started.

Figure 3A shows the glucose levels from the oral glucose tolerance test (OGTT) of the mice in Groups A-F two weeks after treatment.

Figure 3B shows the glucose AUC results from the OGTT of the mice in Groups A-F two weeks after treatment.

Figure 4A shows the glucose levels from the intraperitoneal glucose tolerance test (IPGTT) of the mice in Groups A-F five weeks after treatment.

Figure 4B shows the glucose AUC results from the IPGTT of the mice in Groups A-F five weeks after treatment.

Figure 5A shows the fasting blood glucose levels measured two weeks and five weeks after treatment of the mice in Groups A-F.

Figure 5B shows the serum insulin levels measured two weeks and five weeks after treatment of the mice in Groups A-F.

Figure 5C shows the serum triglyceride levels measured two weeks and five weeks after treatment of the mice in Groups A-F.

Figure 5D shows the serum total cholesterol levels measured two weeks and five weeks after treatment of the mice in Groups A-F.

Figure 6 shows the daily food intake measured three consecutive days a week during the treatment of the mice in Groups A-F.

DETAILED DESCRIPTION

Provided herein is combination therapy comprising a GDF15 molecule and another therapeutic agent or molecule. In one embodiment, the other agent or molecule is a molecule that reduces body weight, food intake and/or treat obesity and/or a related condition. Also provided herein are methods of making the molecules and methods of using the molecules.

In some embodiments, the GDF15 molecule is a GDF15-Fc fusion protein. The fusion protein can comprise a GDF15 region joined to an Fc region. In some embodiments, the GDF15 region is joined to the Fc via a linker. In some embodiments, the GDF15 region comprises wild type GDF15. Both the human and murine GDF15 have a signal peptide and prodomain. The nucleotide sequence for full length human GDF15 is:

atgcccgggc aagaactcag gacggtgaat ggctctcaga tgctcctggt gttgctggtg ctctcgtggc tgccgcatgg gggcgccctg tctctggccg aggcgagccg cgcaagtttc ccgggaccct cagagttgca ctccgaagac tccagattcc gagagttgcg gaaacgctac gaggacctgc taaccaggct gcgggccaac cagagctggg aagattcgaa caccgacctc gtcccggccc ctgcagtccg gatactcacg ccagaagtgc ggctgggatc cggcggccac ctgcacctgc gtatctctcg ggccgccctt cccgaggggc tccccgaggc ctcccgcctt caccgggctc tgttccggct gtccccgacg gcgtcaaggt cgtgggacgt gacacgaccg ctgcggcgtc agctcagcct tgcaagaccc caggcgcccg cgctgcacct gcgactgtcg ccgccgccgt cgcagtcgga ccaactgctg gcagaatctt cgtccgcacg gccccagctg gagttgcact tgcggccgca agccgccagg gggcgccgca gagcgcgtgc gcgcaacggg gaccactgtc cgctcgggcc cgggcgttgc tgccgtctgc acacggtccg cgcgtcgctg gaagacctgg gctgggccga ttgggtgctg tcgccacggg aggtgcaagt gaccatgtgc atcggcgcgt gcccgagcca gttccgggcg gcaaacatgc acgcgcagat caagacgagc ctgcaccgcc tgaagcccga cacggtgcca gcgccctgct gcgtgcccgc cagctacaat cccatggtgc tcattcaaaa gaccgacacc ggggtgtcgc tccagaccta tgatgacttg ttagccaaag actgccactg catatga (SEQ ID NO: 1)

The amino acid sequence for full length human GDF15 (308 amino acids) is:

MPGQELRTVNGSQMLLVLLVLSWLPHGGALSLAEASRASFPGPSELHSEDSRFRELR
KRYEDLLTRLRANQSWEDSNTDLVPAPAVRILTPEVRLGSGGHLHLRISRAALPEGLP
EASRLHRALFRLSPTASRSWDVTRPLRRQLSLARPQAPALHLRLSPPPSQSDQLLAESS
SARPQLELHLRPQAARGRRRARARNGDHCPLGPGRCCRLHTVRASLEDLGWADWV
LSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQ
KTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO: 2)

The nucleotide sequence for human GDF15 without its signal sequence is:

ctgtctctgg ccgaggcgag ccgcgcaagt ttcccgggac cctcagagtt gcactccgaa gactccagat tccgagagtt gcggaaacgc tacgaggacc tgctaaccag gctgcgggcc aaccagagct gggaagattc gaacaccgac ctcgtcccgg cccctgcagt ccggatactc acgccagaag tgcggctggg atccggcggc cacctgcacc tgcgtatctc tcgggccgcc cttcccgagg ggctccccga ggcctcccgc cttcaccggg ctctgttccg gctgtccccg acggcgtcaa ggtcgtggga cgtgacacga ccgctgcggc gtcagctcag ccttgcaaga ccccaggcgc ccgcgctgca cctgcgactg tcgccgccgc cgtcgcagtc ggaccaactg ctggcagaat cttcgtccgc acggccccag ctggagttgc acttgcggcc gcaagccgcc agggggcgcc gcagagcgcg tgcgcgcaac ggggaccact gtccgctcgg gcccgggcgt tgctgccgtc tgcacacggt ccgcgcgtcg ctggaagacc tgggctgggc cgattgggtg ctgtcgccac gggaggtgca agtgaccatg tgcatcggcg cgtgcccgag ccagttccgg gcggcaaaca tgcacgcgca gatcaagacg agcctgcacc gcctgaagcc cgacacggtg ccagcgccct gctgcgtgcc cgccagctac aatcccatgg tgctcattca aaagaccgac accggggtgt cgctccagac ctatgatgac ttgttagcca aagactgcca ctgcatatga (SEQ ID NO: 3)

The amino acid sequence for human GDF15 without its 29 amino acid signal sequence (279 amino acids) is:

LSLAEASRASFPGPSELHSEDSRFRELRKRYEDLLTRLRANQSWEDSNTDLVPAPAVR ILTPEVRLGSGGHLHLRISRAALPEGLPEASRLHRALFRLSPTASRSWDVTRPLRRQLS LARPQAPALHLRLSPPPSQSDQLLAESSSARPQLELHLRPQAARGRRRARARNGDHCP LGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTS LHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO: 4)

The nucleotide sequence for human GDF15 without its signal peptide or prodomain is:

gcgcgcaacggggaccactgtccgctcgggcccgggcgttgctgccgtctgcacacggtccgcgcgtcgctggaagacctgggct gggccgattgggtgctgtcgccacgggaggtgcaagtgaccatgtgcatcggcgcgtgcccgagccagttccgggcggcaaacatg cacgcgcagatcaagacgagcctgcaccgcctgaagcccgacacggtgccagcgccctgctgcgtgcccgccagctacaatcccat ggtgctcattcaaaagaccgacaccggggtgtcgctccagacctatgatgacttgttagccaaagactgccactgcatatga (SEQ ID NO: 5)

The amino acid sequence for human GDF15 without its signal peptide or prodomain (the active domain of GDF15 of 112 amino acids) is:

ARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAAN MHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI (SEQ ID NO: 6)

The nucleotide sequence for full length murine GDF15 is:

atggccccgc ccgcgctcca ggcccagcct ccaggcggct ctcaactgag gttcctgctg ttcctgctgc tgttgctgct gctgctgtca tggccatcgc agggggacgc cctggcaatg cctgaacagc gaccctccgg ccctgagtcc caactcaacg ccgacgagct acggggtcgc ttccaggacc tgctgagccg gctgcatgcc aaccagagcc gagaggactc gaactcagaa ccaagtcctg acccagctgt ccggatactc agtccagagg tgagattggg gtcccacggc cagctgctac tccgcgtcaa ccgggcgtcg ctgagtcagg gtctccccga agcctaccgc gtgcaccgag cgctgctcct gctgacgccg acggcccgcc cctgggacat cactaggccc ctgaagcgtg cgctcagcct ccggggaccc cgtgctcccg cattacgcct gcgcctgacg ccgcctccgg acctggctat gctgccctct ggcggcacgc agctggaact gcgcttacgg gtagccgccg gcaggggggcg ccgaagcgcg catgcgcacc caagagactc gtgcccactg ggtccggggc gctgctgtca

cttggagact gtgcaggcaa ctcttgaaga cttgggctgg agcgactggg tgctgtcccc gcgccagctg cagctgagca tgtgcgtggg cgagtgtccc cacctgtatc gctccgcgaa cacgcatgcg cagatcaaag cacgcctgca tggcctgcag cctgacaagg tgcctgcccc gtgctgtgtc ccctccagct acaccccggt ggttcttatg cacaggacag acagtggtgt gtcactgcag acttatgatg acctggtggc ccggggctgc cactgcgctt ga (SEQ ID NO: 7)

The amino acid sequence for full length murine GDF15 (303 amino acids) is:

MAPPALQAQPPGGSQLRFLLFLLLLLLLSWPSQGDALAMPEQRPSGPESQLNADEL
RGRFQDLLSRLHANQSREDSNSEPSPDPAVRILSPEVRLGSHGQLLLRVNRASLSQGL
PEAYRVHRALLLLTPTARPWDITRPLKRALSLRGPRAPALRLRLTPPPDLAMLPSGGT
QLELRLRVAAGRGRRSAHAHPRDSCPLGPGRCCHLETVQATLEDLGWSDWVLSPRQ
LQLSMCVGECPHLYRSANTHAQIKARLHGLQPDKVPAPCCVPSSYTPVVLMHRTDS
GVSLQTYDDLVARGCHCA (SEQ ID NO: 8)

The nucleotide sequence for murine GDF15 without its signal sequence is:

tcgcaggggacgccctggcaatgcctgaacagcgaccctccggccctgagtcccaactcaacgccgacgagctacggggtcgctt
ccaggacctgctgagccggctgcatgccaaccagagccgagaggactcgaactcagaaccaagtcctgacccagctgtccggatac
tcagtccagaggtgagattggggtcccacggccagctgctactccgcgtcaaccgggcgtcgctgagtcagggtctccccgaagcct
accgcgtgcaccgagcgctgctcctgctgacgccgacggcccgcccctgggacatcactaggcccctgaagcgtgcgctcagcctc
cggggaccccgtgctcccgcattacgcctgcgcctgacgccgcctccggacctggctatgctgccctctggcggcacgcagctgga
actgcgcttacgggtagccgccggcaggggcgccgaagcgcgcatgcgcacccaagagactcgtgcccactgggtccggggcg
ctgctgtcacttggagactgtgcaggcaactcttgaagacttgggctggagcgactgggtgctgtccccgcgccagctgcagctgagc
atgtgcgtgggcgagtgtccccacctgtatcgctccgcgaacacgcatgcgcagatcaaagcacgcctgcatggcctgcagcctgac
aaggtgcctgccccgtgctgtgtcccctccagctacaccccggtggttcttatgcacaggacagacagtggtgtgtcactgcagacttat
gatgacctggtggcccggggctgccactgcgcttga (SEQ ID NO: 9)

The amino acid sequence for murine GDF15 without its 32 amino acid signal sequence (271 amino acids) is:

SQGDALAMPEQRPSGPESQLNADELRGRFQDLLSRLHANQSREDSNSEPSPDPAVRIL
SPEVRLGSHGQLLLRVNRASLSQGLPEAYRVHRALLLLTPTARPWDITRPLKRALSLR
GPRAPALRLRLTPPPDLAMLPSGGTQLELRLRVAAGRGRRSAHAHPRDSCPLGPGRC
CHLETVQATLEDLGWSDWVLSPRQLQLSMCVGECPHLYRSANTHAQIKARLHGLQP
DKVPAPCCVPSSYTPVVLMHRTDSGVSLQTYDDLVARGCHCA (SEQ ID NO: 10)

The nucleotide sequence for murine GDF15 without its signal sequence or prodomain is:

agcgcgcatgcgcacccaagagactcgtgcccactgggtccggggcgctgctgtcacttggagactgtgcaggcaactcttgaagac
ttgggctggagcgactgggtgctgtccccgcgccagctgcagctgagcatgtgcgtgggcgagtgtccccacctgtatcgctccgcg
aacacgcatgcgcagatcaaagcacgcctgcatggcctgcagcctgacaaggtgcctgccccgtgctgtgtcccctccagctacacc
ccggtggttcttatgcacaggacagacagtggtgtgtcactgcagacttatgatgacctggtggcccggggctgccactgcgcttga
(SEQ ID NO: 11)

The amino acid sequence for murine GDF15 without its signal peptide or prodomain (active domain of 115 amino acids) is:

SAHAHPRDSCPLGPGRCCHLETVQATLEDLGWSDWVLSPRQLQLSMCVGECPHLYR
SANTHAQIKARLHGLQPDKVPAPCCVPSSYTPVVLMHRTDSGVSLQTYDDLVARGC
HCA (SEQ ID NO: 12)

In some embodiments, the GDF15 molecule comprises a GDF15 region comprising an active domain of GDF15, *e.g.*, GDF15 without its signal peptide or prodomain. In some embodiments, the GDF15 region comprises the amino acid sequence of SEQ ID NO: 6 or 12. In some embodiments, the GDF15 region comprises a GDF15 sequence with one or more mutations, such as at least one mutation in the active domain of GDF15. In particular embodiments, the mutation or mutations do not reduce or eliminate the activity of GDF15. In some embodiments, the GDF15 region comprises a mutation in the active domain of human GDF15. In one embodiment, the mutation is a deletion of the first three amino acids of the active domain, such as "GDF15(Δ3)" which is an active domain of human GDF15 in which the first three amino acids removed (*i.e.*, SEQ ID NO: 13).

In some embodiments, the GDF15 region comprises a mutation of the asparagine at position 3 (N3) of the active domain of human GDF15 (SEQ ID NO: 6). An N3 mutation can refer to the mutation of the asparagine residue at position 3 of SEQ ID NO: 6 or the mutation of an asparagine residue corresponding to the asparagine at position 3 of SEQ ID NO: 6 in a GDF15 amino acid sequence. In some embodiments, the asparagine at position 3 is mutated to glutamine (N3Q) or aspartate (N3D). Accordingly, in some embodiments, the GDF15 molecule comprises a GDF15 region of GDF15(N3Q), which has the amino acid sequence of SEQ ID NO: 14. In other embodiments, the GDF15 molecule comprises a GDF15 region of GDF15(N3D), which has the amino acid sequence of SEQ ID NO: 15. In some embodiments, the GDF15 region comprises a mutation of the aspartate at position 5 (D5) of the active domain of human GDF15 (SEQ ID NO: 6). A D5 mutation can refer to the mutation of the aspartate residue at position 5 of SEQ ID NO: 6 or the mutation of an aspartate residue corresponding to the aspartate at position 5 of SEQ ID NO: 6 in a GDF15 amino acid sequence. In one embodiment, the aspartate at position 5 is mutated to glutamate (D5E). Accordingly, in some embodiments, the GDF15 molecule comprises a GDF15 region of GDF15(D5E), which has the amino acid sequence of SEQ ID NO: 16.

In yet other embodiments, the GDF15 region comprises a combination of mutations, such as a combination of Δ3 and D5 mutations, *e.g.*, GDF15(Δ3/D5E) (SEQ ID NO: 17) or a combination of N3 and D5 mutations, *e.g.*, GDF15(N3D/D5E) or GDF15(N3Q/D5E). In, the GDF15 region comprises the amino acid sequence of SEQ ID NO: 18.

Table 1 provides examples of GDF15 regions that can be used in the GDF15 molecules.

Table 1 – GDF15 Regions

SEQ ID NO:	Designation	Sequence

6	GDF15	ARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
13	GDF15(Δ3)	GDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNP MVLIQKTDTGVSLQTYDDLLAKDCHCI
14	GDF15(N3Q)	ARQGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
15	GDF15(N3D)	ARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
16	GDF15(D5E)	ARNGEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTYDDLLAKDCHCI
17	GDF15(Δ3/D5E)	GEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTM CIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNP MVLIQKTDTGVSLQTYDDLLAKDCHCI
18	GDF15(N3Q/D5E)	ARQGEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQ VTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTYDDLLAKDCHCI

In some embodiments, the GDF15 molecule is fused to an Fc directly. In other embodiments, the Fc is fused to the GDF15 molecule via a linker. In some embodiments, the linker is a G4S (SEQ ID NO: 19) linker. In other embodiments, the linker is a G4Q (SEQ ID NO: 24) linker. The linker can be a (G4S)n or (G4Q)n linker, wherein n is greater than 0. In some embodiments, n is 1 or 2. In some embodiments, the fusion protein has a linker that is a G4A (SEQ ID NO: 107) linker, such as a (G4A)n linker, wherein n is greater than 0. In some embodiments, n is 1 or 2. In some embodiments, n is greater than 2, such as 3, 4, 5, 6, 7, or 8. In some embodiments, the linker comprises the amino acid sequence of SEQ ID NO: 19, 20, 21, 22, 23, 24, 25 or 107, as shown in Table 2.

Table 2 – Linkers

SEQ ID NO:	Designation	Sequence
19	G4S	GGGGS
20	(G4S)2	GGGGSGGGGS

21	(G4S)4	GGGGSGGGGSGGGGSGGGGS
22	(G4S)8	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
23	G4	GGGG
24	G4Q	GGGGQ
25	(G4Q)4	GGGGQGGGGQGGGGQGGGGQ
107	G4A	GGGGA

In some embodiments, the GDF15 molecule comprises an Fc region. The Fc region can comprise or be derived from the Fc domain of a heavy chain of an antibody. In some embodiments, the Fc region may comprise an Fc domain with a mutation, such as a charged pair mutation, a mutation in a glycosylation site or the inclusion of an unnatural amino acid. The Fc region can be derived from a human IgG constant domain of IgG1, IgG2, IgG3 or IgG4. In some embodiments, the Fc region comprises the constant domain of an IgA, IgD, IgE, and IgM heavy chain.

In some embodiments, the Fc region comprises an Fc domain with a charged pair mutation. By introducing a mutation resulting in a charged Fc region, the GDF15 molecule can dimerize with a corresponding Fc molecule having the opposite charge. For example, an aspartate-to-lysine mutation (E356K, wherein 356 is the position using EU numbering, and corresponds to the positions as noted in Tables 3-5) and a glutamate-to-lysine mutation (D399K wherein 399 is the position using EU numbering, and corresponds to positions as noted in Tables 3-5) can be introduced into the Fc region that is joined to a GDF15 region, optionally via a linker, resulting in a positively charged Fc region for the GDF15 molecule. Lysine-to-aspartate mutations (K392D, K409D; wherein 392 and 409 are the positions using EU numbering and corresponds to the positions as noted in Tables 3-5) can be introduced into an Fc domain of a separate molecule, resulting in a negatively charged Fc molecule. The aspartate residues in the negatively charged Fc molecule can associate with the lysine residues of the positively charged Fc region of the GDF15 molecule through electrostatic force, facilitating formation of Fc heterodimers between the Fc region of the GDF15 molecule and the Fc molecule, while reducing or preventing formation of Fc homodimers between the Fc regions of the GDF15 molecules or between Fc molecules.

In some embodiments, one or more lysine-to-aspartate mutations (K392D, K409D) are introduced into the Fc region that is joined to a GDF15 region, optionally via a linker and an aspartate-to-lysine mutation (E356K) and a glutamate-to-lysine mutation (D399K) is introduced into the Fc domain of another molecule. The aspartate residues in the Fc region of the GDF15 molecule can associate with the lysine residues of the Fc molecule through

electrostatic force, facilitating formation of Fc heterodimers between the Fc region of the GDF15 molecule and the Fc molecule, and reducing or preventing formation of Fc homodimers between the Fc regions of the GDF15 molecules or between Fc molecules.

In some embodiments, the GDF15 molecule comprises an Fc region comprising an Fc domain with a mutated hinge region. In some embodiments, the Fc domain comprises a deletion in the hinge. In some embodiments, ten amino acids from the hinge are deleted, e.g., FcΔ10. In other embodiments, sixteen amino acids from the hinge are deleted, e.g., FcΔ16. In some embodiments, the Fc domain comprises a hinge deletion (e.g., FcΔ10 or FcΔ16) and a charged pair mutation, such that the Fc domain is positively or negatively charged. For example, the Fc domain can comprise a ten-amino acid deletion in the hinge and lysine-to-aspartate mutations (K392D, K409D), such as FcΔ10(-). In another embodiment, the Fc domain can comprise a ten-amino acid deletion in the hinge and an aspartate-to-lysine mutation (E356K) and a glutamate-to-lysine mutation (D399K), such as an FcΔ10(+). In another embodiment, the Fc domain can comprise a sixteen-amino acid deletion in the hinge and lysine-to-aspartate mutations (K392D, K409D), such as FcΔ16(-). In another embodiment, the Fc domain can comprise a sixteen- amino acid deletion in the hinge and an aspartate-to-lysine mutation (E356K) and a glutamate-to-lysine mutation (D399K), such as an FcΔ16(+).

In some embodiments, an Fc molecule comprising a hinge deletion and a charged pair mutation heterodimerizes with such a GDF15 molecule. For example, the Fc molecule can have a hinge deletion and charged pair mutation that complements the hinge deletion and charged pair mutation of the Fc region of a GDF15 molecule. For example, an Fc molecule can comprise an Fc domain with a ten-amino acid deletion in the hinge and lysine-to-aspartate mutations (K392D, K409D), such as FcΔ10(-), which can optionally comprise a C-terminal lysine (e.g., FcΔ10(-, K)). The Fc molecule can heterodimerize with a GDF15 molecule that comprises an FcΔ10(+). In another embodiment, the Fc molecule can comprise a ten-amino acid deletion in the hinge and an aspartate-to-lysine mutation (E356K) and a glutamate-to-lysine mutation (D399K), such as an FcΔ10(+), which can optionally comprise a C-terminal lysine (e.g., FcΔ10(+, K)). The Fc molecule can heterodimerize with a GDF15 molecule that comprises an FcΔ10(-). In another embodiment, the Fc molecule can comprise a sixteen-amino acid deletion in the hinge and lysine-to-aspartate mutations (K392D, K409D), such as FcΔ16(-), which can optionally comprise a C-terminal lysine (e.g., FcΔ16(-, K)). The Fc molecule which can heterodimerize with a GDF15 molecule that comprises an FcΔ16(+). In another embodiment, the Fc molecule can comprise a sixteen-amino acid deletion in the hinge and an aspartate-to-lysine mutation (E356K) and a glutamate-to-lysine mutation (D399K), such as an FcΔ16(+), which can optionally comprise a C-terminal lysine (e.g., FcΔ16(-, K)). The Fc molecule can heterodimerize with a GDF15 molecule that comprises an FcΔ16(-).

In some embodiments, the Fc region or Fc molecule comprises an Fc domain with an L234A and/or L235A mutation, wherein 234 and 235 are the positions using EU numbering and corresponds to the positions as noted in Tables 3-5. The Fc domain can comprise an L234A mutation, an L235A mutation, a charged pair mutation, a hinge deletion, or any combination thereof. In some embodiments, the Fc domain comprises both an L234A mutation and an L235A mutation. In some embodiments, the Fc domain comprises a hinge deletion, an L234A mutation, an L235A mutation, and a charged pair mutation, such as FcΔ10(+, L234A/L235A), FcΔ10(-, L234A/L235A), FcΔ16(+, L234A/L235A), or FcΔ16(-, L234A/L235A). In some embodiments, the Fc domain comprises an optional C-terminal lysine, e.g., FcΔ10(+,K,L234A/L235A), FcΔ10(-,K,L234A/L235A), FcΔ16(+,K,L234A/L235A), or FcΔ16(-,K,L234A/L235A).

In some embodiments, the Fc region or Fc molecule comprises an Fc domain with a "cysteine clamp." A cysteine clamp mutation involves the introduction of a cysteine into the Fc domain at a specific location through mutation so that when incubated with another Fc domain that also has a cysteine introduced at a specific location through mutation, a disulfide bond (cysteine clamp) may be formed between the two Fc domains (*e.g.*, between an FcΔ16 (+) domain having a "cysteine clamp" mutation and an FcΔ16(-) domain having a "cysteine clamp" mutation). The cysteine can be introduced into the CH3 domain of an Fc domain. In some embodiments, an Fc domain may contain one or more such cysteine clamp mutations. In one embodiment, a cysteine clamp is provided by introducing a serine to cysteine mutation (S354C, wherein 354 is the position using EU numbering, and corresponds to the position as noted in Tables 3-5) into a first Fc domain and a tyrosine to cysteine mutation (Y349C, wherein 349 is the position using EU numbering, and corresponds to the position as noted in Tables 3-5) into a second Fc domain. In one embodiment, a GDF15 molecule comprises an Fc region comprising an Fc domain with a cysteine clamp, a negatively charged pair mutation and a sixteen-amino acid hinge deletion (e.g., GDF15- FcΔ16(-,CC)), and an Fc molecule comprising an Fc domain comprising a cysteine clamp, a positively charged pair mutation and a sixteen-amino acid hinge deletion, and an optional C-terminal lysine (e.g., FcΔ16(+,K,CC)). The cysteine clamp may augment the heterodimerization of the GDF-Fc molecule with the Fc molecule.

Examples of Fc regions that can be used in a GDF15 molecule are shown in Table 3.

Table 3 – Fc Regions

SEQ ID NO:	Designation	Sequence
26	FcΔ10(-)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR

		EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG *Underlined and bolded residues are K392D and K409D mutations.*
27	FcΔ10(+)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSR**K**EMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVL**K**SDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG *Underlined and bolded residues are E356K and D399K mutations.*
28	FcΔ10(-,CC)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQV<u>C</u>TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG *Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.*
29	FcΔ16(-,CC)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV<u>C</u>TL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN Y**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVM HEALHNHYTQKSLSLSPG *Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.*
30	FcΔ16(-)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG *Underlined and bolded residues are K392D and K409D mutations.*

31	FcΔ10(-,L234A/L235A)	APE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPG *Underlined and italicized residues are L234A and L235A mutations; underlined and bolded residues are K392D and K409D mutations.*

Examples of Fc molecules are shown in Table 4, in which the C-terminal lysine is optional.

Table 4 – Fc Molecules

SEQ ID NO:	Designation	Sequence
32	FcΔ10(+,K)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSR**K**EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVL**K**SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK *Underlined and bolded residues are E356K and D399K mutations.*
33	FcΔ10(-,K)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY **D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK *Underlined and bolded residues are K392D and K409D mutations.*
34	FcΔ10(+,K,CC)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PP*C*R**K**EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVL**K**SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK *Underlined and italicized residue is S354C mutation; underlined and bolded residues are E356K and D399K mutations.*
35	FcΔ16(+,K,CC)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP*C*R**K**E

		MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK *Underlined and italicized residue is S354C mutation; underlined and bolded residues are E356K and D399K mutations.*
36	FcΔ16(+,K)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNW YVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNG KEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRKE MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV LKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHY TQKSLSLSPGK *Underlined and bolded residues are E356K and D399K mutations.*
37	FcΔ10(+,K,L234A/L235A)	APE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTL PPSRKEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLKSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEA LHNHYTQKSLSLSPGK *Underlined and italicized residues are L234A and L235A mutations; underlined and bolded residues are E356K and D399K mutations.*

The Fc molecules can be used to dimerize with a molecule comprising a complementary Fc domain. For example, an Fc molecule of FcΔ10(+,K) can dimerize with a molecule comprising an Fc region comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ10(-) (e.g., a GDF15 molecule comprising an Fc region of FcΔ10(-)). An Fc molecule of FcΔ10(-,K)can dimerize with a molecule comprising an Fc region comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ10(+) (e.g., a GDF15 molecule comprising an Fc region of FcΔ10(+)).

An Fc molecule of FcΔ10(+,K,CC) can dimerize with a molecule comprising an Fc region comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ10(-,CC) (e.g., a GDF15 molecule comprising an Fc region of FcΔ10(-, CC)). An Fc molecule of FcΔ16(+,K,CC) can dimerize with a molecule comprising an Fc region comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ16(-, CC) (e.g., a GDF15 molecule comprising an Fc region of FcΔ16(-, CC)). An Fc molecule of FcΔ16(+,K) can dimerize with a molecule comprising an Fc region comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ16(-) (e.g., a GDF15 molecule comprising an Fc region of FcΔ16(+)). An Fc molecule of FcΔ10(+,K,L234A/L235A) can dimerize with a molecule comprising an Fc region

comprising a ten-amino acid hinge deletion and a negatively charged pair mutation such as FcΔ10(-,L234A/L235A) (e.g., a GDF15 molecule comprising an Fc region of FcΔ10(-, L234A/L235A)).

Examples of GDF15 molecules that are GDF15-Fc fusion proteins are shown in Table 5.

Table 5 – GDF15 Molecules

GDF15-Fc Fusion Protein			GDF15-Fc Fusion Protein Components SEQ ID NOs		
SEQ ID NO.	**Designation**	**Sequence**	**Fc Region**	**Linker**	**GDF15 Region**
38	scFc-GDF15	GGGERKSSVECPPCPAPPVA GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVQF NWYVDGVEVHNAKTKPRE EQFNSTFRVVSVLTVVHQD WLNGKEYKCKVSNKGLPA PIEKTISKTKGQPREPQVYT LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNYKTTPPMLDSDGSFFLY SKLTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGGGGSGGGGSGGGGSGG GGSGGGGSGGGGSGGGGS GGGGSERKSSVECPPCPAPP VAGPSVFLFPPKPKDTLMIS RTPEVTCVVVDVSHEDPEV QFNWYVDGVEVHNAKTKP REEQFNSTFRVVSVLTVVH QDWLNGKEYKCKVSNKGL PAPIEKTISKTKGQPREPQV YTLPPSREEMTKNQVSLTC LVKGFYPSDIAVEWESNGQ PENNYKTTPPMLDSDGSFFL YSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSL SPGSGGGGSGGGGSGGGGS GGGGSARNGDHCPLGPGRC CRLHTVRASLEDLGWADW VLSPREVQVTMCIGACPSQF RAANMHAQIKTSLHRLKPD	---	---	---

		TVPAPCCVPASYNPMVLIQ KTDTGVSLQTYDDLLAKDC HCI			
39	FcΔ10(-)-(G4S)4-GDF15	APELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPR EPQVYTLPPSREEMTKNQV SLTCLVKGFYPSDIAVEWES NGQPENNY**D**TTPPVLDSDG SFFLYS**D**LTVDKSRWQQGN VFSCSVMHEALHNHYTQKS LSLSPGGGGGSGGGGSGGG GSGGGGSARNGDHCPLGPG RCCRLHTVRASLEDLGWA DWVLSPREVQVTMCIGACP SQFRAANMHAQIKTSLHRL KPDTVPAPCCVPASYNPMV LIQKTDTGVSLQTYDDLLA KDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	26	21	6
40	FcΔ10(+)-(G4)-GDF15	APELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHE DPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPR EPQVYTLPPSR**K**EMTKNQV SLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVL**K**SDG SFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKS LSLSPGGGGGARNGDHCPL GPGRCCRLHTVRASLEDLG WADWVLSPREVQVTMCIG ACPSQFRAANMHAQIKTSL HRLKPDTVPAPCCVPASYN PMVLIQKTDTGVSLQTYDD LLAKDCHCI	27	23	6

		Underlined and and bolded residues are E356K and D399K mutations.			
41	FcΔ10(-)-GDF15(Δ3)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	26	---	13
42	FcΔ10(-)-GDF15(N3D)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI	26	---	15

		Underlined and bolded residues are K392D and K409D mutations.			
43	FcΔ10(-,CC)-GDF15(Δ3)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.*	28	---	13
44	FcΔ10(-,CC)-GDF15(N3D)	APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVCTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARDGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI	28	---	15

		Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.			
45	FcΔ16(-,CC)-GDF15(Δ3/D5E)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQV<u>C</u>T LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**<u>D</u>**TTPPVLDSDGSFFLYS **<u>D</u>**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGEHCPLGPGRCCRLHTVR ASLEDLGWADWVLSPREV QVTMCIGACPSQFRAANMH AQIKTSLHRLKPDTVPAPCC VPASYNPMVLIQKTDTGVS LQTYDDLLAKDCHCI *Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.*	29	---	17
46	FcΔ16(-,CC)-GDF15(N3Q/D5E)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQV<u>C</u>T LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**<u>D</u>**TTPPVLDSDGSFFLYS **<u>D</u>**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GARQGEHCPLGPGRCCRLH TVRASLEDLGWADWVLSP REVQVTMCIGACPSQFRAA NMHAQIKTSLHRLKPDTVP APCCVPASYNPMVLIQKTD TGVSLQTYDDLLAKDCHCI	29	---	18

		Underlined and italicized residue is Y349C mutation; underlined and bolded residues are K392D and K409D mutations.			
47	FcΔ16(-)-GDF15(N3Q/D5E)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARQGEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	30	---	18
48	FcΔ16(-)-(G4Q)4-GDF15	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGQGGGGQGGGGQGGGGQARNGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI	30	25	6

		Underlined and bolded residues are K392D and K409D mutations.			
49	FcΔ16(-)-(G4Q)4-GDF15(N3Q)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGQGGGGQGGGGQGGGGQARQGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	30	25	14
50	FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGQGGGGQGGGGQGGGGQARQGEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI	30	25	18

		Underlined and bolded residues are K392D and K409D mutations.			
51	FcΔ16(-)-(G4S)2-GDF15(N3Q)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**D**TTPPVLDSDGSFFLYS **D**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGGGGSGGGGSARQGDHC PLGPGRCCRLHTVRASLED LGWADWVLSPREVQVTMC IGACPSQFRAANMHAQIKT SLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTY DDLLAKDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	30	20	14
52	FcΔ16(-)-(G4S)2-GDF15(N3Q/D5E)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**D**TTPPVLDSDGSFFLYS **D**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGGGGSGGGGSARQGEHC PLGPGRCCRLHTVRASLED LGWADWVLSPREVQVTMC IGACPSQFRAANMHAQIKT SLHRLKPDTVPAPCCVPAS YNPMVLIQKTDTGVSLQTY DDLLAKDCHCI	30	20	18

		Underlined and bolded residues are K392D and K409D mutations.			
53	FcΔ16(-)-G4S-GDF15(N3Q)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**D**TTPPVLDSDGSFFLYS **D**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGGGGSARQGDHCPLGPG RCCRLHTVRASLEDLGWA DWVLSPREVQVTMCIGACP SQFRAANMHAQIKTSLHRL KPDTVPAPCCVPASYNPMV LIQKTDTGVSLQTYDDLLA KDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	30	19	14
54	FcΔ16(-)-G4S-GDF15(N3Q/D5E)	GPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQD WLNGKEYKCKVSNKALPA PIEKTISKAKGQPREPQVYT LPPSREEMTKNQVSLTCLV KGFYPSDIAVEWESNGQPE NNY**D**TTPPVLDSDGSFFLYS **D**LTVDKSRWQQGNVFSCS VMHEALHNHYTQKSLSLSP GGGGGSARQGEHCPLGPGR CCRLHTVRASLEDLGWAD WVLSPREVQVTMCIGACPS QFRAANMHAQIKTSLHRLK PDTVPAPCCVPASYNPMVLI QKTDTGVSLQTYDDLLAKD CHCI	30	19	18

		Underlined and bolded residues are K392D and K409D mutations.			
55	FcΔ16(-)-GDF15(N3Q)	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGARQGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and bolded residues are K392D and K409D mutations.*	30	---	14
56	FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q)	APE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGQGGGGQGGGGGGQGGGGQARQGDHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and italicized residues are L234A and L235A mutations; underlined and*	31	25	14

		bolded residues are K392D and K409D mutations.			
57	FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E)	APE*AA*GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY**D**TTPPVLDSDGSFFLYS**D**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGGGGQGGGGQGGGGQGGGGQARQGEHCPLGPGRCCRLHTVRASLEDLGWADWVLSPREVQVTMCIGACPSQFRAANMHAQIKTSLHRLKPDTVPAPCCVPASYNPMVLIQKTDTGVSLQTYDDLLAKDCHCI *Underlined and italicized residues are L234A and L235A mutations; underlined and bolded residues are K392D and K409D mutations.*	31	25	18

In some embodiments, the fusion protein is an scFc-GDF15 in which the GDF15 region is joined to two Fc regions. In some embodiments, the fusion protein comprises an amino acid sequence that has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 38. In some embodiments, the fusion protein comprises an amino acid sequence of SEQ ID NO: 38. In calculating percent sequence identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. A computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., (1984) Nucl. Acid Res. 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP can be used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension

penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., (1978) Atlas of Protein Sequence and Structure 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., (1992) Proc. Natl. Acad. Sci. U.S.A. 9:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm. Parameters that can be used for determining percent identity using the GAP program are the following:

Algorithm: Needleman et al., 1970, J. Mol. Biol. 48:443-453;

Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, supra;

Gap Penalty: 12 (but with no penalty for end gaps)

Gap Length Penalty: 4

Threshold of Similarity: 0

Certain alignment schemes for aligning two amino acid sequences can result in matching of only a short region of the two sequences, and this small aligned region can have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (e.g., the GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

In some embodiments, the GDF15 molecule is FcΔ10(-)-(G4S)4-GDF15, FcΔ10(+)-(G4)-GDF15, FcΔ10(-)-GDF15(Δ3), FcΔ10(-)-GDF15(N3D), FcΔ10(-,CC)-GDF15(Δ3), FcΔ10(-,CC)-GDF15(N3D), FcΔ16(-,CC)-GDF15(Δ3/D5E), FcΔ16(-,CC)-GDF15(N3Q/D5E), FcΔ16(-)-GDF15(N3Q/D5E), FcΔ16(-)-(G4Q)4-GDF15, FcΔ16(-)-(G4Q)4-GDF15(N3Q), FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E), FcΔ16(-)-(G4S)2-GDF15(N3Q), FcΔ16(-)-(G4S)2- GDF15(N3Q/D5E), FcΔ16(-)-G4S-GDF15(N3Q), FcΔ16(-)-G4S-GDF15(N3Q/D5E), FcΔ16(-)-GDF15(N3Q), FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q), or FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E).

In some embodiments, the GDF15 molecule comprises the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, or 57. In some embodiments, the GDF15 molecules comprises an amino acid sequence that has at least 85% sequence identity to SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, or 57. In some embodiments, the GDF15 molecules comprises an amino acid sequence that has at least 90% sequence identity to SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, or 57. In some embodiments, the GDF15 molecules comprises an amino acid sequence that has at least 95% sequence identity to SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, or 57. In some embodiments, the GDF15 molecules comprises an amino acid sequence that has at least 99% sequence

identity to SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, or 57.

In some embodiments, the GDF15 molecule is a FcΔ10(-)-(G4S)4-GDF15, FcΔ10(+)-(G4)-GDF15, FcΔ10(-)-GDF15(Δ3), FcΔ10(-)-GDF15(N3D), FcΔ10(-,CC)-GDF15(Δ3), FcΔ10(-,CC)-GDF15(N3D), FcΔ16(-,CC)-GDF15(Δ3/D5E), FcΔ16(-,CC)-GDF15(N3Q/D5E), FcΔ16(-)-GDF15(N3Q/D5E), FcΔ16(-)-(G4Q)4-GDF15, FcΔ16(-)-(G4Q)4-GDF15(N3Q), FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E), FcΔ16(-)-(G4S)2-GDF15(N3Q), FcΔ16(-)-(G4S)2- GDF15(N3Q/D5E), FcΔ16(-)-G4S-GDF15(N3Q), FcΔ16(-)-G4S-GDF15(N3Q/D5E), FcΔ16(-)-GDF15(N3Q), FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q), or FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E) molecule that has at least 85%, 90%, 95% or 99% sequence identity to its Fc region and/or GDF15 region. For example, a FcΔ10(-)-(G4S)4-GDF15 molecule with at least 85%, 90%, 95% or 99% sequence identity to its Fc region and/or GDF15 region, includes a GDF15 molecule with an Fc region that has a ten-amino acid deletion of the hinge region and a negatively charged pair mutation, and has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 26 and/or a GDF15 region that has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 6. In another example, a FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E) molecule with at least 85%, 90%, 95% or 99% sequence identity to its Fc region and/or a GDF15 region, includes a GDF15 molecule with an Fc region that has a sixteen-amino acid deletion of the hinge region and a negatively charged pair mutation that has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 30 and/or a GDF15 region that has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 18. In yet another example, a FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E) molecule with at least 85%, 90%, 95% or 99% sequence identity to its Fc region and/or a GDF15 region, includes a GDF15 molecule with an Fc region that has a ten-amino acid deletion of the hinge region, a negatively charged pair mutation and leucine to alanine mutations at positions 234 and 235 and has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 31 and/or a GDF15 region that has at least 85%, 90%, 95% or 99% sequence identity to SEQ ID NO: 18.

Also provided herein are dimers and tetramers comprising a GDF15 molecule provided herein. In one embodiment, the dimer comprises a GDF15-Fc fusion comprising the amino acid sequence of any one of SEQ ID NOs: 39-57. In some embodiments, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 dimerizes with an Fc molecule comprising the amino acid sequence of SEQ ID NO: 32, 33, 34, 35, 36, or 37 (in which the C-terminal lysine is optional), such as shown in Table 6. For example, in some embodiments, the dimer is FcΔ10(-)-(G4S)4-GDF15: FcΔ10(+,K). In another embodiment, the dimer is FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q): FcΔ10(+,K,L234A/L235A). In yet another

embodiment, the dimer is FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q):FcΔ10(+,K,L234A/L235A).

Table 6 – Dimers

GDF15-Fc Fusion SEQ ID NO.	GDF15-Fc Fusion Designation	Fc Molecule SEQ ID NO.	Corresponding Fc Molecule Designation
39	FcΔ10(-)-(G4S)4-GDF15	32	FcΔ10(+,K)
40	FcΔ10(+)-(G4)-GDF15	33	FcΔ10(-,K)
41	FcΔ10(-)-GDF15(Δ3)	32	FcΔ10(+,K)
42	FcΔ10(-)-GDF15(N3D)	32	FcΔ10(+,K)
43	FcΔ10(-,CC)-GDF15(Δ3)	34	FcΔ10(+,K,CC)
44	FcΔ10(-,CC)-GDF15(N3D)	34	FcΔ10(+,K,CC)
45	FcΔ16(-,CC)-GDF15(Δ3/D5E)	35	FcΔ16(+,K,CC)
46	FcΔ16(-,CC)-GDF15(N3Q/D5E)	35	FcΔ16(+,K,CC)
47	FcΔ16(-)-GDF15(N3Q/D5E)	36	FcΔ16(+,K)
48	FcΔ16(-)-(G4Q)4-GDF15	36	FcΔ16(+,K)
49	FcΔ16(-)-(G4Q)4-GDF15(N3Q)	36	FcΔ16(+,K)
50	FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E)	36	FcΔ16(+,K)
51	FcΔ16(-)-(G4S)2-GDF15(N3Q)	36	FcΔ16(+,K)
52	FcΔ16(-)-(G4S)2- GDF15(N3Q/D5E)	36	FcΔ16(+,K)
53	FcΔ16(-)-G4S- GDF15(N3Q)	36	FcΔ16(+,K)
54	FcΔ16(-)-G4S-GDF15(N3Q/D5E)	36	FcΔ16(+,K)
55	FcΔ16(-)-GDF15(N3Q)	36	FcΔ16(+,K)
56	FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q)	37	FcΔ10(+,K,L234A/L235A)
57	FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E)	37	FcΔ10(+,K,L234A/L235A)

In one embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 39 dimerizes with an Fc molecule comprising SEQ ID NO: 32 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 40 dimerizes with an Fc molecule comprising SEQ ID NO: 33 (C-terminal

lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 41 dimerizes with an Fc molecule comprising SEQ ID NO: 32 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 42 dimerizes with an Fc molecule comprising SEQ ID NO: 32 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 43 dimerizes with an Fc molecule comprising SEQ ID NO: 34 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 44 dimerizes with an Fc molecule comprising SEQ ID NO: 34 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 44 dimerizes with an Fc molecule comprising SEQ ID NO: 34 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 45 dimerizes with an Fc molecule comprising SEQ ID NO: 35 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 46 dimerizes with an Fc molecule comprising SEQ ID NO: 35 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 47 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 48 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 49 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 50 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 51 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 52 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 53 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 54 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 55 dimerizes with an Fc molecule comprising SEQ ID NO: 36 (C-terminal lysine optional). In another embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 56 dimerizes with an Fc molecule comprising SEQ ID NO: 37 (C-terminal lysine optional). In another

embodiment, a GDF15-Fc fusion comprising the amino acid sequence of SEQ ID NO: 57 dimerizes with an Fc molecule comprising SEQ ID NO: 37 (C-terminal lysine optional).

In some embodiments, the dimers form tetramers. For example, the dimers in Table 6 can form tetramers. In some embodiments, the tetramers are formed form the same dimers. In some embodiments, two dimers of FcΔ10(-)-(G4S)4-GDF15:FcΔ10(+,K); FcΔ10(+)-(G4)-GDF15:FcΔ10(-,K); FcΔ10(-)-GDF15(Δ3):FcΔ10(+,K); FcΔ10(-)-GDF15(N3D):FcΔ10(+,K); FcΔ10(-,CC)-GDF15(Δ3):FcΔ10(+,K,CC); FcΔ10(-,CC)-GDF15(N3D):FcΔ10(+,K,CC); FcΔ16(-,CC)-GDF15(Δ3/D5E):FcΔ16(+,K,CC); FcΔ16(-,CC)-GDF15(N3Q/D5E):FcΔ16(+,K,CC); FcΔ16(-)-GDF15(N3Q/D5E):FcΔ16(+,K); FcΔ16(-)-(G4Q)4-GDF15:FcΔ16(+,K); FcΔ16(-)-(G4Q)4-GDF15(N3Q):FcΔ16(+,K); FcΔ16(-)-(G4Q)4-GDF15(N3Q/D5E):FcΔ16(+,K); FcΔ16(-)-(G4S)2-GDF15(N3Q):FcΔ16(+,K); FcΔ16(-)-(G4S)2- GDF15(N3Q/D5E):FcΔ16(+,K); FcΔ16(-)-G4S- GDF15(N3Q):FcΔ16(+,K); FcΔ16(-)-G4S-GDF15(N3Q/D5E): FcΔ16(+,K); FcΔ16(-)-GDF15(N3Q): FcΔ16(+,K); FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q):FcΔ10(+,K,L234A/L235A); or FcΔ10(-,L234A/L235A)-(G4Q)4-GDF15(N3Q/D5E):FcΔ10(+,K,L234A/L235A) form a tetramer, such as through the dimerization of the two GDF15 regions.

Also provided herein are host cells comprising the nucleic acids and vectors for producing the GDF15 and Fc molecules disclosed herein. In various embodiments, the vector or nucleic acid is integrated into the host cell genome, which in other embodiments the vector or nucleic acid is extra-chromosomal.

Recombinant cells, such as yeast, bacterial (*e.g.*, *E. coli*), and mammalian cells (*e.g.*, immortalized mammalian cells) comprising such a nucleic acid, vector, or combinations of either or both thereof are provided. In various embodiments, cells comprising a non-integrated nucleic acid, such as a plasmid, cosmid, phagemid, or linear expression element, which comprises a sequence coding for expression of a GDF15 molecule and/or an Fc molecule. In some embodiments, the cell comprises a nucleic acid for producing a GDF15 molecule and another cell comprises a nucleic acid for producing an Fc molecule for dimerization with the GDF15 molecule (e.g., a vector for encoding a GDF15 molecule in one cell and a second vector for encoding an Fc molecule in a second cell). In other embodiments, a host cell comprises a nucleic acid for producing a GDF15 molecule and an Fc molecule (e.g., a vector that encodes both molecules). In another embodiment, a host cell comprises a nucleic acid for producing a GDF15 molecule and another nucleic acid for producing an Fc molecule (e.g., two separate vectors, one that encodes a GDF15 molecule and one that encodes an Fc molecule, in a single host cell)

A vector comprising a nucleic acid sequence encoding a GDF15 molecule and/or an Fc molecule can be introduced into a host cell by transformation or by transfection, such as by methods known in the art.

A nucleic acid encoding a GDF15 molecule can be positioned in and/or delivered to a host cell or host animal via a viral vector. A viral vector can comprise any number of viral polynucleotides, alone or in combination with one or more viral proteins, which facilitate delivery, replication, and/or expression of the nucleic acid of the invention in a desired host cell. The viral vector can be a polynucleotide comprising all or part of a viral genome, a viral protein/nucleic acid conjugate, a virus-like particle (VLP), or an intact virus particle comprising viral nucleic acids and a nucleic acid encoding a polypeptide comprising a GDF15 region. A viral particle viral vector can comprise a wild-type viral particle or a modified viral particle. The viral vector can be a vector which requires the presence of another vector or wild-type virus for replication and/or expression (*e.g.*, a viral vector can be a helper-dependent virus), such as an adenoviral vector amplicon. Suitable viral vector particles in this respect, include, for example, adenoviral vector particles (including any virus of or derived from a virus of the adenoviridae), adeno-associated viral vector particles (AAV vector particles) or other parvoviruses and parvoviral vector particles, papillomaviral vector particles, flaviviral vectors, alphaviral vectors, herpes viral vectors, pox virus vectors, retroviral vectors, including lentiviral vectors.

A GDF15 molecule can be isolated using standard protein purification methods. A polypeptide comprising a GDF15 region can be isolated from a cell that has been engineered to express a polypeptide comprising a GDF15 region, for example a cell that does not naturally express native GDF15. Protein purification methods known in the art can be employed to isolate GDF15 molecules, as well as associated materials and reagents. Methods of purifying a GDF15 molecule are also provided in the Examples herein. Additional purification methods that may be useful for isolating GDF15 molecules can be found in references such as Bootcov MR, 1997, *Proc. Natl. Acad. Sci. USA 94:11514-9*, Fairlie WD, 2000, *Gene 254: 67-76.*

Pharmaceutical compositions comprising a GDF15 molecule (and optionally, an Fc molecule, such as a dimer or tetramer disclosed herein) are also provided. Such polypeptide pharmaceutical compositions can comprise a therapeutically effective amount of a GDF15 molecule in admixture with a pharmaceutically or physiologically acceptable formulation agent or carrier selected for suitability with the mode of administration. The pharmaceutically or physiologically acceptable formulation agent can be one or more formulation agents suitable for accomplishing or enhancing the delivery of a GDF15 molecule into the body of a human or non-human subject. Pharmaceutically acceptable substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of

the GDF15 molecule can also act as, or form a component of, a formulation carrier. Acceptable pharmaceutically acceptable carriers are preferably nontoxic to recipients at the dosages and concentrations employed. The pharmaceutical composition can contain formulation agent(s) for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption, or penetration of the composition.

The effective amount of pharmaceutical composition comprising a GDF15 molecule which is to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which a GDF15 molecule is being used, the route of administration, and the size (body weight, body surface, or organ size) and condition (the age and general health) of the subject. The frequency of dosing will depend upon the pharmacokinetic parameters of the GDF15 molecule in the formulation being used.

The route of administration of the pharmaceutical composition can be orally; through injection by intravenous, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intraportal, or intralesional routes; by sustained release systems (which may also be injected); or by implantation devices. Where desired, the compositions can be administered by bolus injection or continuously by infusion, or by an implantation device. The composition can also be administered locally via implantation of a membrane, sponge, or other appropriate material onto which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

A GDF15 molecule can be used to treat, diagnose or ameliorate, a metabolic condition or disorder. In one embodiment, the metabolic disorder is diabetes, *e.g.*, type 2 diabetes. In another embodiment, the metabolic condition or disorder is obesity. In other embodiments, the metabolic condition or disorder is dyslipidemia, elevated glucose levels, elevated insulin levels or diabetic nephropathy. For example, a metabolic condition or disorder that can be treated or ameliorated using a GDF15 molecule includes a state in which a human subject has a fasting blood glucose level of 125 mg/dL or greater, for example 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200 or greater than 200 mg/dL. Blood glucose levels can be determined in the fed or fasted state, or at random. The metabolic condition or disorder can also comprise a condition in which a subject is at increased risk of developing a metabolic condition. For a human subject, such conditions include a fasting blood glucose level of 100 mg/dL. Conditions that can be treated using a pharmaceutical composition comprising a GDF15 molecule can also be found in the

American Diabetes Association Standards of Medical Care in Diabetes Care-2011, American Diabetes Association, Diabetes Care Vol. 34, No. Supplement 1, S11-S61, 2010.

The administration can be performed such as by IV injection, intraperitoneal (IP) injection, subcutaneous injection, intramuscular injection, or orally in the form of a tablet or liquid formation. A therapeutically effective dose of a GDF15 molecule will depend upon the administration schedule, the unit dose of agent administered, whether the GDF15 molecule is administered in combination with other therapeutic agents, the immune status and the health of the recipient. A therapeutically effective dose is an amount of a GDF15 molecule that elicits a biological or medicinal response in a tissue system, animal, or human being sought by a researcher, medical doctor, or other clinician, which includes alleviation or amelioration of the symptoms of the disease or disorder being treated, *i.e.*, an amount of a GDF15 molecule that supports an observable level of one or more desired biological or medicinal response, for example, lowering blood glucose, insulin, triglyceride, or cholesterol levels; reducing body weight; or improving glucose tolerance, energy expenditure, or insulin sensitivity; or reducing food intake. A therapeutically effective dose of a GDF15 molecule can also vary with the desired result.

Also provided herein is a method comprising measuring a baseline level of one or more metabolically-relevant compounds such as glucose, insulin, cholesterol, lipid in a subject, administering a pharmaceutical composition comprising a GDF15 molecule to the subject, and after a desired period of time, measure the level of the one or more metabolically-relevant compounds (*e.g.*, blood glucose, insulin, cholesterol, lipid) in the subject. The two levels can then be compared to determine the relative change in the metabolically-relevant compound in the subject. Depending on the outcome of that comparison another dose of the pharmaceutical composition can be administered to achieve a desired level of one or more metabolically-relevant compound.

A GDF15 molecule (and optionally, its corresponding Fc molecule) can be administered in combination with another therapeutic agent, such as an agent that lowers blood glucose, insulin, triglyceride, or cholesterol levels; lowers body weight; reduces food intake; improves glucose tolerance, energy expenditure, or insulin sensitivity; or any combination thereof (e.g., antidiabetic agent, hypolipidemic agent, anti-obesity agent, anti-hypertensive agent, or agonist of peroxisome proliferator-activator receptor). For example, the agent can be selected from insulin, insulin derivatives and mimetics; insulin secretagogues; glyburide, Amaryl; insulinotropic sulfonylurea receptor ligands; thiazolidinediones, pioglitazone, balaglitazone, rivoglitazone, netoglitazone, troglitazone, englitazone, ciglitazone, adaglitazone, darglitazone, Cholesteryl ester transfer protein (CETP) inhibitors, GSK3 (glycogen synthase kinase-3) inhibitors; RXR ligands; sodium-dependent glucose cotransporter inhibitors; glycogen phosphorylase A inhibitors; biguanides; alpha-

glucosidase inhibitors, GLP-1 (glucagon like peptide-1), GLP-1 analogs, GLP-1 mimetics; DPPIV (dipeptidyl peptidase IV) inhibitors, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors; squalene synthase inhibitors; FXR (farnesoid X receptor), LXR (liver X receptor) ligands; cholestyramine; fibrates; nicotinic acid, aspirin; orlistat or rimonabant; loop diuretics, furosemide, torsemide; angiotensin converting enzyme (ACE) inhibitors; inhibitors of the Na-K-ATPase membrane pump; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors; angiotensin II antagonists; renin inhibitors; .beta.-adrenergic receptor blockers; inotropic agents, dobutamine, milrinone; calcium channel blockers; aldosterone receptor antagonists; aldosterone synthase inhibitors; fenofibrate, pioglitazone, rosiglitazone, tesaglitazar, BMS-298585 and L-796449.

The agent administered with a GDF15 molecule disclosed herein can be a GLP-1R agonist or a GIPR antagonist. A GLP-1R agonist can be a compound with GLP-1R activity. The GLP-1R agonist can be an exendin, exendin analog, or exendin agonist. Exendin includes naturally occurring (or synthetic versions of naturally occurring) exendin peptides that are found in the salivary secretions of the Gila monster. The exendin can be exendin-3: HSDGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2 (SEQ ID NO: 58); or exendin-4: HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH_2 (SEQ ID NO: 59). The exendin, exendin analog, and exendin agonist described herein may optionally be amidated, in an acid form, in a pharmaceutically acceptable salt form, or any other physiologically active form. Synthetic exendin-4, also known as exenatide, is commercially available as BYETTA® (Amylin Pharmaceuticals, Inc. and Eli Lilly and Company). Other examples of exendin analogs and exendin agonists that can be used in combination with a GDF15 molecule disclosed herein are described in WO 98/05351; WO 99/07404; WO 99/25727; WO 99/25728; WO 99/40788; WO 00/41546; WO 00/41548; WO 00/73331; WO 01/51078; WO 03/099314; U.S. Pat. No. 6,956,026; U.S. Pat. No. 6,506,724; U.S. Pat. No. 6,703,359; U.S. Pat. No. 6,858,576; U.S. Pat. No. 6,872,700; U.S. Pat. No. 6,902,744; U.S. Pat. No. 7,157,555; U.S. Pat. No. 7,223,725; U.S. Pat. No. 7,220,721; US Publication No. 2003/0036504; US Publication No. 2006/0094652; and US Publication No. 2018/0311372, the disclosures of which are incorporated by reference herein in their entirety.

In one embodiment, the GLP-1R agonist is GLP-1 or analog thereof, such as GLP-1(7-37): HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG (SEQ ID NO: 60) or a GLP-1(7-37) analog. A GLP-1(7-37) analog can be a peptide that elicits a biological activity similar to that of GLP-1(7-37) when evaluated by art-known measures such as receptor binding assays or in vivo blood glucose assays as described, e.g., by Hargrove et al., *Regulatory Peptides*, 141:113-119 (2007), the disclosure of which is incorporated by reference herein. In one embodiment, a GLP-1(7-37) analog refers to a peptide that has an amino acid sequence with 1, 2, 3, 4, 5, 6, 7 or 8 amino acid substitutions, insertions, deletions, or a combination of two

or more thereof, when compared to the amino acid sequence of GLP-1(7-37). In one embodiment, the GLP-1(7-37) analog is GLP-1(7-36)-NH_2. GLP-1(7-37) analogs include the amidated forms, the acid form, the pharmaceutically acceptable salt form, and any other physiologically active form of the molecule. In some embodiments a simple nomenclature is used to describe the GLP-1R agonist, e.g., [Aib8]GLP-1(7-37) designates an analogue of GLP-1(7-37) wherein the naturally occurring Ala in position 8 has been substituted with Aib. Other GLP-1(7-37) or GLP-1(7-37) analogs that can be used in combination with a GDF15 molecule disclosed herein include liraglutide (VICTOZA®, Novo Nordisk); albiglutide (SYNCRIA®, GlaxoSmithKline); taspoglutide (Hoffman La-Roche); dulaglutide (also known LY2189265; Eli Lilly and Company); or LY2428757 (Eli Lilly and Company). In one embodiment, the GLP-1R agonist is dulaglutide and comprises the amino acid sequence: HGEGTFTSDVSSYLEEQAAKEFIAWLVKGGGGGGGSGGGGSGGGGSAESKYGPPCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEV HNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKG QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLG (SEQ ID NO: 61), which optionally has a lysine at its C-terminus. One or more of the GLP-1 analogs described in U.S. Pat. No. 6,268,343; US Pat. No. 7,452,966; and US Publication No. 2018/0311372, which is incorporated by reference herein in its entirety, can also be used in combination with a GDF15 molecule disclosed herein.

In one embodiment, a GDF15 molecule comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 is administered with a molecule comprising the amino acid sequence of SEQ ID NO: 58, 59, 60 or an amidated analog there. In one embodiment, a GDF15 molecule comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 is administered with dulaglutide, such as a molecule comprising the amino acid sequence of SEQ ID NO: 61.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional), respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine

optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; is administered with a molecule comprising the amino acid sequence of SEQ ID NO: 58, 59, 60 or an amidated analog there.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional), respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; is administered with dulaglutide, such as a molecule comprising the amino acid sequence of SEQ ID NO: 61.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with a molecule comprising the amino acid sequence of SEQ ID NO: 58, 59, 60 or an amidated analog there. In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with dulaglutide, such as a molecule comprising the amino acid sequence of SEQ ID NO: 61.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with a molecule comprising the amino acid sequence of SEQ ID NO: 58, 59, 60 or an amidated analog there. In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37

(C-terminal lysine optional), respectively, is administered with dulaglutide, such as a molecule comprising the amino acid sequence of SEQ ID NO: 61.

In some embodiments, a GDF15 molecule disclosed herein is administered with an antagonist to GIPR, such as an antigen binding protein that specifically binds to a human GIPR. In one embodiment, the antigen binding protein specifically binds to human GIPR comprising or consisting of the amino acid sequence of:

MTTSPILQLLLRLSLCGLLLQRAETGSKGQTAGELYQRWERYRRECQETLAAAEPPS
GLACNGSFDMYVCWDYAAPNATARASCPWYLPWHHHVAAGFVLRQCGSDGQWG
LWRDHTQCENPEKNEAFLDQRLILERLQVMYTVGYSLSLATLLLALLILSLFRRLHCT
RNYIHINLFTSFMLRAAAILSRDRLLPRPGPYLGDQALALWNQALAACRTAQIVTQY
CVGANYTWLLVEGVYLHSLLVLVGGSEEGHFRYYLLLGWGAPALFVIPWVIVRYLY
ENTQCWERNEVKAIWWIIRTPILMTILINFLIFIRILGILLSKLRTRQMRCRDYRLRLAR
STLTLVPLLGVHEVVFAPVTEEQARGALRFAKLGFEIFLSSFQGFLVSVLYCFINKEVQ
SEIRRGWHHCRLRRSLGEEQRQLPERAFRALPSGSGPGEVPTSRGLSSGTLPGPGNEA
SRELESYC (SEQ ID NO: 62);

MTTSPILQLLLRLSLCGLLLQRAETGSKGQTAGELYQRWERYRRECQETLAAAEPPS
VAAGFVLRQCGSDGQWGLWRDHTQCENPEKNEAFLDQRLILERLQVMYTVGYSLS
LATLLLALLILSLFRRLHCTRNYIHINLFTSFMLRAAAILSRDRLLPRPGPYLGDQALA
LWNQALAACRTAQIVTQYCVGANYTWLLVEGVYLHSLLVLVGGSEEGHFRYYLLL
GWGAPALFVIPWVIVRYLYENTQCWERNEVKAIWWIIRTPILMTILINFLIFIRILGILLS
KLRTRQMRCRDYRLRLARSTLTLVPLLGVHEVVFAPVTEEQARGALRFAKLGFEIFL
SSFQGFLVSVLYCFINKEVQSEIRRGWHHCRLRRSLGEEQRQLPERAFRALPSGSGPG
EVPTSRGLSSGTLPGPGNEASRELESYC (SEQ ID NO: 63); or

MTTSPILQLLLRLSLCGLLLQRAETGSKGQTAGELYQRWERYRRECQETLAAAEPPS
GLACNGSFDMYVCWDYAAPNATARASCPWYLPWHHHVAAGFVLRQCGSDGQWG
LWRDHTQCENPEKNEAFLDQRLILERLQVMYTVGYSLSLATLLLALLILSLFRRLHCT
RNYIHINLFTSFMLRAAAILSRDRLLPRPGPYLGDQALALWNQALAACRTAQIVTQY
CVGANYTWLLVEGVYLHSLLVLVGGSEEGHFRYYLLLGWGAPALFVIPWVIVRYLY
ENTQCWERNEVKAIWWIIRTPILMTILINFLIFIRILGILLSKLRTRQMRCRDYRLRLAR
STLTLVPLLGVHEVVFAPVTEEQARGALRFAKLGFEIFLSSFQGFLVSVLYCFINKEVG
RDPAAAPALWRRRGTAPPLSAIVSQVQSEIRRGWHHCRLRRSLGEEQRQLPERAFRA
LPSGSGPGEVPTSRGLSSGTLPGPGNEASRELESYC (SEQ ID NO:64).

The antigen binding protein that specifically binds to a human GIPR polypeptide can inhibit activation of GIPR by GIP ligand and/or inhibit GIP ligand binding to GIPR. The antigen binding protein may have the ability to prevent or reduce binding of GIP to GIPR, where the levels can be measured, for example, by the methods such as radioactive- or fluorescence-labeled ligand binding study, or by the methods described herein (e.g. cAMP assay or other functional assays). The decrease can be at least 10, 25, 50, 100% or more relative to the pre-treatment levels of SEQ ID NO: 62, 63, or 64 under comparable conditions. In certain embodiments, the antigen binding protein has a KD (equilibrium binding affinity) of less than 25 pM, 50 pM, 100 pM, 500 pM, 1 nM, 5 nM, 10 nM, 25 nM or 50 nM.

The antigen binding protein can be a human antigen binding protein, such as a human antibody. In another embodiment, the antigen binding protein is an antibody, such as a

monoclonal antibody. In some embodiments, the antigen binding protein is a GIPR antibody disclosed in US Publication No. 2017/0275370 or 2018/0311372, each of which is incorporated by reference herein in its entirety.

In one embodiment, the GIPR antigen binding protein, such as an antibody, comprises a CDRL1, CDRL2 and CDRL3 comprising the amino acid sequence of: RASQSVSSNLA (SEQ ID NO: 65), GAATRAT (SEQ ID NO: 66) and QQYNNWPLT (SEQ ID NO: 67), respectively; SGSSSNIGSQTVN (SEQ ID NO: 68), TNNQRPS (SEQ ID NO: 69) and ATFDESLSGPV (SEQ ID NO: 70), respectively; RASQDIRDYLG (SEQ ID NO: 71), GASSLQS (SEQ ID NO: 72) and LQHNNYPFT (SEQ ID NO: 73), respectively; or RASQGLIIWL (SEQ ID NO: 74), AASSLQS (SEQ ID NO: 75) and QQTNSFPPT (SEQ ID NO: 76), respectively. In one embodiment, the GIPR antigen binding protein comprises a CDRH1, CDRH2 and CDRH3 comprising the amino acid sequence of: NYGMH (SEQ ID NO: 77), AIWFDASDKYYADAVKG (SEQ ID NO: 78) and DQAIFGVVPDY (SEQ ID NO: 79), respectively; GYYMH (SEQ ID NO: 80), WINPNSGGTNYAQKFQG (SEQ ID NO: 81) and GGDYVFGTYRPHYYYGMDV (SEQ ID NO: 82), respectively; YFGMH (SEQ ID NO: 83), VIWYDASNKYYADAVKG (SEQ ID NO: 84) and DGTIFGVLLGDY (SEQ ID NO: 85), respectively; or SYYWS (SEQ ID NO: 86), RIYTSGSTNYNPSLKS (SEQ ID NO: 87) and DVAVAGFDY (SEQ ID NO: 88), respectively.

In one embodiment, the GIPR antigen binding protein, such as an antibody, comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively.

In one embodiment, the GIPR antigen binding protein, such as an antibody, comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGAATRATGI PARVSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEIKR (SEQ ID NO: 89) and

QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGEGLEWVAAIWFDA SDKYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQAIFGVVPDYW GQGTLVTVSS (SEQ ID NO: 90), respectively;

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSQTVNWYQHLPGTAPKLLIYTNNQRPSGV PDRFSGSKSGTSASLAISGLQSEDEADYFCATFDESLSGPVFGGGTKLTVLG (SEQ ID NO: 91) and

QMQVVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINP NSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGGDYVFGTYRP HYYYGMDVWGQGTTVTVSS (SEQ ID NO: 92), respectively;

DIQMTQSPSSLSASIGDRVTITCRASQDIRDYLGWYQQKPGKAPKLLIYGASSLQSGV PSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNNYPFTFGQGTKVDIKR (SEQ ID NO: 93) and

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYFGMHWVRQAPGKGLEWVAVIWYDA SNKYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGTIFGVLLGDYW GQGTLVTVSS (SEQ ID NO: 94), respectively; or

DIQMTQSPSSVSASVGDRVTITCRASQGLIIWLAWYQQKPGKAPKLLIYAASSLQSGV PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTNSFPPTFGQGTKVEIKR (SEQ ID NO: 95) and

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTN YNPSLKSRVTMSIDTSKNQFSLKLNSVTAADTAVYYCARDVAVAGFDYWGQGTLVT VSS (SEQ ID NO: 96), respectively.

In one embodiment, the GIPR antigen protein, such as an antibody, comprises a light chain and heavy chain comprising the amino acid sequences of

EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGAATRATGI PARVSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEIKRTVAAPSVF IFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTY SLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 97) and

QVQLVESGGGVVQPGRSLRLSCAASGFTFSNYGMHWVRQAPGEGLEWVAAIWFDA SDKYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDQAIFGVVPDYW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 98), respectively;

QSVLTQPPSASGTPGQRVTISCSGSSSNIGSQTVNWYQHLPGTAPKLLIYTNNQRPSGV PDRFSGSKSGTSASLAISGLQSEDEADYFCATFDESLSGPVFGGGTKLTVLGQPKAAP SVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADSSPVKAGVETTTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 99) and

QMQVVQSGAEVKKPGASVKVSCKASGYTFTGYYMHWVRQAPGQGLEWMGWINP NSGGTNYAQKFQGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARGGDYVFGTYRP HYYYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVD KKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO: 100), respectively;

DIQMTQSPSSLSASIGDRVTITCRASQDIRDYLGWYQQKPGKAPKLLIYGASSLQSGV PSRFSGSGSGTEFTLTISSLQPEDFATYYCLQHNNYPFTFGQGTKVDIKRTVAAPSVFIF PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 101) and

QVQLVESGGGVVQPGRSLRLSCAASGFTFSYFGMHWVRQAPGKGLEWVAVIWYDA
SNKYYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDGTIFGVLLGDYW
GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTS
GVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIS
KAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ
ID NO: 102), respectively;

DIQMTQSPSSVSASVGDRVTITCRASQGLIIWLAWYQQKPGKAPKLLIYAASSLQSGV
PSRFSGSGSGTDFTLTISSLQPEDFATYYCQQTNSFPPTFGQGTKVEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 103) and

QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPAGKGLEWIGRIYTSGSTN
YNPSLKSRVTMSIDTSKNQFSLKLNSVTAADTAVYYCARDVAVAGFDYWGQGTLVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPA
VLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCP
APELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA
KTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPR
EPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSD
GSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO:
104), respectively; or

MKLPVRLLVLMFWIPASSSDVVMTQTPLSLPVSLGDQASISCRSSQSLVHSNGDTYLH
WYLQKPGQSPKLLIYKVSNRFSGVPDRFSGSGSGTDFTLKISRVEAADLGVYFCSQST
HVPPFTFGGGTKLEIKRADAAPTVSIFPPSSEQLTSGGASVVCFLNNFYPKDINVKWKI
DGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTSPIVK
SFNRNEC (SEQ ID NO: 105) and

MGWSYIILFLVATATDVHSQVQLQQPGAELVKPGASVKLSCRASGYTFTSNWMHW
VKQRPRQGLEWIGEINPSNGRSNYNEKFKTKATLTVDKSSSTAYMQLSSLTSEDSAV
YYCARFYYGTSWFAYWGQGTLVAVSAAKTTPPSVYPLAPGSAAQTNSMVTLGCLV
KGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVPSSTWPSETVTCNVAHP
ASSTKVDKKIVPRDCGCKPCICTVPEVSSVFIFPPKPKDVLTITLTPKVTCVVVDISKDD
PEVQFSWFVDDVEVHTAQTQPREEQFASTFRSVSELPIMHQDWLNGKEFKCRVNSA
AFPAPIEKTISKTKGRPKAPQVYTIPPPKEQMAKDKVSLTCMITDFFPEDITVEWQWN
GQPAENYKNTQPIMDTDGSYFVYSKLNVQKSNWEAGNTFTCSVLHEGLHNHHTEKS
LSHSPGK (SEQ ID NO: 106), respectively.

In one embodiment, a GDF15 molecule comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 is administered with a GIPR antigen binding protein, such as an antibody, that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional), respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32

(C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; is administered with a GIPR antigen binding protein, such as an antibody, that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively. In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively. In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79.

In one embodiment, a GDF15 molecule comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional), respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively. In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional),

respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively. In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90.

In one embodiment, a GDF15 molecule comprising the amino acid sequence of SEQ ID NO: 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56 or 57 is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and 106, respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional), respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and 106, respectively.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID

NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and 106, respectively. In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with a GIPR antigen binding protein, such as an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and 106, respectively. In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, is administered with an antibody that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98.

In some embodiments, a GDF15 molecule disclosed herein is administered with a GIPR antibody conjugated to a GLP-1R agonist, such as disclosed in US Publication No. 2018/0311372, which is incorporated by reference herein in its entirety.

Other examples of agents that can be used in combination with a GDF15 molecule disclosed herein include rosiglitizone, pioglitizone, repaglinide, nateglitinide, metformin, exenatide, stiagliptin, pramlintide, glipizide, glimepriridеacarbose, orlistat, lorcaserin, phenterminetopiramate, naltrexonebupropion, setmelanotide, semaglutide, efpeglenatide, lixisenatide, canagliflozin, LIK-066, SAR-425899, Tt-401, FGFR4Rx, HDV-biotin and miglitol.

A GDF15 molecule administered with another therapeutic agent can include concurrent administration of a therapeutically effective amount of the GDF15 molecule (and optionally, its corresponding Fc molecule) and a therapeutically effective amount of the other therapeutic agent. A GDF15 molecule administered with another therapeutic agent can include subsequent administration of a therapeutically effective amount of the GDF15 molecule (and optionally, its corresponding Fc molecule) and a therapeutically effective amount of the other therapeutic agent, e.g., administration of a therapeutically effective amount of the GDF15 molecule (and optionally, its corresponding Fc molecule) followed by a therapeutically effective amount of the other therapeutic agent or administration of a therapeutically effective amount of the other therapeutic agent followed by administration of a therapeutically effective amount of the GDF15 molecule (and optionally, its corresponding Fc molecule). Administration of a therapeutically effective amount of the GDF15 molecule

(and optionally, its corresponding Fc molecule) can be at least 1, 2, 3, 4, 5, 6, or 7 days after administration of a therapeutically effective amount of the other therapeutic agent. In another embodiment, administration of a therapeutically effective amount of a therapeutically effective amount of the other therapeutic agent can be at least 1, 2, 3, 4, 5, 6, or 7 days after at least 1, 2, 3, 4, 5, 6, or 7 days after administration of a therapeutically effective amount of the GDF15 molecule (and optionally, its corresponding Fc molecule).

A GDF15 molecule administered concurrently with another therapeutic agent can comprise administration of a composition comprising both the GDF15 molecule (and optionally its corresponding Fc molecule) and the other therapeutic agent, e.g., a therapeutically effective amount of the GDF15 molecule (and optionally its corresponding Fc molecule) is combined with a therapeutically effective amount of the other agent prior to administration. In another embodiment, concurrent administration of GDF15 molecule (and optionally its corresponding Fc molecule) and another therapeutic agent can comprise concurrent administration of a first composition comprising the GDF15 molecule and a second composition comprising the other therapeutic agent.

In some embodiments, administration of a GDF15 molecule with another therapeutic agent has a synergistic effect. In one embodiment, the effect is greater than the GDF15 molecule (and optionally its corresponding Fc molecule) alone or the other agent. In another embodiment, the effect is greater than an additive effect of both agents (the GDF15 molecule, and optionally its corresponding Fc molecule, plus the other agent). In one embodiment, combination therapy (i.e., administration of a GDF15 molecule, optionally with its corresponding Fc molecule, with another therapeutic agent) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy (administration of the GDF15 molecule, and optionally its corresponding Fc molecule). In another embodiment, combination therapy (i.e., administration of a GDF15 molecule, optionally with its corresponding Fc molecule, with another therapeutic agent) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 fold effect than monotherapy with the other agent. The effect can be the amount of body weight lost (e.g., the decrease in total mass or percent body change); the decrease in blood glucose, insulin, triglyceride, or cholesterol levels; the improvement in glucose tolerance, energy expenditure, or insulin sensitivity; or the reduction food intake. The synergistic effect can be about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration.

In one embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 39 and 32 (C-terminal lysine optional),

respectively; SEQ ID NOs: 40 and 33 (C-terminal lysine optional), SEQ ID NOs: 41 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 42 and 32 (C-terminal lysine optional) , respectively; SEQ ID NOs: 43 and 34 (C-terminal lysine optional) , respectively; SEQ ID NOs: 44 and 34 (C-terminal lysine optional), respectively; SEQ ID NOs: 45 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 46 and 35 (C-terminal lysine optional), respectively; SEQ ID NOs: 47 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 48 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 49 and 36 (C-terminal lysine optional) respectively; SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 51 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 52 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 53 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 54 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 55 and 36 (C-terminal lysine optional), respectively; SEQ ID NOs: 56 and 37 (C-terminal lysine optional), respectively; or SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively; administered with a GLP-1R agonist or a GIPR antagonist has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy; a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GLP-1R agonist or GIPR antagonist monotherapy (i.e., administration of GLP-1R agonist alone or GIPR antagonist alone); or both, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration of the agent(s).

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, administered with a GLP-1R agonist (e.g., dulaglutide) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy; a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GLP-1R agonist (e.g., dulaglutide) monotherapy; or both, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration of the GDF15 molecule and corresponding Fc molecule and/or dulaglutide.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, administered with a GLP-1R agonist (e.g., dulaglutide) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0,

8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy; a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GLP-1R agonist (e.g., dulaglutide) monotherapy; or both, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration of the GDF15 molecule and corresponding Fc molecule and/or dulaglutide.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 50 and 36 (C-terminal lysine optional), respectively, administered with a GIPR antigen binding protein (e.g., an antibody that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively; or an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively; or an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and 106, respectively) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy; a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GIPR antigen binding protein monotherapy; or both, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration of the GDF15 molecule and corresponding Fc molecule and/or GIPR antigen binding protein.

In another embodiment, a GDF15 molecule and corresponding Fc molecule comprising the amino acid sequences of SEQ ID NOs: 57 and 37 (C-terminal lysine optional), respectively, administered with a GIPR antigen binding protein (e.g., an antibody that comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprising the amino acid sequences of: SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively; or an antibody, that comprises a light chain variable region and heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90, SEQ ID NOs: 91 and 92, SEQ ID NOs: 93 and 94, or SEQ ID NOs: 95 and 96, respectively; or an antibody, that comprises a light chain and heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98, SEQ ID NOs: 99 and 100, SEQ ID NOs: 101 and 102, SEQ ID NOs: 103 and 104, or SEQ ID NOs: 105 and

106, respectively) has a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GDF15 monotherapy; a greater than 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25,26, 27, 28, 29, or 30 fold effect than GIPR antigen binding protein monotherapy; or both, about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 28, 35, 42, 49, 56, 63, or 70 days after administration of the GDF15 molecule and corresponding Fc molecule and/or GIPR antigen binding protein.

In one embodiment, the molar ratio of the GDF15 molecule to the GLP-1R agonist or GIPR antagonist is from about 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, or 1:1 to 1:5. In one embodiment, the molar ratio of the GDF15 molecule to the GLP-1R agonist or GIPR antagonist is about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:10, about 1:20, about 1:30, about 1:40, or about 1:50. In one embodiment, the molar ratio of the GDF15 molecule to the GLP-1R agonist (e.g., dulaglutide) is from about 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, or 1:1 to 1:5; or about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:10, about 1:20, about 1:30, about 1:40, or about 1:50. In another embodiment, the molar ratio of the GDF15 molecule to the GIPR antagonist (e.g., GIPR antibody) is from about 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, or 1:1 to 1:5; or about 1:1 to 1:110, 1:1 to 1:100, 1:1 to 1:75, 1:1 to 1:50, 1:1 to 1:25, 1:1 to 1:10, or 1:1 to 1:5, or is about 1:1, about 1:2, about 1:3, about 1:4, about 1:5, about 1:10, about 1:20, about 1:30, about 1:33, about 1:40, or about 1:50.

In one embodiment, the GDF15 molecule and the GLP-1R agonist or GIPR antagonist are present in doses that are at least about 1.1 to 1.4, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold lower than the doses of each compound alone required to have a therapeutic effect (e.g., treat a condition and/or disease; decrease body weight lost; decrease blood glucose, insulin, triglyceride, or cholesterol levels; improve glucose tolerance, energy expenditure, or insulin sensitivity; or reduce food intake).

The detailed description and following examples illustrate the present invention and are not to be construed as limiting the present invention thereto. Various changes and modifications can be made by those skilled in the art on the basis of the description of the invention, and such changes and modifications are also included in the present invention.

EXAMPLES

The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

Example 1: GDF15 Molecule Production

FcΔ10(-)-(G4S)4-GDF15 (SEQ ID NO: 39) was stably expressed in a serum free, suspension adapted CHO-K1 cell line. It was cloned into a stable expression vector containing puromycin resistance while the Fc chain for forming a heterodimer with FcΔ10(-)-(G4S)4-GDF15, FcΔ10(+,K) (SEQ ID NO: 32), was cloned into a hygromycin containing expression vector (Selexis, Inc.). The plasmids were transfected at a 1:1 ratio using lipofectamine LTX and cells were selected 2 days post transfection in a proprietary growth media containing 10ug/mL puromycin and 600ug/mLhygromycin. Media was exchanged 2 times per week during selection. When cells reached about 90% viability, they were scaled up for a batch production run. Cells were seeded at $2x10^6$/mL in production media. The conditioned medium (CM) produced by the cells was harvested on day 7 and clarified. Endpoint viabilities typically were above 90%.

FcΔ10(-)-(G4S)4-GDF15 (SEQ ID NO: 39) (and any paired Fc) were clarified. Conditioned media was purified using a two-step chromatography procedure. Approximately 5 L of the CM was applied directly to a GE MabSelect SuRe column that had previously been equilibrated with Dulbecco's Phosphate Buffered Saline (PBS). The bound protein underwent three wash steps: first, 3 column volumes (CV) of PBS; next, 1 CV of 20 mM Tris, 100 mM sodium chloride, pH 7.4; and finally, 3 CV of 500 mM L-arginine, pH 7.5. These wash steps remove unbound or lightly bound media components and host cell impurities. The column was then re-equilibrated with 5 CV of 20 mM Tris, 100 mM sodium chloride at pH 7.4 which brings the UV absorbance back to baseline. The desired protein was eluted with 100 mM acetic acid at pH 3.6 and collected in bulk. The protein pool was quickly titrated to within a pH range of 5.0 to 5.5 with 1 M Tris-HCl, pH 9.2. The pH adjusted protein pool was next loaded onto a GE SP Sepharose HP column that had been previously equilibrated with 20 mM MES at pH 6.0. The bound protein was then washed with 5 CV of equilibration buffer, and finally eluted over a 20 CV, 0 to 50% linear gradient from 0 to 400 mM sodium chloride in 20 mM MES at pH 6.0. Fractions were collected during the elution and analyzed by analytical size-exclusion chromatography (Superdex 200) to determine the appropriate fractions to pool for a homogeneous product. The SP HP chromatography removes product-related impurities such as free Fc, clipped species, and Fc-GDF15 multimers. The SP HP pool was then buffer exchanged into 10 mM sodium acetate, 5% proline, pH 5.2 by dialysis. It was concentrated to approximately 15 mg/ml using the Sartorius Vivaspin 20 Ten kilo-Dalton molecular weight cut-off centrifugal device. Finally, it was sterile filtered and the resulting solution containing the purified Fc-GDF15 molecules is stored at 5° C. Final products were assessed for identity and purity using mass spectral analysis, sodium dodecyl sulfate polyacrylamide electrophoresis and size exclusion high performance liquid chromatography.

Example 2: GDF15, Dulaglutide, and/or GIPR Antibody Administration

Male *C57Bl/6 DIO* mice, 19-20 weeks old (13-14 weeks on high fat diet) at beginning of dosing, were placed into the following treatment groups: Group A - Vehicle, in which the animals were administered vehicle weekly; Group B - Dulaglutide, in which the animals were administered 0.1 mg/kg (2nmol/kg) of dulaglutide twice per week; Group C - GIPR Ab, in which the animals were administered 5 mg/kg (33 nmol/kg) of antibody 2.63.1 (having a light and heavy chain sequence of SEQ ID NOs: 105 and 106, respectively) weekly and vehicle weekly (the latter being on the alternate dulaglutide dosing day); Group D – GDF15, in which the animals were administered 0.125 mg/kg (1nmol/kg) of FcΔ10(-)-(G4S)4-GDF15 (SEQ ID NO: 39) (along with its heterodimerization partner, FcΔ10(+,K) (SEQ ID NO: 32)) weekly and vehicle weekly (the latter on the alternate dulaglutide dosing day); Group E – GDF15 + Dulaglutide, in which the animals were administered 0.125 mg/kg (1nmol/kg) of FcΔ10(-)-(G4S)4-GDF15) (along with its heterodimerization partner, FcΔ10(+,K)) weekly and 0.1 mg/kg (2nmol/kg) of dulaglutide twice per week; Group F - GDF15 + GIPR Ab, in which the animals were administered 0.125 mg/kg (1nmol/kg) of FcΔ10(-)-(G4S)4-GDF15 (along with its heterodimerization partner, FcΔ10(+,K)) weekly and 5 mg/kg (33 nmol/kg) of antibody 2.63.1 weekly. The animals were dosed for 5 weeks with through subcutaneous injection.

Body weight was measured twice per week. **Figure 1** shows the body weight change (**Figure 1A** in grams, **Figure 1B** in percent body weight change). The significance of the body weight change is shown in **Table 7**.

Table 7 - Significance of Body Weight Change

Group	D-4	D0	D3	D7	D10	D14	D17	D21	D31	D35
A	---	---	---	---	---	---	---	---	---	---
B	ns	ns	ns	ns	**	**	****	***	***	***
C	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
D	ns	ns	ns	**	****	****	****	****	***	***
E	ns	ns	**	****	****	****	****	****	****	****
F	ns	ns	ns	****	****	****	****	****	****	****

ns: not significant; *p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 2 shows the percent body weight change 2 weeks (**Figure 2A**) and 5 weeks (**Figure 2B**) after treatment started. The data shows that combination treatment of GDF15 with either Dulaglutide or GIPR Ab was synergistic. At two weeks after treatment, mice in Group D (GDF15) had -9.33% change in body weight, while mice in Group B (Dulaglutide) or Group C (GIPR Ab) had a -4.40% and -0.91% change in body weight, respectively.

However, mice in Group E (GDF15+Dulaglutide) had a -18.28% change in body weight, greater than an additive effect of -13.73%. The decrease was more than three-fold as compared to Dulaglutide treatment alone and almost two-fold the decrease seen in GDF15 treatment alone. Mice in Group F (GDF15+GIPR Ab) had a -13.65% change in body weight, greater than an additive effect of -14.56%. The decrease was more than thirteen-fold as compared to GIPR Ab treatment alone and almost 1.5 fold the decrease seen in GDF15 treatment alone.

At five weeks after treatment, mice in Group D (GDF15) had -14.62% change in body weight, while mice in Group B (Dulaglutide) or Group C (GIPR Ab) had a -1.96% and 2.24% change in body weight, respectively. However, mice in Group E (GDF15+Dulaglutide) had a -33.56% change in body weight, greater than an additive effect of -15.58%. The decrease was more than fifteen-fold as compared to Dulaglutide treatment alone and more than two-fold the decrease seen in GDF15 treatment alone. Mice in Group F (GDF15+GIPR Ab) had a -22.62% change in body weight, greater than an additive effect of -12.38%. The decrease was more than twenty-fold as compared to GIPR Ab treatment alone and more than 1.5 fold the decrease seen in GDF15 treatment alone.

An oral glucose tolerance test (OGTT) was conducted 2 weeks after first treatment and **Figure 3** shows the glucose levels (**Figure 3A**) and glucose AUC (**Figure 3B**) during oral glucose tolerance test 2 weeks after treatment started, with the AUC differences between treatment groups and vehicle group labeled on top of each bar in **Figure 3B**. Combination therapy did not have a greater effect than GDF15 monotherapy (Groups E and F having -40.0% AUC and -33.1% AUC, respectively, as compared to Group D having -39.0% AUC).

Similarly, combination therapy did not have a greater effect than GDF15 monotherapy in an intraperitoneal glucose tolerance test (IPGTT). An IPGTT was conducted 5 weeks after first treatment and **Figure 4** shows the glucose levels (**Figure 4A**) and glucose AUC (**Figure 4B**) of the IPGTT test 5 weeks after treatment started, with the AUC differences between treatment groups and vehicle group labeled on top of each bar in **Figure 4B**. The combination therapy groups, Groups E and F, had a -42.4% AUC and -40.4% AUC, respectively, as compared to the GDF15 monotherapy group, Group D, with -38.0% AUC.

Fasting blood glucose, serum insulin, serum triglyceride and serum total cholesterol levels were measured 2 weeks and 5 weeks after first treatment (**Figures 5A-5D**, respectively). Combination therapy (Groups E and F) did not have a greater effect in reducing fasting blood glucose levels or triglyceride levels than GDF15 monotherapy (Group D) (**Figures 5A** and **5C**, respectively), but at two weeks, combination therapy did have a greater effect than GDF15 monotherapy in reducing serum insulin levels, and at five weeks, the combination of GDF15+Dulaglutide had a greater effect in reducing serum insulin levels

than GDF15 monotherapy (**Figure 5B**). The combination of GDF15+Dulaglutide also had a greater effect than GDF15 monotherapy in reducing the total cholesterol level (**Figure 5D**).

Food intake was measured three consecutive days per week and the results are shown in **Figure 6**. The significance of the data is shown in **Table 8.**

Table 8 - Significance of Food Intake Assay

Group	D2	D8	D9	D10	D15	D16	D17	D22	D23	D24	D29	D30	D31
A	---	---	---	---	---	---	---	---	---	---	---	---	---
B	ns	ns	ns	ns	ns	ns	*	****	ns	ns	ns	ns	ns
C	ns	ns	ns	ns	ns	ns	ns	*	ns	ns	ns	ns	ns
D	ns	*	ns	ns	ns	ns	ns	****	**	ns	*	ns	ns
E	*	*	*	ns	**	**	ns	****	**	ns	***	ns	ns
F	ns	*	ns	ns	ns	ns	ns	****	***	ns	**	ns	ns

ns: not significant; *p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

While the present invention has been described in terms of various embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the invention as claimed. In addition, the section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

All references cited in this application are expressly incorporated by reference herein for any purpose.

CLAIMS

What is claimed is:

1. A method of treating a metabolic condition in a subject comprising administering a GDF15 molecule and a GIPR antagonist, wherein administration of the GDF15 molecule and the GIPR antagonist has a synergistic effect as compared to administration of the GDF15 molecule or GIPR antagonist alone.
2. The method of claim 1, wherein the GDF15 molecule and the GIPR antagonist are administered concurrently.
3. The method of claim 1, wherein the GDF15 molecule and the GIPR antagonist are administered sequentially.
4. The method of claim 1, wherein the GIPR antagonist is an antibody.
5. The method of claim 1, wherein the GIPR antagonist comprises a CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, wherein the CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3 comprises the amino acid sequences of SEQ ID NOs: 65-67 and 77-79; SEQ ID NOs: 68-70 and 80-82; SEQ ID NOs: 71-73 and 83-85; or SEQ ID NOs: 74-76 and 86-88; respectively.
6. The method of claim 5, wherein the GIPR antagonist comprises a light chain variable region and a heavy chain variable region comprising the amino acid sequences of SEQ ID NOs: 89 and 90; 91 and 92; 93 and 94; or 95 and 96, respectively.
7. The method of claim 5, wherein the GIPR antagonist comprises a light chain and a heavy chain comprising the amino acid sequences of SEQ ID NOs: 97 and 98; 99 and 100; 101 and 102; 103 and 104, or 105 and 106, respectively.
8. A method of treating a metabolic condition in a subject comprising administering a GDF15 molecule and dulaglutide, wherein administration of the GDF15 molecule and dulaglutide has a synergistic effect as compared to administration of the GDF15 molecule or dulaglutide alone.
9. The method of claim 8, wherein the GDF15 molecule and dulaglutide are administered concurrently.
10. The method of claim 8, wherein the GDF15 molecule and dulaglutide are administered sequentially.
11. The method of any one of claims 1-10, wherein the synergistic effect is in decreasing body weight.
12. The method of any one of claims 1-11, wherein the GDF15 molecule is a fusion protein comprising a GDF15 region joined to an Fc region.
13. The method of claim 12, wherein the GDF15 region is joined to the Fc region via a linker.
14. The method of claim 12 or 13, wherein the GDF15 region comprises the amino acid sequence of SEQ ID NO: 6 and at least one mutation.

15. The method of claim 14, wherein at least one of the mutations is of the aspartate at position 5.
16. The method of claim 15, wherein the aspartate at position 5 is mutated to glutamate.
17. The method of claim 15 or 16, wherein the GDF15 region further comprises a mutation of the asparagine at position 3.
18. The method of claim 17, wherein the asparagine at position 3 mutated to glutamine.
19. The method of any one of claims 13-18, wherein the linker is a (G4S)n or (G4Q)n linker, wherein n is greater than 0.
20. The method of claim 19, wherein n is 1 or 2.
21. The method of any one of claims 12-20, wherein the Fc region comprises a charged pair mutation.
22. The method of any one of claims 12-21, wherein the Fc region comprises a truncated hinge region.
23. The method of any one of claims 12-22, wherein the Fc region is selected from Table 3.
24. A pharmaceutical composition comprising a GDF15 molecule and a GIPR antagonist, wherein administration of the composition has a synergistic effect as compared to administration of the GDF15 molecule or GIPR antagonist alone.
25. A pharmaceutical composition comprising a GDF15 molecule and dulaglutide, wherein administration of the composition has a synergistic effect as compared to administration of the GDF15 molecule or dulaglutide alone.
26. The composition of claim 24 or 25, wherein the synergistic effect is in decreasing body weight.

Figure 1A

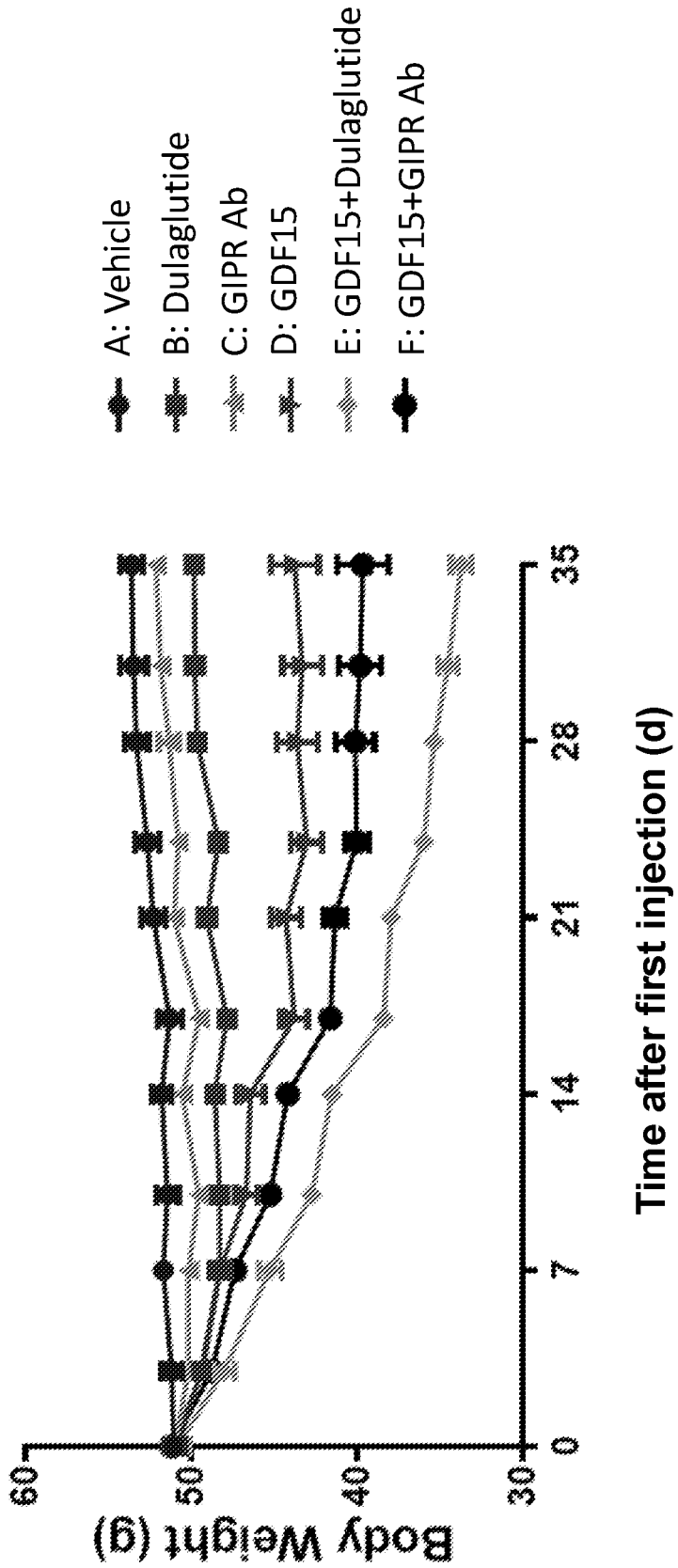

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Body Weight (g)
60
50
40
30
0
7
14
21
28
35
Time after first injection (d)

Figure 1B

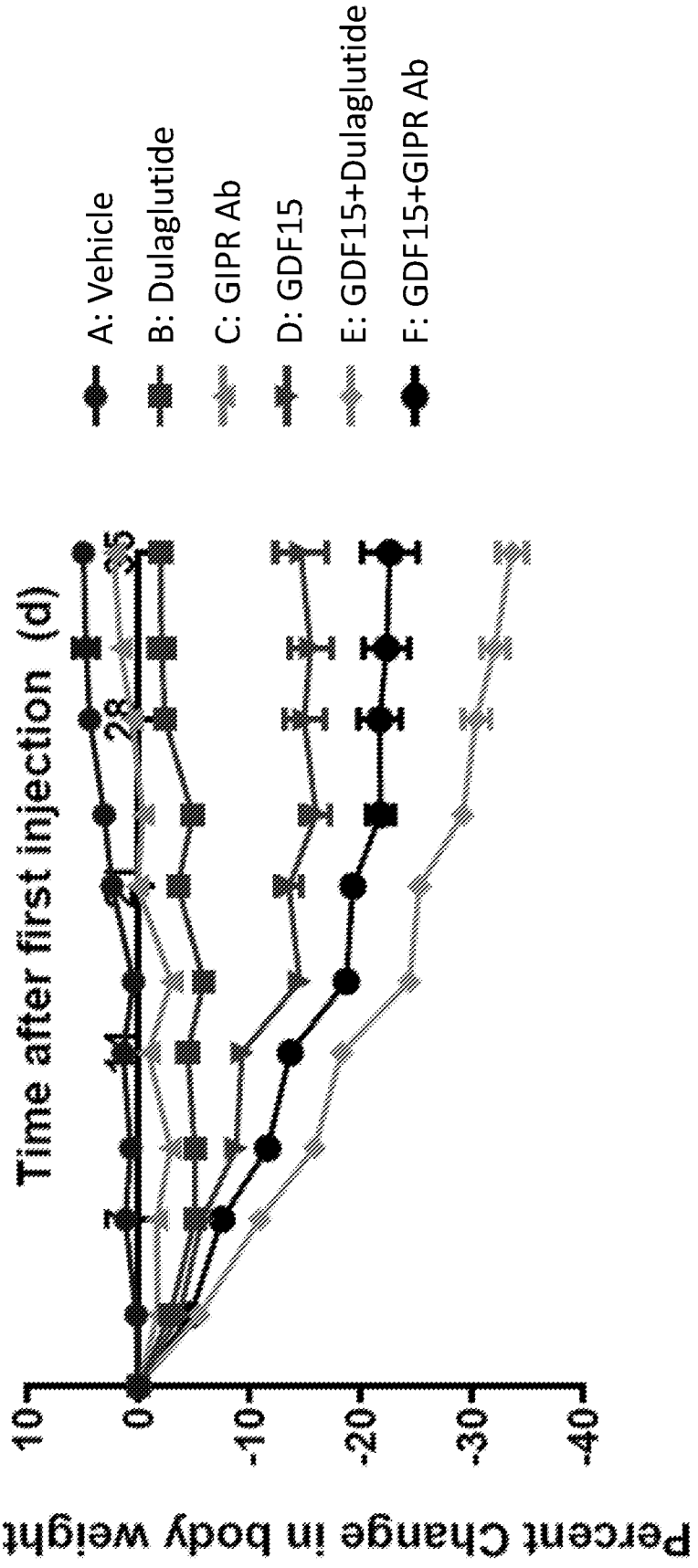

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Time after first injection (d)
1
7
14
21
28
35
10
0
-10
-20
-30
-40
Percent Change in body weight (%)

Figure 2A

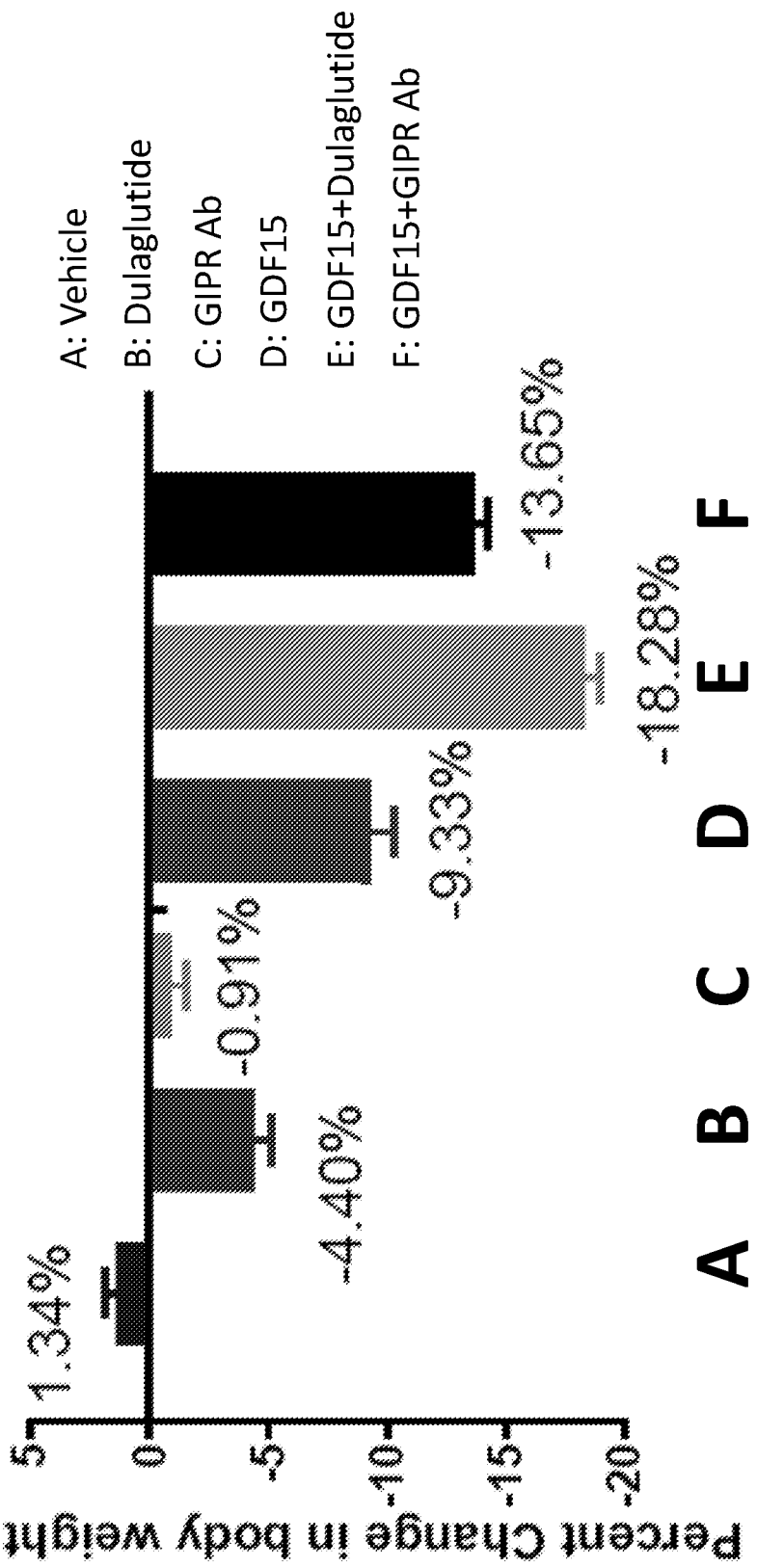

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Percent Change in body weight (%)
5
0
-5
-10
-15
-20
1.34%
-4.40%
-0.91%
-9.33%
-18.28%
-13.65%
A
B
C
D
E
F

Figure 2B

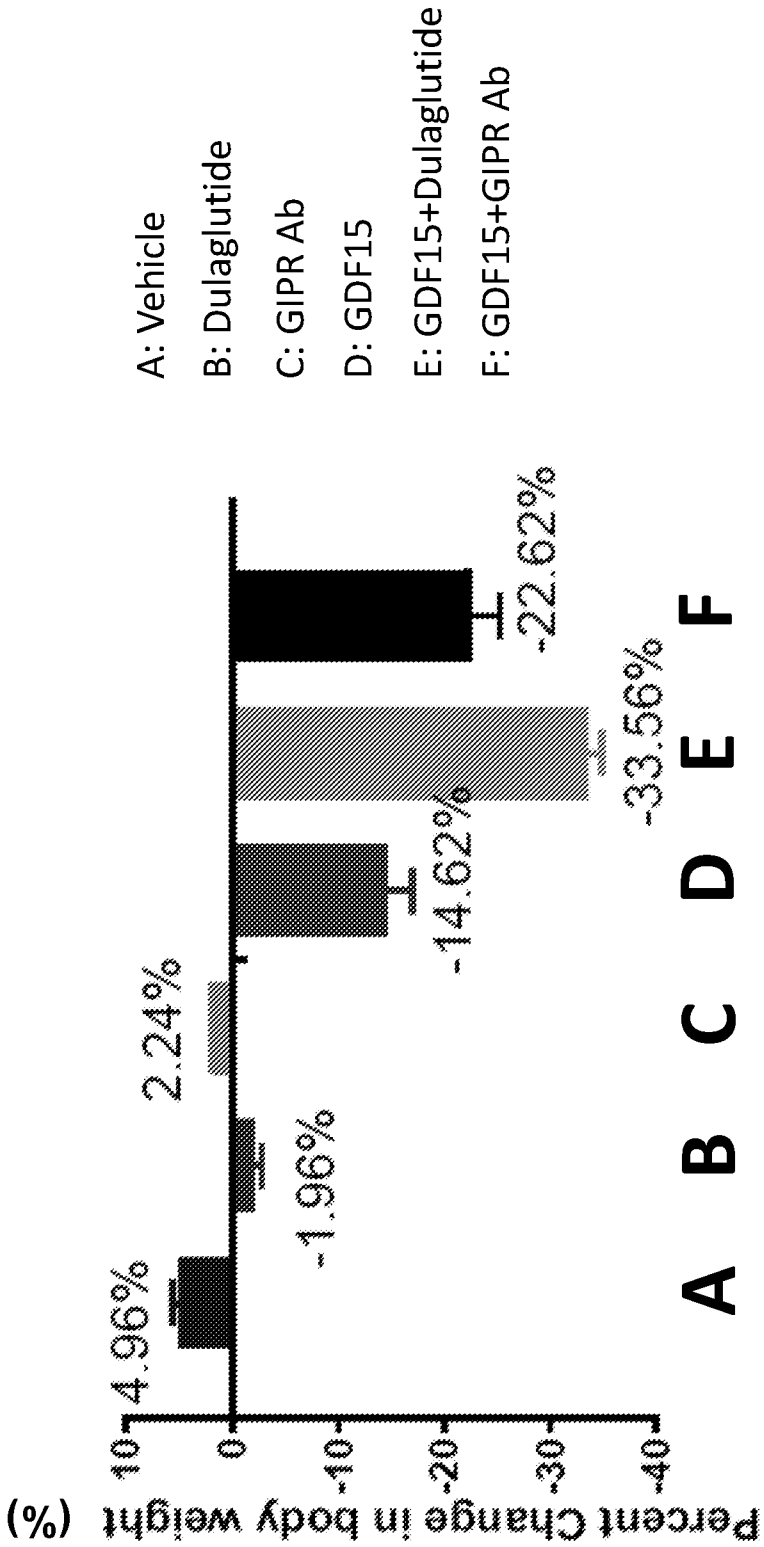
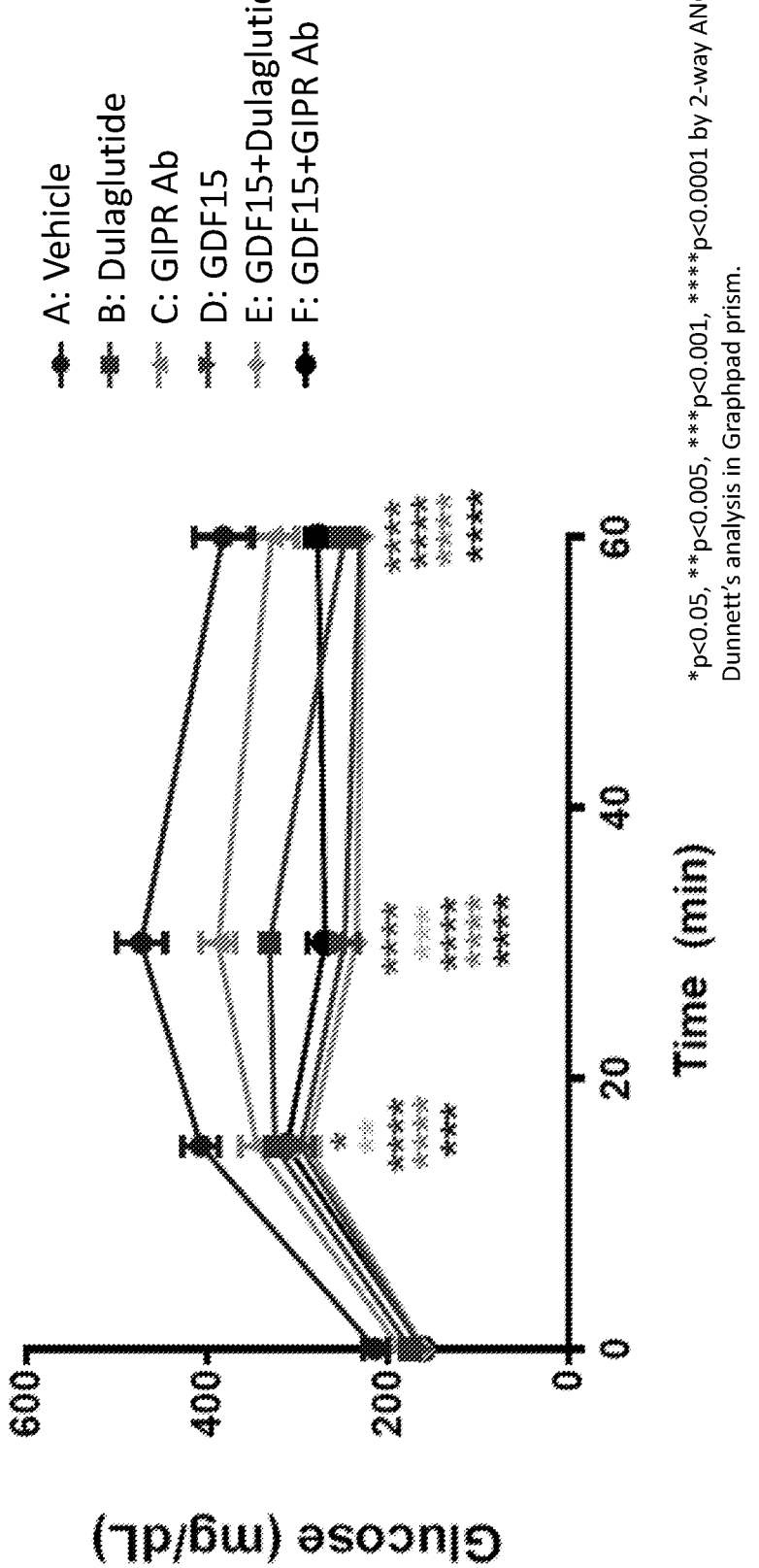

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Percent Change in body weight (%)
10
0
-10
-20
-30
-40
4.96%
2.24%
-1.96%
-14.62%
-22.62%
-33.56%
A
B
C
D
E
F

Figure 3A



*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 3B

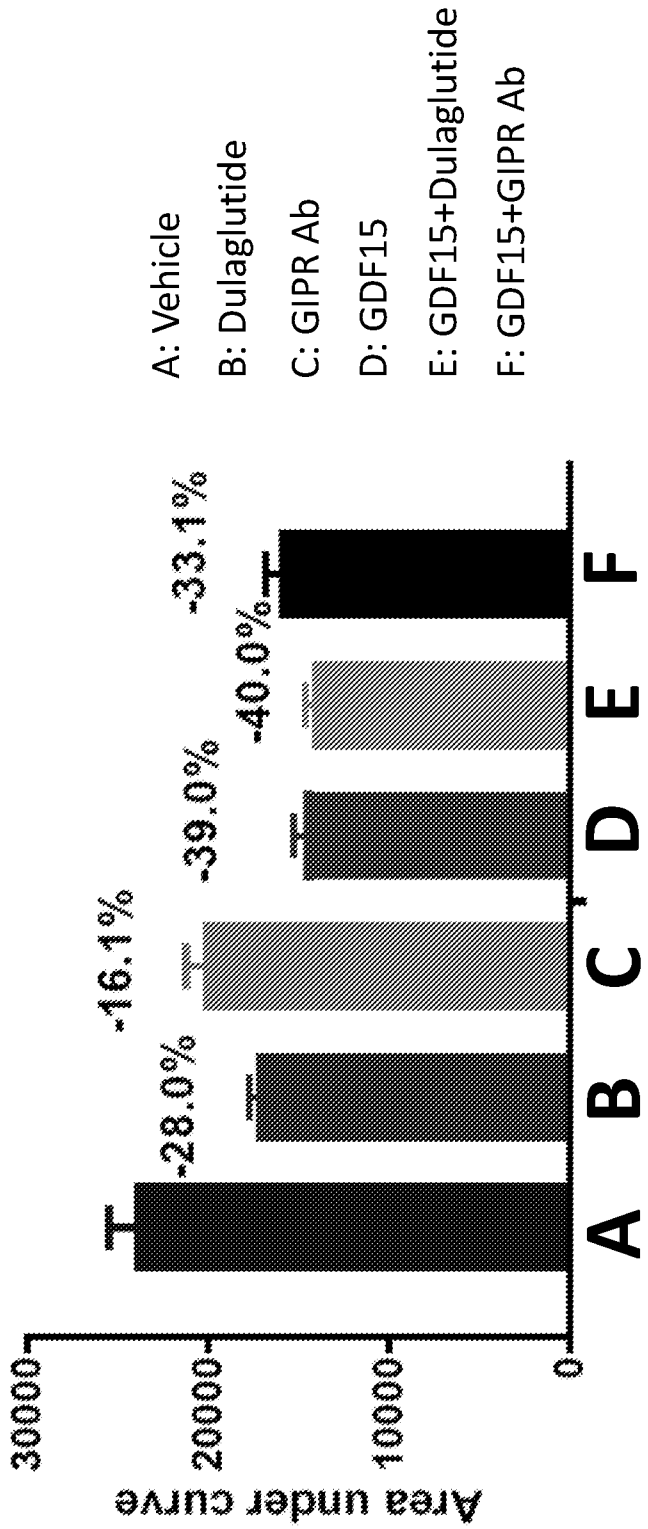

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Area under curve
30000
20000
10000
0
-28.0%
-16.1%
-39.0%
-40.0%
-33.1%
A
B
C
D
E
F

Figure 4A

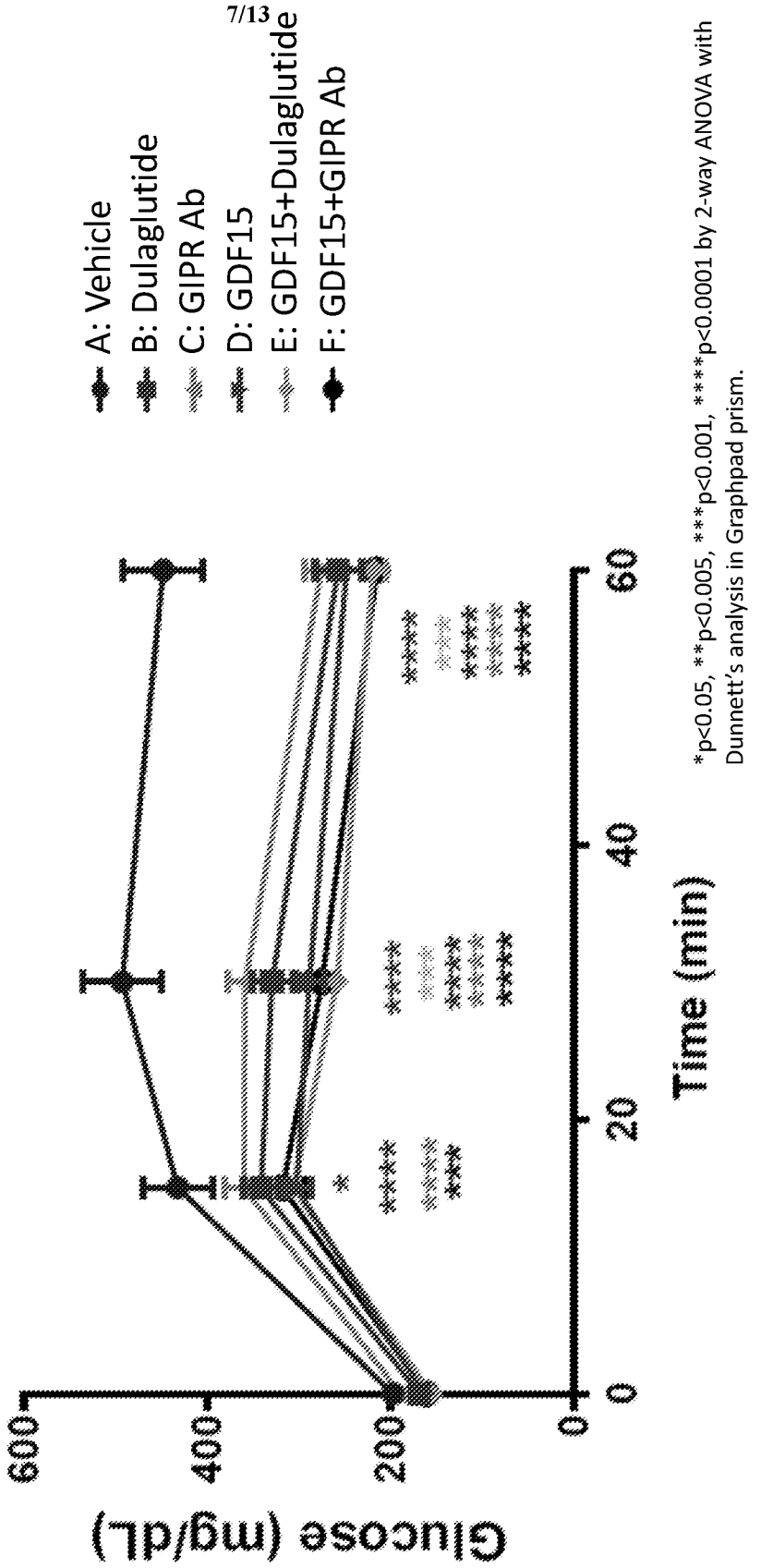

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Glucose (mg/dL)
600
400
200
0
0
20
40
60
Time (min)
*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 4B

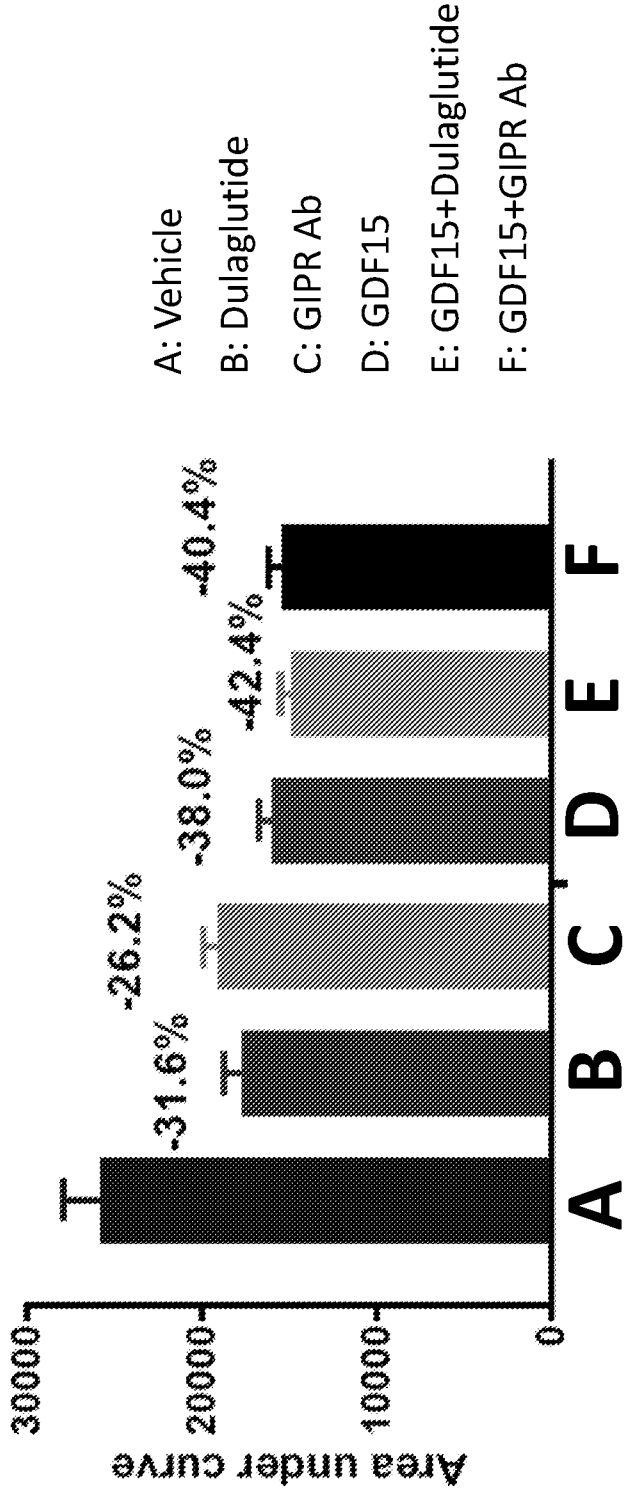

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Area under curve
30000
20000
10000
0
-31.6%
-26.2%
-38.0%
-42.4%
-40.4%
A
B
C
D
E
F

Figure 5A

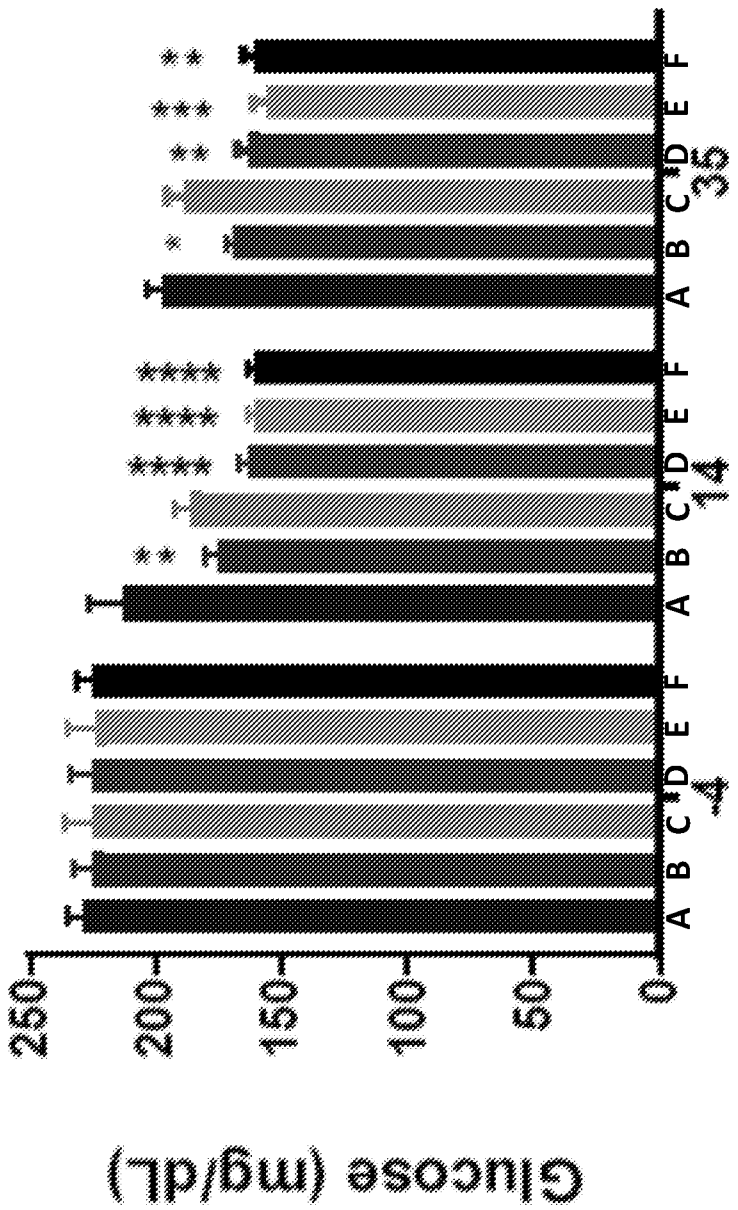

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Glucose (mg/dL)
250
200
150
100
50
0
A B C D E F
4
A B C D E F
14
A B C D E F
35
*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 5B

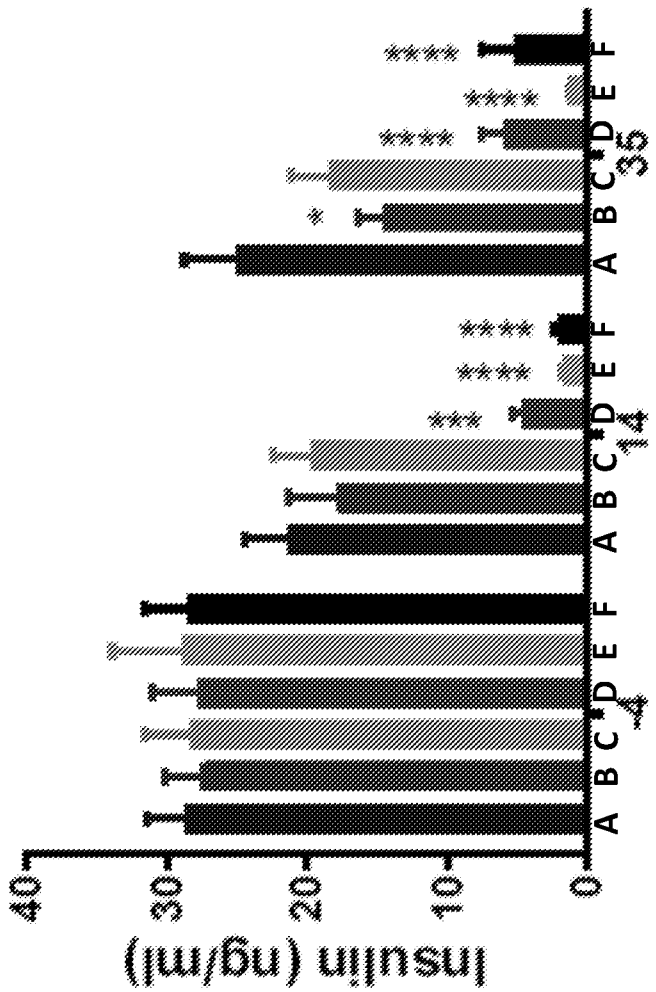
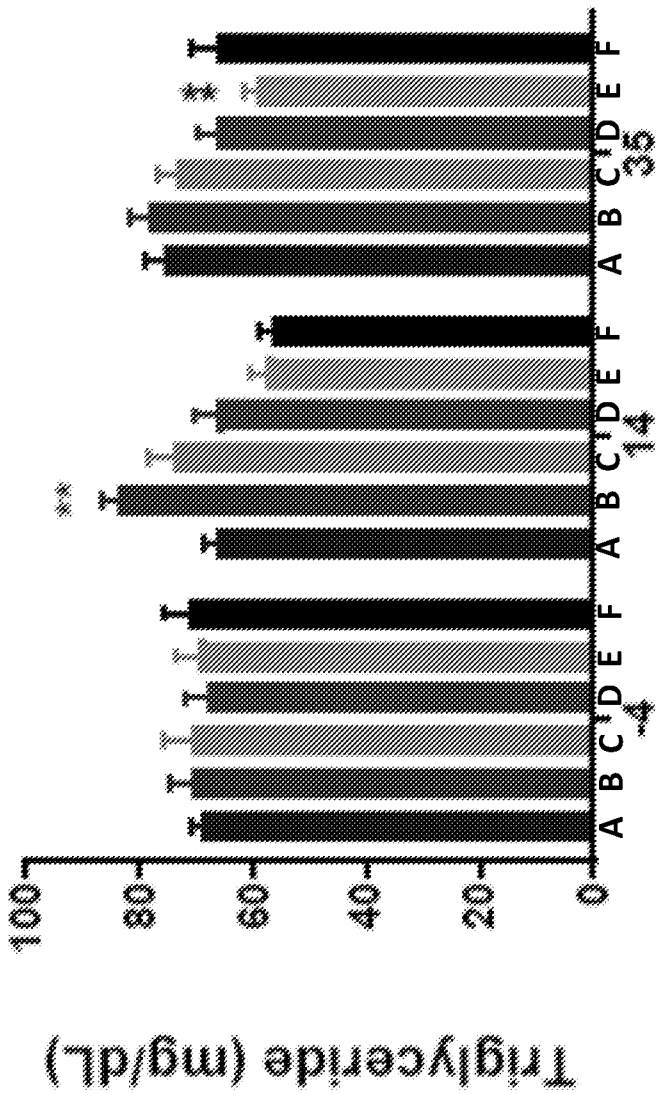

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Insulin (ng/ml)
0
10
20
30
40
4
14
35
A B C D E F
A B C D E F
A B C D E F
*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 5C



*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 5D

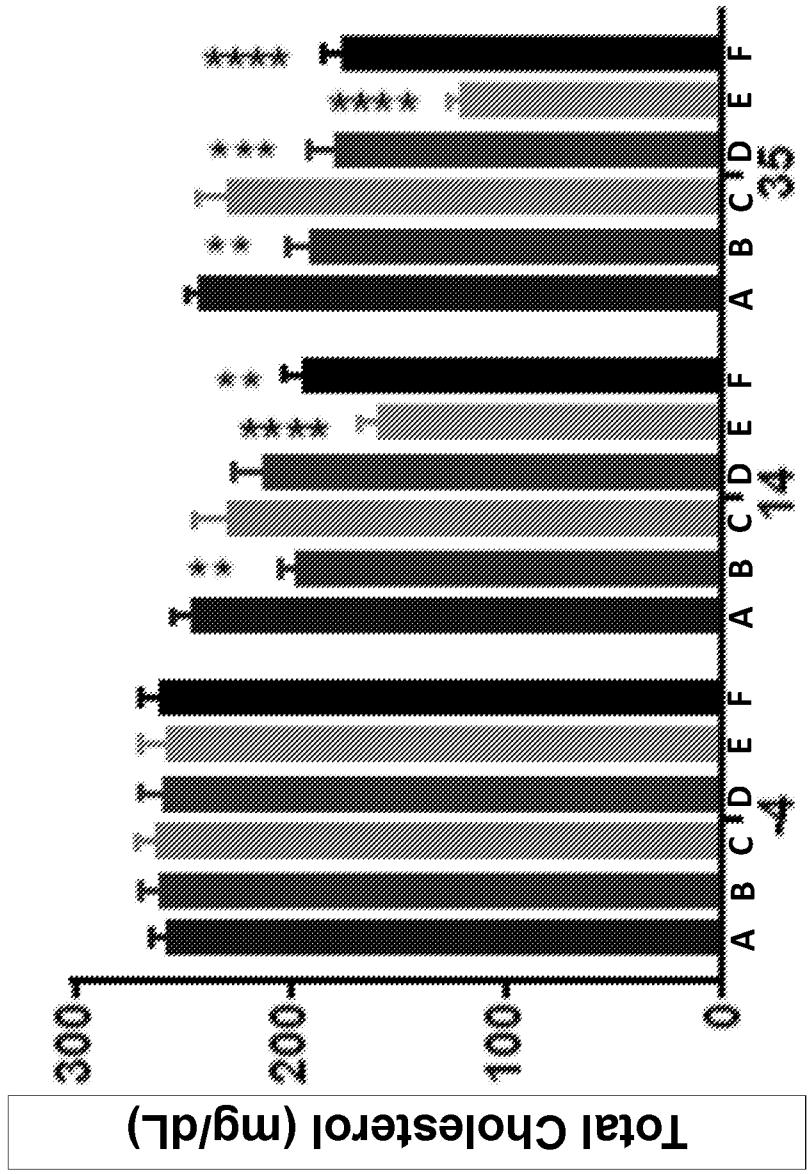
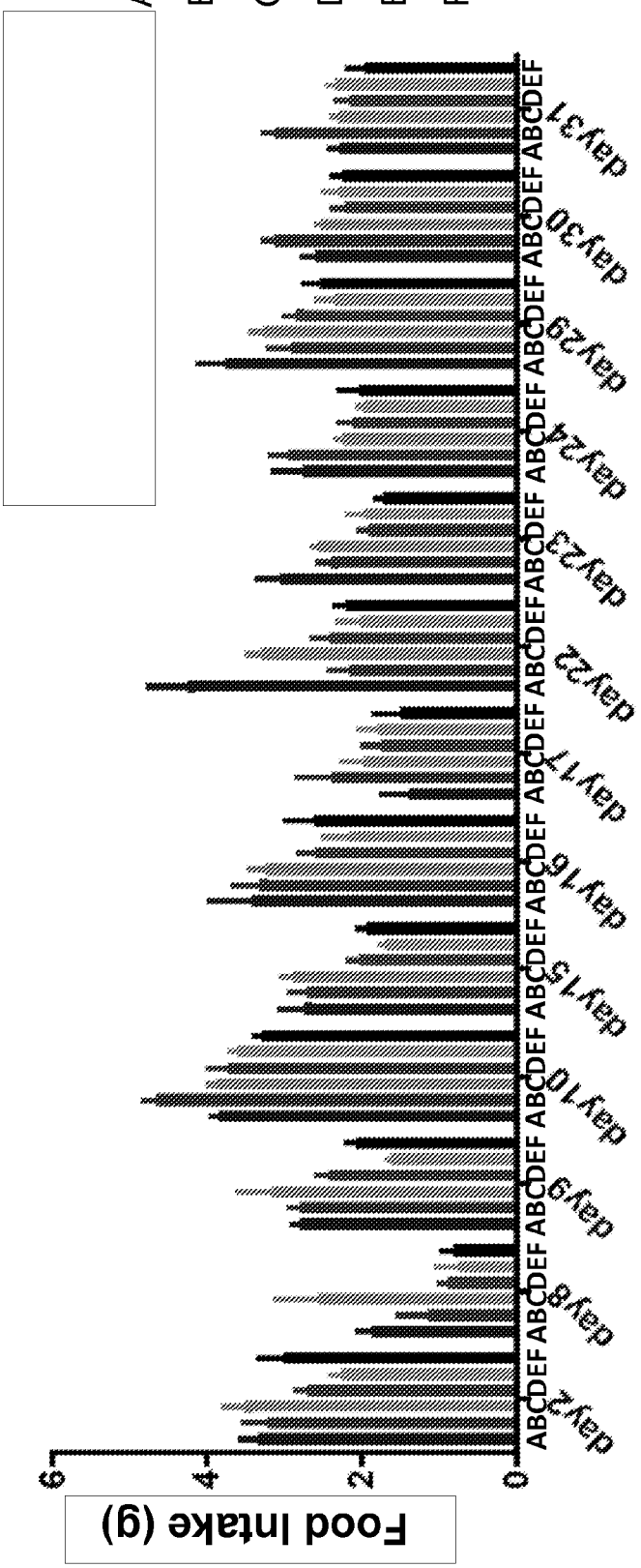

A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Total Cholesterol (mg/dL)
300
200
100
0
A B C D E F
4
A B C D E F
14
A B C D E F
35
*p<0.05, **p<0.005, ***p<0.001, ****p<0.0001 by 2-way ANOVA with Dunnett's analysis in Graphpad prism.

Figure 6


A: Vehicle
B: Dulaglutide
C: GIPR Ab
D: GDF15
E: GDF15+Dulaglutide
F: GDF15+GIPR Ab
Food Intake (g)
0
2
4
6
day2
day8
day9
day10
day15
day16
day17
day22
day23
day24
day29
day30
day31
ABCDEF