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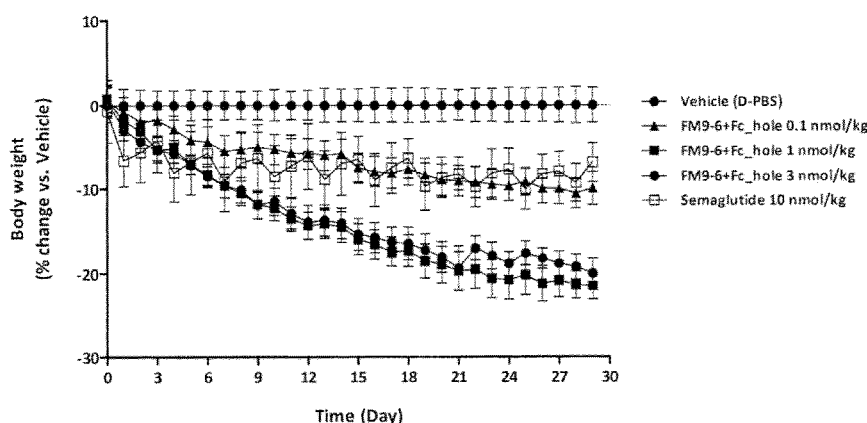
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## (54) Title: LONG-ACTING GDF15 FUSION PROTEIN AND PHARMACEUTICAL COMPOSITION COMPRISING SAME

[FIG. 13]



(57) Abstract: The present invention relates to a fusion protein including a GDF15 variant having increased physiological activity and *in vivo* stability, and a pharmaceutical composition comprising the same. The GDF15 variant or long-acting GDF15 fusion protein, according to the present invention, is superior to conventional GDF15 variants in terms of *in vivo* efficacy, binding affinity for GDF15 receptors, and body weight loss effect. Therefore, a pharmaceutical composition, which comprises, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or a dimer of the fusion protein, of the present invention, causes appetite suppression, and thus can be effectively used as a therapeutic agent for metabolic diseases or obesity. Furthermore, the pharmaceutical composition, which comprises, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer, can be used in combination therapy or the like with chemical drugs and other therapeutic agents for metabolic diseases, and can be effectively used in combination therapy with conventional therapeutic agents for metabolic diseases or obesity.



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## Description

### Title of Invention

LONG-ACTING GDF15 FUSION PROTEIN AND  
5 PHARMACEUTICAL COMPOSITION COMPRISING SAME

### Technical Field

The present invention relates to a fusion protein that includes a GDF15 variant having increased physiological activity and *in vivo* stability, and a pharmaceutical  
10 composition comprising the same.

### Background Art

Growth differentiation factor-15 (GDF15) is also called macrophage inhibitory cytokine-1 (MIC-1), placental bone morphogenetic protein (PBMP), or nonsteroidal  
15 anti-inflammatory drug-activated gene-1 (NAG-1), and is a protein that is a member of the transforming growth factor-beta (TGF- $\beta$ ) superfamily.

Recently, study results have shown that GDF15 inhibits dietary intake through binding to GDNF family receptor alpha-like (GFRAL) and ret proto-oncogene (RET), which are specifically expressed in brain tissue, and thus results in body weight loss  
20 (Tsai VW, *et al.*, PLoS One 2013; 8(2): e55174; US 8,192,735). In addition, several studies have demonstrated that GDF15 has an excellent body weight loss effect in a case of being administered to various obese animal models, and have identified that in addition to such an effect, GDF15 further has metabolic advantages such as lowering blood glucose level, improving lipid level, and improving insulin resistance.

25 However, the wild-type GDF15 is problematic in that in a case where it is used medically, high frequency of administration is needed due to its short *in vivo* half-life.

Accordingly, efforts are being made to develop long-acting formulations that are intended to increase an *in vivo* half-life of GDF15.

Meanwhile, among several techniques of producing long-acting formulations, an immunoglobulin Fc fusion technique is most widely used in that it results in increased *in vivo* half-life and there is little concern about adverse effects such as toxicity or induction of immune responses. To develop an immunoglobulin Fc-fused GDF15 protein into a long-acting therapeutic drug, the following several conditions must be satisfied.

First, decrease in *in vitro* activity caused by fusion should be minimized. It is known that activity of GDF15 fusion proteins varies greatly depending on fusion site. Therefore, activity of Fc-fused GDF15 proteins, in which a mutation has been introduced into the GDF15, may vary depending on whether fusion has occurred or fusion site. Second, fusion should result in increased *in vivo* half-life, and the increased *in vivo* half-life should display a pharmacokinetic profile which enables administration at an interval of once a week in humans. Third, considering that most biopharmaceuticals may cause immunogenicity in patients, risk of immunogenicity caused by a fusion linker or mutation should be minimized. Fourth, there should be no stability problems due to fusion site or mutation introduction. Fifth, since an unwanted immune response may occur depending on isotypes of fused immunoglobulin, an alternative thereto is required.

While making efforts to improve physiological activity and stability of GDF15, the present inventors have identified that in a case where a mutation is introduced at a particular location of GDF15 and an immunoglobulin Fc region is bound thereto, the GDF15 has enhanced activity and increased *in vivo* half-life, and thus have completed the present invention.

## Disclosure of Invention

### Technical Problem

An object of the present invention is to provide a GDF15 variant having improved physiological activity and stability, and a long-acting GDF15 fusion protein.

Another object of the present invention is to provide a pharmaceutical composition for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome, comprising, as an active ingredient, the GDF15 variant or the long-acting GDF15 fusion protein.

### Solution to Problem

To achieve the above objects, in an aspect of the present invention, there is provided a GDF15 variant represented by Formula (I).

N-terminal extension domain - core domain (I)

In another aspect of the present invention, there is provided a long-acting GDF15 fusion protein, in which the GDF15 variant is bound to human IgG Fc or a variant thereof.

In yet another aspect of the present invention, there is provided a fusion protein dimer, comprising two of the long-acting GDF15 fusion protein.

In still yet another aspect of the present invention, there is provided an isolated nucleic acid molecule, encoding the GDF15 variant or the GDF15 fusion protein.

In still yet another aspect of the present invention, there is provided an expression vector, comprising the nucleic acid molecule.

In still yet another aspect of the present invention, there is provided a host cell, comprising the expression vector.

In still yet another aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome, comprising, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer.

### Advantageous Effects of Invention

The GDF15 variant or the long-acting GDF15 fusion protein, according to the present invention, is superior to conventional GDF15 variants in terms of *in vitro* efficacy, binding affinity for GDF15 receptors, and body weight loss effect.

Therefore, a pharmaceutical composition, which comprises, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer, of the present invention, causes appetite suppression, and thus can be effectively used as a therapeutic agent for metabolic diseases or obesity.

Furthermore, the pharmaceutical composition, which comprises, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer, can be used in combination therapy or the like with chemical drugs and other therapeutic agents for metabolic diseases, and can be effectively used in combination therapy with conventional therapeutic agents for metabolic diseases or obesity.

### Brief Description of Drawings

FIG. 1 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM4, FM4-1, FM4-2, and FM4-3) in which asparagine (N), which is the amino acid at position 56 in mature GDF15, and/or aspartic acid (D), which is the amino acid at position 103 in mature GDF15, is substituted with another amino acid.

FIG. 2 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM9, FM13, FM14, FM15, and FM16) in which serine (S), which is the amino acid at position 64 in mature GDF15 is substituted with another amino acid.

FIG. 3 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM4, FM5, and FM9).

FIG. 4 illustrates results obtained by comparing, in terms of binding affinity for GDF15 receptors (GFRAL and RET), long-acting GDF15 fusion proteins (dimers: FM4, FM5, and FM9).

FIG. 5 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM1, and FM10).

FIG. 6 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM2, and FM11).

FIG. 7 illustrates results obtained by comparing, in terms of activity, long-acting GDF15 fusion proteins (dimers: FM3, and FM12).

FIG. 8 illustrates results obtained by comparing, in terms of binding affinity for GDF15 receptors (GFRAL and RET), long-acting GDF15 fusion proteins (dimers: FM10 and FM11).

FIG. 9 illustrates results obtained by comparing, in terms of activity depending on linker type and length, long-acting GDF15 fusion proteins (dimers: FM9-1, FM9-2, FM9-3, FM9-4, FM9-5, and FM9-6).

FIG. 10 illustrates results obtained by comparing, in terms of activity depending on linker type and length, long-acting GDF15 fusion proteins (dimers: FM11-1, FM11-2, FM11-3, FM11-4, FM11-5, and FM11-6).

FIG. 11 illustrates results obtained by comparing long-acting GDF15 fusion proteins (dimers; FM9-4, FM9-6, FM11-4, and FM11-6) in terms of change of body weight (%) in diet-induced obese mice (DIO mice), by repeated administration.

FIG. 12 illustrates results obtained by comparing long-acting GDF15 fusion proteins (dimers; FM9-6) in terms of change of body weight (%) in diet-induced obese mice (DIO mice), by single administration.

FIG. 13 illustrates results obtained by comparing long-acting GDF15 fusion proteins (dimers; FM9-6) in terms of change of body weight (%) in ob/ob mice, by repeated administration.

## Best Mode for Carrying out the Invention

Hereinafter, the present invention will be described in more detail.

### GDF15 variant

5 In an aspect of the present invention, there is provided a GDF15 variant represented by Formula (I):

N-terminal extension domain - core domain (I).

In Formula (I),

10 the N-terminal extension domain is a polypeptide consisting of any one amino acid sequence of SEQ ID NOs: 3 to 5; and

the core domain is a polypeptide represented by SEQ ID NO: 20, or a polypeptide derived from SEQ ID NO: 20 in which any one amino acid selected from the group consisting of amino acids at positions 15, 50, 58, 97, and combinations thereof in the amino acid sequence of SEQ ID NO: 20 is substituted with another  
15 amino acid;

wherein arginine (R), which is the amino acid at position 15, may be substituted with alanine (A), aspartic acid (D), asparagine (N), cysteine (C), glutamic acid (E), glutamine (Q), glycine (G), histidine (H), isoleucine (I), leucine (L), lysine (K), methionine (M), phenylalanine (F), proline (P), serine (S), threonine (T),  
20 tryptophan (W), tyrosine (Y), or valine (V),

asparagine (N), which is the amino acid at position 50, may be substituted with alanine, arginine (R), aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine,

25 serine (S), which is the amino acid at position 58, may be substituted with alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, glycine,

histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tryptophan, tyrosine, or valine, and

aspartic acid (D), which is the amino acid at position 97, may be substituted with alanine, arginine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

As used herein, the term "core domain" refers to a polypeptide having an amino acid sequence from positions 7 to 112 in the amino acid sequence of GDF15 of SEQ ID NO: 1, including a polypeptide represented by SEQ ID NO: 20, or a polypeptide derived from SEQ ID NO: 20 in which any one amino acid selected from the group consisting of amino acids at positions 15, 50, 58, 97, and combinations thereof in the amino acid sequence of SEQ ID NO: 20 is substituted with another amino acid. The first core domain may consist of the amino acid sequence of SEQ ID NO: 2.

Specifically, the core domain may include any one variation selected from the group consisting of the following variations (1) to (6):

(1) a variation in which arginine (R), which is the amino acid at position 15 in the amino acid sequence of SEQ ID NO: 20, is substituted with asparagine (N);

(2) a variation in which asparagine (N), which is the amino acid at position 50 in the amino acid sequence of SEQ ID NO: 20, is substituted with leucine (L);

(3) a variation in which serine (S), which is the amino acid at position 58 in the amino acid sequence of SEQ ID NO: 20, is substituted with lysine (K), arginine (R), asparagine (N), aspartic acid (D), glutamic acid (E), cysteine (C), or leucine (L);

(4) a variation in which aspartic acid (D), which is the amino acid at position 97 in the amino acid sequence of SEQ ID NO: 20, is substituted with leucine (L);

(5) a variation in which asparagine (N), which is the amino acid at position 50 in the amino acid sequence of SEQ ID NO: 20, and aspartic acid (D), which is the amino acid at position 97 in the amino acid sequence of SEQ ID NO: 20, are each

substituted with cysteine (C) or serine (S); and

(6) a variation in which arginine (R), which is the amino acid at position 15 in the amino acid sequence of SEQ ID NO: 20, is substituted with asparagine (N), and serine (S), which is the amino acid at position 58 in the amino acid sequence of SEQ ID NO: 20, is substituted with lysine (K) or arginine (R).

Here, the core domain may consist of any one amino acid sequence selected from SEQ ID NOs: 6 to 19.

The N-terminal extension domain is a domain bound to the N-terminus of the above-described core domain, and may be a polypeptide consisting of any one amino acid sequence of SEQ ID NOs: 3 to 5.

As used herein, the expression " $\Delta$ N2" may also be indicated as "delta N2", meaning that in the amino acid sequence of human GDF15 represented by SEQ ID NO: 1, the amino acids at positions 1 and 2 are deleted. In a case where  $\Delta$ N2 is expressed as an N-terminal extension domain, it may be expressed as "NGDH".

As used herein, the expression " $\Delta$ N3, WS insertion, G4N, D5S, H6T" may also be indicated as "delta N3, WS insertion, G4N, D5S, H6T", meaning that in the amino acid sequence of human GDF15 represented by SEQ ID NO: 1, the amino acids at positions 1 to 3 are deleted, and tryptophan and serine are inserted therein; glycine, which is the amino acid at position 4, is substituted with asparagine; aspartic acid, which is the amino acid at position 5, is substituted with serine; and histidine, which is the amino acid at position 6, is substituted with threonine. In a case where the  $\Delta$ N3, WS insertion, G4N, D5S, H6T is expressed as an N-terminal extension domain, it may be indicated as "WSNST".

As used herein, the expression " $\Delta$ N3, G4N, D5S, H6T" may also be indicated as "delta N3, G4N, D5S, H6T", meaning that in the amino acid sequence of human GDF15 represented by SEQ ID NO: 1, the amino acids at positions 1 to 3 are deleted; glycine, which is the amino acid at position 4, is substituted with asparagine; aspartic acid, which is the amino acid at position 5, is substituted with serine; and histidine,

which is the amino acid at position 6, is substituted with threonine. In a case where the "ΔN3, G4N, D5S, H6T" is expressed as an N-terminal extension domain, it may be expressed as "NST."

The GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a core domain consisting of any one amino acid sequence selected from SEQ ID NOs: 6 to 20. In addition, the GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 4 and a core domain consisting of any one amino acid sequence selected from SEQ ID NOs: 6 to 20. Furthermore, the GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 5 and a core domain consisting of any one amino acid sequence selected from SEQ ID NO: 6 to 19.

Preferably, the GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 3 and a core domain consisting of an amino acid sequence represented by SEQ ID NO: 8, 9, or 20. In addition, the GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 4 and a core domain consisting of an amino acid sequence represented by SEQ ID NO: 8, 9, or 20. Furthermore, the GDF15 variant may include an N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 5 and a core domain consisting of any one amino acid sequence selected from SEQ ID NOs: 6, 7, and 10 to 19. Here, the GDF15 variant may consist of any one amino acid sequence selected from SEQ ID NOs: 21 to 39.

### **Long-acting GDF15 fusion protein**

In another aspect of the present invention, there is provided a long-acting GDF15 fusion protein, in which the GDF15 variant is bound to human IgG Fc or a variant thereof.

The human IgG Fc or a variant thereof may be Fc of IgG1, IgG2, IgG3, or IgG4, or a variant thereof. Specifically, the human IgG Fc or a variant thereof may

be human IgG1 Fc or a variant thereof, and the human IgG1 Fc may consist of an amino acid sequence represented by SEQ ID NO: 41.

The human IgG Fc or a variant thereof may be a contiguous amino acid sequence that is 90%, 92%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41, or a fragment of the Fc including a CH3 domain. In certain embodiments, the human IgG Fc or a variant thereof may be a contiguous amino acid sequence that is 90%, 92%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41, or a fragment of the Fc including a CH2 domain and a CH3 domain. In certain embodiments, the human IgG Fc or a variant thereof may be a contiguous amino acid sequence that is 90%, 92%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41, or a fragment of the Fc including a partial hinge region, a CH2 domain, and a CH3 domain. In certain embodiments, the human IgG Fc or a variant thereof may have an amino acid sequence that is 90%, 92%, 95%, 96%, 97%, 98%, 99%, or 100% identical to SEQ ID NO: 41.

The IgG Fc or a variant thereof includes a first polypeptide including an IgG1 Fc sequence, the IgG Fc sequence including a CH3 sequence that includes at least one engineered protuberance; and a second polypeptide including an IgG1 Fc sequence, the IgG Fc sequence including a CH3 sequence that includes at least one engineered cavity, in which the first polypeptide dimerizes with the second polypeptide via positioning of the protuberance of the first polypeptide into the cavity of the second polypeptide.

Specifically, the first polypeptide may include an engineered protuberance that allows binding to another IgG Fc polypeptide (for example, second polypeptide) including an engineered cavity. The second polypeptide may include an engineered cavity that allows binding to another IgG Fc polypeptide (for example, first polypeptide) including an engineered protuberance. In addition, the protuberance of the first polypeptide and the cavity of the second polypeptide may be each engineered into a CH3 domain of IgG Fc. Here, the protuberance of the first polypeptide and the cavity of the second polypeptide are neither connected nor bound to the GDF15

variant.

The engineered protuberance may include at least one substitution in the amino acid sequence of human IgG1 Fc having an amino acid sequence represented by SEQ ID NO: 41. Here, the amino acid positions are numbered according to EU numbering. The substitution may be present at a position selected from the group consisting of amino acid residues 347, 366, and 394. For example, the substitution may be any one selected from the group consisting of Q347W/Y, T366W/Y, T394W/Y, and combinations thereof. In addition, the engineered cavity may include at least one substitution in corresponding amino acids in the human IgG1 Fc sequence, and the substitution may be present at a position selected from the group consisting of amino acid residues 366, 368, 394, 405, and 407. For example, the substitution may be any one selected from the group consisting of T366S, L368A, T394S, F405T/V/A, Y407T/V/A, and combinations thereof.

Preferably, the protuberance may include the substitution T366W/Y, and the cavity may include any one substitution selected from the group consisting of T366S, L368A, Y407T/V/A, and combinations thereof. For example, the protuberance may include the substitution T366W/Y, and the cavity may include the substitution Y407T/V/A. In addition, the protuberance may include the substitution T366Y, and the cavity may include the substitution Y407T. In addition, the protuberance may include the substitution T366W, and the cavity may include the substitution Y407A. In addition, the protuberance may include the substitution T394Y, and the cavity may include the substitution Y407T.

The first polypeptide may consist of any one amino acid sequence selected from SEQ ID NOs: 42, 44, and 46, and the second polypeptide may consist of any one amino acid sequence selected from SEQ ID NOs: 43, 45, and 47.

The protuberance is referred to as "knob" and the cavity is referred to as "hole".

The first polypeptide is Fc 'knob' including an engineered protuberance, and the second polypeptide is Fc 'hole' including an engineered protuberance. The first and second polypeptides may be physically associated with each other via non-

covalent interactions (for example, hydrophobic effects, such as hydrophobic interaction between the knob and hole regions of the Fc), covalent bonds (for example, disulfide bonds such as one or two or more disulfide bonds between hinge regions of the Fc in the first and second polypeptides), or both.

5           As used herein, the term "dimer" refers to a protein complex including at least two polypeptides. Each of these polypeptides includes an N-terminus and a C-terminus. At least two polypeptides may be associated with each other via one or both of covalent and non-covalent (for example, electrostatic,  $\pi$ -effects, van der Waals forces, and hydrophobic effects) interactions. The two polypeptides may have the  
10       same amino acid sequence or may be different from each other. In a case where the two polypeptides are identical to each other, the dimer is referred to as a (homo)dimer; and in a case where the two polypeptides are different from each other, the dimer is referred to as a heterodimer.

          The human IgG Fc or a variant thereof may be a heterodimer including a first  
15       polypeptide and a second polypeptide; and the heterodimer may be a heterodimer formed of A-1 (SEQ ID NO: 42) and A-2 (SEQ ID NO: 43), a heterodimer formed of B-1 (SEQ ID NO: 44) and B-2 (SEQ ID NO: 45), or a heterodimer formed of C-1 (SEQ ID NO: 46) and C-2 (SEQ ID NO: 47).

          In addition, the IgG Fc or a variant thereof may include an additional mutation,  
20       to improve properties of a long-acting GDF15 fusion protein. Specifically, a heterodimer consisting of the first polypeptide and the second polypeptide may include an additional mutation.

          For example, the IgG Fc or a variant thereof may include mutation(s) that abolish (for example, decrease or eliminate) IgG effector function. Specifically, an  
25       Fc partner sequence may include mutation(s) that abolish effector functions such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). For example, the mutations E233A and L235A may be introduced into the IgG Fc formed of A-1 and A-2 or a variant thereof (which is a heterodimer), to eliminate IgG1 effector function.

The heterodimer formed of B-1 and B-2, which includes the mutation N297A, can be used to eliminate N-linked glycans. Into the heterodimer formed of C-1 and C-2 may be introduced the mutations L234A, L235A, and N297A, to eliminate IgG1 effector function and N-linked glycans.

5 Binding between the GDF15 variant and the IgG Fc or a variant thereof may be such that the C-terminus of the first polypeptide or the C-terminus of the second polypeptide, in the IgG Fc or a variant thereof, is bound to the N-terminus of the GDF15 variant. In addition, binding between the GDF15 variant and the IgG Fc or a variant thereof may be such that the N-terminus of the first polypeptide or the N-terminus of the second polypeptide, in the IgG Fc or a variant thereof, is bound to the C-terminus of the GDF15 variant. Preferably, binding between the GDF15 variant and the IgG Fc or a variant thereof may be such that the C-terminus of the first polypeptide in the IgG Fc or a variant thereof is bound to the N-terminus of the GDF15 variant.

15 In addition, binding between the GDF15 variant and the IgG Fc or a variant thereof may be made through a linker. The linker may be a peptide that consists of 10 to 50 amino acid residues, including glycine, serine, alanine, and glutamic acid residues. The linker may include (G4S)<sub>n</sub>, where n may be an integer of 1 to 10 or an integer of 2 to 7. For example, n may be 2, 3, 4, 5, 6, or 7. In an embodiment of the present invention, a linker including (G4S)<sub>5</sub>, which is a case where n is an integer of 5, was used.

As an example of a suitable linker other than the linker including (G4S)<sub>n</sub>, a linker including GS(G4S)<sub>n</sub>, GS(EEEA)<sub>n</sub>, (EEEE)<sub>n</sub>, GS(EAAAK)<sub>n</sub>, (EAAAK)<sub>n</sub>, or GSGGSS(PT)<sub>n</sub> may be mentioned, where n may be an integer of 1 to 10. However, 25 the suitable linker is not limited thereto. In an embodiment of the present invention, a linker including GS(EEEA)<sub>6</sub>, which is a case where n is an integer of 6, or a linker including GS(EAAAK)<sub>5</sub>, which is a case where n is an integer of 5, was used.

Specifically, the linker may be GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 48), GSGGGGSGGGGSGGGGS (SEQ ID NO: 92),

5 GSEAAAKEAAAKEAAAKEAAAKEAAAK (SEQ ID NO: 97). Preferably, the linker may be GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 48), GSEEEAEEEEEEEEEEEEEEEEEEA (SEQ ID NO: 95), or GSEAAAKEAAAKEAAAKEAAAKEAAAK (SEQ ID NO: 97).

heterodimer consisting of a first polypeptide and a second polypeptide. The GDF15 variant may include at least one N-linked glycan.

15    NOs: 42, 44, and 46, and iii) a second polypeptide consisting of any one amino acid  
sequence selected from SEQ ID NOs: 43, 45, and 47.

20 polypeptide consisting of the amino acid sequence of SEQ ID NO: 42, and iv) a  
second polypeptide consisting of the amino acid sequence of SEQ ID NO: 43.

25 92 to 97, iii) a first polypeptide consisting of the amino acid sequence of SEQ ID NO:  
46, and iv) a second polypeptide consisting of the amino acid sequence of SEQ ID NO:  
47.

### Fusion protein dimer

In still yet another aspect of the present invention, there is provided a fusion protein dimer, comprising two of the long-acting GDF15 fusion protein. Specifically, the two long-acting GDF15 fusion proteins are dimerized through GDF15-GDF15 interaction, and this was designated "fusion protein dimer".

5           **Nucleic acid molecule, expression vector, and host cell**

In still yet another aspect of the present invention, there is provided an isolated nucleic acid molecule, encoding the GDF15 variant or the long-acting GDF15 fusion protein.

10           As used herein, the term "isolated nucleic acid molecule" refers to a nucleic acid molecule of the present invention that has been separated from at least about 50% of proteins, lipids, carbohydrates, or other materials with which it is naturally found when the entire nucleic acid is isolated from source cells; is operably linked to a polynucleotide which it is not linked to in nature; or does not occur in nature as part of a larger polynucleotide sequence. Specifically, the isolated nucleic acid molecule of  
15           the present invention is substantially free from any other contaminating nucleic acid molecules, or other contaminants that are found in its natural environment and would interfere with its use in polypeptide production, or its therapeutic, diagnostic, prophylactic, or research application.

20           Here, the isolated nucleic acid molecule that encodes the GDF15 variant or the long-acting GDF15 fusion protein may have different sequences due to codon redundancy. In addition, the isolated nucleic acid molecule may be appropriately modified or may have a nucleotide added to the N-terminus or C-terminus, depending on purposes, as long as it can produce the GDF15 variant or the long-acting GDF15 fusion protein.

25           In still yet another aspect of the present invention, there is provided an expression vector, comprising the isolated nucleic acid molecule that encodes the GDF15 variant or the long-acting GDF15 fusion protein.

As used herein, the term "expression vector" refers to a vector which is

suitable for transformation of a host cell and contains a nucleic acid sequence that directs or controls expression of an inserted heterologous nucleic acid sequence. The vector includes linear nucleic acids, plasmids, phagemids, cosmids, RNA vectors, viral vectors, and analogs thereof. Examples of the viral vector include, but are not limited to, a retrovirus, an adenovirus, and an adeno-associated virus.

As used herein, the term "expression of a heterologous nucleic acid sequence" or "expression" of a target protein refers to transcription of an inserted DNA sequence, translation of an mRNA transcript, and production of a fusion protein product, an antibody, or an antibody fragment.

A useful expression vector may be RcCMV (Invitrogen, Carlsbad) or a variant thereof. The useful expression vector may include a human cytomegalovirus (CMV) promoter for promoting continuous transcription of a target gene in mammalian cells, and a bovine growth hormone polyadenylation signal sequence for increasing a post-transcriptional RNA stability level.

In still yet another aspect of the present invention, there is provided a host cell, comprising the expression vector.

As used herein, the term "host cell" refers to a prokaryotic or eukaryotic cell into which a recombinant expression vector can be introduced. As used herein, the term "transformed" or "transfected" means that a nucleic acid (for example, vector) is introduced into a cell by a number of techniques known in the art.

The host cell may be transformed or transfected with a DNA sequence of the present invention, and may be used for expression and/or secretion of a target protein. Examples of the host cell that can be used in the present invention may include immortal hybridoma cells, NS/O myeloma cells, 293 cells, Chinese hamster ovary (CHO) cells, HeLa cells, CAP cells (human amniotic fluid-derived cells), and COS cells.

### **Pharmaceutical composition**

In a still yet another aspect of the present invention, there is provided a

pharmaceutical composition for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome, comprising, as an active ingredient, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer.

The pharmaceutical composition of the present invention can be administered  
5 via any route. The composition of the present invention may be provided to an animal either directly (for example, topically, by injection, implantation, or local administration to a tissue site) or systemically (for example, by parenteral or oral administration) using any appropriate means. In a case where the composition of the present invention is parenterally provided, such as by intravenous, subcutaneous,  
10 ophthalmic, intraperitoneal, intramuscular, rectal, intraorbital, intracerebral, intracranial, intraspinal, intraventricular, intrathecal, intracisternal, intracapsular, intranasal, or aerosol administration, the composition may be aqueous or include a portion of a physiologically applicable body fluid suspension or solution. Accordingly, since a carrier or vehicle is physiologically acceptable, it may be added  
15 to the composition and delivered to a patient. Therefore, physiological saline may be generally included as a body fluid-like carrier for formulations.

In addition, frequency of administration may vary depending on pharmacokinetic parameters of the GDF15 variant in a formulation used. Typically, physicians would administer the pharmaceutical composition until the dose thereof  
20 reaches a dose that achieves a desired effect. Thus, the pharmaceutical composition may be administered as a single dose, or two or more doses at time intervals (which may or may not contain an equal amount of a target fusion protein), or may be administered as continuous infusion through an implantable device or catheter. Further refinement of an appropriate dose is routinely made by those skilled in the art  
25 and falls within the scope of work which is routinely performed by them.

In addition, a unit dose of the fusion protein in humans is 0.01  $\mu$ g to 100 mg/kg body weight, and specifically, 1  $\mu$ g to 10 mg/kg body weight. Although the above-mentioned amount is an optimal amount, the amount may vary depending on a disease to be treated, or presence or absence of adverse effects. An optimal dose

may be determined using a conventional experiment. Administration of the fusion protein may be made by periodic bolus injections, or continuous intravenous, subcutaneous, or intraperitoneal administration from an external reservoir (for example, intravenous bag) or an internal reservoir (for example, biodegradable  
5 implant).

In addition, the fusion protein of the present invention may be administered to a subject recipient together with other biologically active molecules. However, an optimal combination of the fusion protein and other molecules, and dosage forms and precise doses thereof may be determined by conventional experiments well known in  
10 the art.

In still yet another aspect of the present invention, there is provided a use of the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer, for prevention or treatment of diabetes, obesity, dyslipidemia, or metabolic syndrome.

In still yet another aspect of the present invention, there is provided a use of  
15 the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer, for manufacture of a medicament for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome.

In still yet another aspect of the present invention, there is provided a method for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome,  
20 comprising a step of administering, to an individual, the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer.

Dose, frequency of administration, and route of administration of the GDF15 variant, the long-acting GDF15 fusion protein, or the fusion protein dimer are the same as described above. The individual may be an individual suffering from  
25 diabetes, obesity, dyslipidemia, or metabolic syndrome. In addition, the individual may be a mammal, preferably a human.

## Mode for the Invention

Hereinafter, for better understanding of the present invention, the present invention will be described in detail by way of examples. However, the examples according to the present invention may be modified in a variety of different forms, and the scope of the present invention should not be construed as being limited to the following examples.

### Example 1: Production of long-acting GDF15 fusion protein

#### Example 1.1: Gene cloning

In general, in a case where a substance is fused to long-acting Fc or albumin to increase its half-life, the fusion results in a decrease in activity of the substance. To improve this, various GDF15 variants were designed.

First, first polypeptides were prepared by performing substitutions of respective amino acids at positions 32, 51, 56, 60, 64, 90, 92, 93, 97, 101, and 103 in GDF15, which are predicted to have a large effect on protein activity through three-dimensional structure analysis of GDF15, and causing the resulting GDF15's to be bound to IgG1 Fc\_knob, and these first polypeptides are shown in Table 1 below.

[Table 1]

| Changes in sequence of GDF15 | Fusion carrier               | Linker sequence                    | SEQ ID NO of fusion protein |
|------------------------------|------------------------------|------------------------------------|-----------------------------|
| $\Delta$ N2                  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 49               |
| $\Delta$ N2, N56C, D103C     | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 65               |
| $\Delta$ N2, W32F            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 69               |
| $\Delta$ N2, W32H            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 70               |
| $\Delta$ N2, W32Y            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 71               |
| $\Delta$ N2, Q51H            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 72               |
| $\Delta$ N2, Q51L            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 73               |
| $\Delta$ N2, Q51E            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 74               |
| $\Delta$ N2, Q51N            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 75               |
| $\Delta$ N2, Q90H            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 76               |
| $\Delta$ N2, Q90E            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 77               |
| $\Delta$ N2, Q90K            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 78               |
| $\Delta$ N2, D93E            | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 79               |

|            |                              |                                    |               |
|------------|------------------------------|------------------------------------|---------------|
| ΔN2, D93L  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 80 |
| ΔN2, D93N  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 81 |
| ΔN2, D93Q  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 82 |
| ΔN2, Q60L  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 83 |
| ΔN2, Q60N  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 84 |
| ΔN2, S64K  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 54 |
| ΔN2, S64Q  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 85 |
| ΔN2, T92S  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 86 |
| ΔN2, T92E  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 87 |
| ΔN2, S97N  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 88 |
| ΔN2, S97Q  | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 89 |
| ΔN2, Y101F | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 90 |
| ΔN2, Y101Q | IgG1 Fc_knob (SEQ ID NO: 42) | (G4S) <sub>5</sub> (SEQ ID NO: 48) | SEQ ID NO: 91 |

Specifically, to produce a first polypeptide (FM series) having a structure of Fc\_knob-(G4S)<sub>5</sub>-GDF15 variant and a second polypeptide having Fc\_hole structure, gene cloning was conducted using pcDNA3.3 (Invitrogen) expression vector that includes a gene encoding a first polypeptide consisting of any one amino acid sequence of SEQ ID NOs: 49, 60, 65, and 69 to 90 and a gene encoding a second polypeptide consisting of the amino acid sequence of SEQ ID NO: 43. Here, nucleotide sequences encoding the amino acid sequences of SEQ ID NOs: 43, 49, 60, 65, and 69 to 90 were synthesized by making a request to MacroGen, Inc.

### **Example 1.2: Expression and purification of long-acting GDF15 fusion protein (dimer)**

The pcDNA3.3 expression vector cloned in Example 1.1 was transiently transfected into ExpiCHO cell line (Invitrogen). Then, on Day 8, the cell culture was harvested and purified. To purify the first polypeptide and the second polypeptide in the harvest cell culture fluid (HCCF), affinity purification using Protein A resin was performed.

Specifically, the HCCF was loaded onto MabSelect SuRe Protein A resin (GE Healthcare) equilibrated with 1× PBS (pH 7.4), to induce binding. After completion of the binding between the first polypeptide and the second polypeptide, the

MabSelect SuRe Protein A resin was washed with 1X PBS (pH 7.4). Then, elution was performed using 0.1 M glycine (pH 3.0) solution, to obtain a final substance.

The first polypeptide and the second polypeptide were neutralized to a level of about pH 8.0 using 1 M Tris-HCl solution. The first polypeptide and the second polypeptide were completely dimerized through knob-in-hole interaction, and this was designated "long-acting GDF15 fusion protein". Two molecules of the long-acting GDF15 fusion protein were dimerized again through GDF15-GDF15 interaction, and this was designated "fusion protein dimer".

#### **Example 2: Measurement of activity of long-acting GDF15 fusion protein (dimer)**

Using a fusion protein that includes mature GDF15 consisting of the amino acid sequence of SEQ ID NO: 49, as a control, the long-acting GDF15 fusion proteins produced in Example 1 were compared in terms of GDF15 activity. The GDF15 activity was measured using a Bright-Glo™ luciferase assay kit (Promega) and human embryonic kidney 293 (HEK293) cell line overexpressing GFRAL/RET/SRE-luc.

Specifically,  $1 \times 10^5$  HEK293 cells overexpressing GFRAL/RET/SRE-luc were dispensed into each well of a 96-well-plate in DMEM medium containing 10% FBS, and then incubated for 24 hours at 37°C and 5% CO<sub>2</sub>. After 24 hours, each medium in the 96-well-plate was replaced with 50 µl of serum-free medium, and incubated for 4 hours at 37°C and 5% CO<sub>2</sub>.

In addition, each of the long-acting GDF15 fusion proteins produced in Example 1 was prepared by 3-fold serial dilution starting from a concentration of 2000 nM using serum-free medium. Then, 50 µl of the long-acting GDF15 fusion protein dilution was added to each well that contains 50 µl of the replaced serum-free medium and the GFRAL/RET/SRE-luc cell line, so that the actual concentration was obtained by 3-fold serial dilution starting from 1000 nM. Then, reaction was allowed to proceed for 4 hours at 37°C and 5% CO<sub>2</sub>. After 4 hours, each well was treated with 100 µl of Bright-Glo™ solution, which had been prepared by adding

Bright-Glo™ buffer to Bright-Glo™ substrate, and reaction was allowed to proceed for 1 minute at room temperature.

Thereafter, relative light unit (RLU) values were measured with a microplate reader (Perkin Elmer, Wallac Victor X5) capable of measuring luminescence. The results are shown in Table 2 below. Here, two improved long-acting GDF15 fusion proteins were selected based on *in vitro* GDF15 activity ( $E_{max}$  of 100%) of the fusion protein (FWT+Fc\_hole) including mature GDF15, which was a control.

[Table 2]

| Changes in sequence of GDF15 in long-acting GDF15 fusion protein: | $E_{max}$ (%)<br>[relative to FWT 100%] | $EC_{50}$ (nM) |
|-------------------------------------------------------------------|-----------------------------------------|----------------|
| $\Delta N2$ : FWT+Fc_hole                                         | 100.0                                   | 7.0            |
| $\Delta N2$ , N56C, D103C: FM4+Fc_hole                            | 133.3                                   | 3.4            |
| $\Delta N2$ , W32F                                                | 51.3                                    | 19.4           |
| $\Delta N2$ , W32H                                                | Not active                              | Not active     |
| $\Delta N2$ , W32Y                                                | Not active                              | Not active     |
| $\Delta N2$ , Q51H                                                | 90.8                                    | 24.1           |
| $\Delta N2$ , Q51L                                                | 88.6                                    | 15.2           |
| $\Delta N2$ , Q51E                                                | 41.9                                    | 44.2           |
| $\Delta N2$ , Q51N                                                | 87.8                                    | 14.2           |
| $\Delta N2$ , Q90H                                                | 73.2                                    | 43.4           |
| $\Delta N2$ , Q90E                                                | 10.5                                    | 9.3            |
| $\Delta N2$ , Q90K                                                | Not active                              | Not active     |
| $\Delta N2$ , D93E                                                | 87.6                                    | 6.5            |
| $\Delta N2$ , D93L                                                | 59.1                                    | 9.0            |
| $\Delta N2$ , D93N                                                | 99.6                                    | 22.6           |
| $\Delta N2$ , D93Q                                                | Not active                              | Not active     |
| $\Delta N2$ , Q60L                                                | 96.3                                    | 11.9           |
| $\Delta N2$ , Q60N                                                | 43.5                                    | 7.0            |
| $\Delta N2$ , S64K: FM5+Fc_hole                                   | 147.2                                   | 7.7            |
| $\Delta N2$ , S64Q                                                | 100.0                                   | 7.9            |
| $\Delta N2$ , T92S                                                | 112.0                                   | 14.9           |
| $\Delta N2$ , T92E                                                | 12.3                                    | 1.1            |

|                    |       |      |
|--------------------|-------|------|
| $\Delta$ N2, S97N  | 100.2 | 5.6  |
| $\Delta$ N2, S97Q  | 117.6 | 9.2  |
| $\Delta$ N2, Y101F | 37.5  | 31.8 |
| $\Delta$ N2, Y101Q | 16.3  | 12.9 |

As a result, the two selected long-acting GDF15 fusion proteins were a long-acting GDF15 fusion protein (hereinafter referred to as FM4+Fc\_hole) having the mutations  $\Delta$ N2, N56C, and D103C, and a long-acting GDF15 fusion protein (hereinafter referred to as FM5+Fc\_hole) having the mutations  $\Delta$ N2 and S64K; and their *in vitro* GDF15 activity ( $E_{\max}$ ) was measured to be 133.3% and 147.2%, respectively. From these results, it was identified that the FM4+Fc\_hole and the FM5+Fc\_hole had improved *in vitro* GDF15 activity.

### Example 3: Measurement of activity of long-acting GDF15 fusion protein (dimer: FM4+Fc\_hole)

In GDF15-GDF15 interaction between the long-acting GDF15 fusion proteins, it was identified in Example 2 that the FM4+Fc\_hole, to which an additional disulfide bond was introduced, had improved *in vitro* GDF15 activity. On the basis of these results, to identify importance of the disulfide bond, long-acting GDF15 fusion proteins, which were based on the FM4+Fc\_hole and in which asparagine (N), which is the amino acid at position 56 in mature GDF15, and/or aspartic acid (D), which is the amino acid at position 103 in mature GDF15, was substituted with another amino acid, were additionally designed as shown in Table 3 below, and produced in the same manner as in Example 1. Then, *in vitro* GDF15 activity was evaluated in the same manner as in Example 2.

[Table 3]

| Designation of substance<br>(SEQ ID NO) | Changes in sequence of GDF15 in long-acting GDF15 fusion protein | $E_{\max}$ (%)<br>[relative to FWT<br>100%] | EC <sub>50</sub> (nM) |
|-----------------------------------------|------------------------------------------------------------------|---------------------------------------------|-----------------------|
| FWT+Fc_hole<br>(SEQ ID NOs: 49 and 43)  | $\Delta$ N2                                                      | 100.0                                       | 5.4                   |
| FM4+Fc_hole<br>(SEQ ID NOs: 65 and 43)  | $\Delta$ N2, N56C, D103C                                         | 140.1                                       | 3.6                   |

|                                          |                          |       |       |
|------------------------------------------|--------------------------|-------|-------|
| FM4-1+Fc_hole<br>(SEQ ID NOs: 66 and 43) | $\Delta$ N2, N56S, D103S | 86.4  | 8.9   |
| FM4-2+Fc_hole<br>(SEQ ID NOs: 64 and 43) | $\Delta$ N2, D103L       | 109.7 | 10.6  |
| FM4-3+Fc_hole<br>(SEQ ID NOs: 53 and 43) | $\Delta$ N2, N56L        | 34.3  | 140.1 |

As a result, as shown in Table 3, it was identified that only the FM4+Fc\_hole improved *in vitro* GDF15 activity ( $E_{\max}$ ) as compared with the FWT+Fc\_hole (FIG. 1). From these results, it was identified that introduction of cysteine and resultant introduction of a disulfide bond played an important role in improving *in vitro* GDF15 activity of the FM4+Fc\_hole.

#### Example 4: Measurement of activity of long-acting GDF15 fusion protein (dimer: FM5+Fc\_hole)

It was identified in Example 2 that the FM5+Fc\_hole, which is an S64K variant of GDF15, had improved *in vitro* GDF15 activity. On the basis of these results, long-acting GDF15 fusion proteins, which were based on the FM5+Fc\_hole and in which serine (S), which is the amino acid at position 64 in mature GDF15 was substituted with another amino acid, were additionally designed as shown in Table 4 below, and produced in the same manner as in Example 1. Then, *in vitro* GDF15 activity was evaluated in the same manner as in Example 2.

[Table 4]

| Designation of substance<br>(SEQ ID NO) | Changes in sequence of GDF15 in<br>long-acting GDF15 fusion protein | $E_{\max}$ (%)<br>[relative to FWT<br>100%] | EC <sub>50</sub> (nM) |
|-----------------------------------------|---------------------------------------------------------------------|---------------------------------------------|-----------------------|
| FWT+Fc_hole<br>(SEQ ID NOs: 49 and 43)  | $\Delta$ N2                                                         | 100.0                                       | 7.3                   |
| FM9+Fc_hole<br>(SEQ ID NOs: 57 and 43)  | $\Delta$ N2, S64R                                                   | 123.2                                       | 5.0                   |
| FM13+Fc_hole<br>(SEQ ID NOs: 60 and 43) | $\Delta$ N2, S64N                                                   | 93.3                                        | 9.6                   |
| FM14+Fc_hole<br>(SEQ ID NOs: 61 and 43) | $\Delta$ N2, S64D                                                   | 48.2                                        | 7.9                   |

|                                         |                   |      |      |
|-----------------------------------------|-------------------|------|------|
| FM15+Fc_hole<br>(SEQ ID NOs: 62 and 43) | $\Delta$ N2, S64E | 41.0 | 33.6 |
| FM16+Fc_hole<br>(SEQ ID NOs: 63 and 43) | $\Delta$ N2, S64L | 74.7 | 17.6 |

As a result, as shown in Table 4, it was identified that only the FM9+Fc\_hole had improved *in vitro* GDF15 activity ( $E_{max}$ ) as compared with FWT (FIG. 2).

**Example 5: Measurement of binding affinity of long-acting GDF15 fusion proteins (dimers: FM4+Fc\_hole, FM5+Fc\_hole, and FM9+Fc\_hole)**

The FM4+Fc\_hole, the FM5+Fc\_hole, and the FM9+Fc\_hole, having improved *in vitro* GDF15 activity, in Examples 3 and 4 were compared in terms of binding affinity for GFRAL and RET which are GDF15 receptors. To measure binding affinity for the GDF15 receptors, a cell-based enzyme-linked immunosorbent assay (ELISA) was performed using the HEK293 cell line overexpressing GFRAL and RET.

Specifically,  $1 \times 10^5$  HEK293 cells overexpressing GFRAL/RET/SRE-luc were dispensed into each well of a 96-well-plate in DMEM medium containing 10% FBS, and then incubated for 24 hours at 37°C and 5% CO<sub>2</sub>. After 24 hours, the medium was removed from each well of the 96-well-plate. Then, each medium was treated with 4% paraformaldehyde and reaction was allowed to proceed for 20 minutes at room temperature. Paraformaldehyde was removed therefrom. Treatment with 0.6% hydrogen peroxide solution was performed, and reaction was allowed to proceed again for 20 minutes. Then, treatment with 3% bovine serum albumin (BSA)-phosphate buffered saline with Tween 20 (PBST) buffer was performed, and blocking was allowed to proceed for 2 hours.

In addition, the FM4+Fc\_hole, the FM5+Fc\_hole, or the FM9+Fc\_hole was subjected to 2-fold serial dilution, starting from 200 µg/mL, using PBS buffer containing 1% BSA. 100 µl of the FM4+Fc\_hole, the FM5+Fc\_hole, or the FM9+Fc\_hole, each of which was diluted in various concentrations, was applied to a 96-well-plate containing a GFRAL/RET-overexpressing cell line, and reaction was

allowed to proceed for 2 hours at room temperature. Then, each well was treated with horseradish peroxidase (HRP)-conjugated anti-human IgG-Fc antibody (Jackson ImmunoResearch #109-035-098), and then developed with 3,3',5,5'-tetramethylbenzidine (TMB) buffer (Bio-Rad #172-1066).

5 Each well was treated with 100  $\mu$ l of TMB solution, and reaction was allowed to proceed for 10 minutes at room temperature. Then, the reaction was stopped using a 2N sulfuric acid ( $H_2SO_4$ ) reagent. Then, absorbance was measured at 450 nm with a microplate reader (Perkin Elmer, Wallac Victor X5) to evaluate binding capacity, to the GDF15 receptors, of the GDF15 variant in the long-acting GDF15 fusion protein  
10 (dimer).

As a result, as illustrated in FIG. 4, as compared with the FWT+Fc\_hole as a control, the FM9+Fc\_hole showed remarkably superior binding affinity for the GDF15 receptors, and the FM4 + Fc\_hole and the FM5+Fc\_hole also showed high binding affinity for the GDF15 receptors.

15 **Example 6: Purity improvement after purification for long-acting GDF15 fusion protein (dimer)**

To improve purification yield, purity, and the like of each long-acting GDF15 fusion protein at the time of producing the same, N-linked glycans were introduced at various positions in GDF15. Presence of N-linked glycans in the GDF15 sequence is  
20 known to increase retention time of the corresponding protein in the endoplasmic reticulum and Golgi apparatus during a process of protein secretion, thereby minimizing misfolded products and helping protein expression. Increased retention time has a beneficial effect on folding kinetics and can result in significantly improved heterodimeric (Fc/Fc) knob-in-hole assembly and recovery from mammalian tissue  
25 culture.

Evaluation of purity improvement after purification for a substance, obtained by introducing N-linked glycans into a long-acting GDF15 fusion protein, as compared with a dimer of the fusion protein FWT+Fc\_hole as a control, was performed in terms of correctly-assembled fusion protein dimer purity using size-

exclusion chromatography analysis.

Specifically, long-acting GDF15 fusion proteins, in which N-linked glycans were introduced at various positions in GDF15, were additionally designed. In this regard, variants having increased correctly-assembled fusion protein dimer purity, which was obtained in a case where the variants were produced and subjected to first-step purification in the same manner as in Example 1, as compared with a dimer of the fusion protein FWT+Fc\_hole, are shown in Table 6.

[Table 6]

| Designation of substance<br>(SEQ ID NO)    | Changes in sequence of GDF15 in long-acting<br>GDF15 fusion protein | Purity after first-<br>step purification<br>(Intact %) |
|--------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------------|
| FWT+Fc_hole<br>(SEQ ID NOs: 49 and 43)     | $\Delta$ N2                                                         | 50.9                                                   |
| FM1+Fc_hole<br>(SEQ ID NOs: 50 and 43)     | $\Delta$ N3, WS insertion, G4N, D5S, H6T                            | 80.2                                                   |
| FM2+Fc_hole<br>(SEQ ID NOs: 51 and 43)     | $\Delta$ N3, G4N, D5S, H6T                                          | 73.0                                                   |
| FM3+Fc_hole<br>(SEQ ID NOs: 52 and 43)     | $\Delta$ N2, R21N                                                   | 86.3                                                   |
| FM10+Fc_hole<br>(SEQ ID NOs: 58 and 43)    | $\Delta$ N3, WS insertion, G4N, D5S, H6T, S64R                      | 65.2                                                   |
| FM11+Fc_hole<br>(SEQ ID NOs: 59 and 43)    | $\Delta$ N3, G4N, D5S, H6T, S64R                                    | 70.3                                                   |
| FM12+Fc_hole<br>(SEQ ID NOs: 68 and 43)    | $\Delta$ N2, R21N, S64R                                             | 82.8                                                   |
| B13a/B13b<br>(see sequences in US 9920118) | $\Delta$ N2, D5T                                                    | 75.8                                                   |

As a result, it was identified that the FWT+Fc\_hole had correctly-assembled fusion protein dimer purity after first-step purification of 50.9%, whereas the FM1+Fc\_hole, the FM2+Fc\_hole, the FM3+Fc\_hole, the FM10+Fc\_hole, the FM11+Fc\_hole, and the FM12+Fc\_hole, in each of which N-linked glycans were introduced into GDF15, had improved, correctly-assembled fusion protein dimer purity of 80.2%, 73.0%, 86.3%, 65.2%, and 70.3%, respectively.

In addition, the NGM Biopharmaceuticals, Inc.'s fusion protein dimer (B13a/B13b (into which N-linked glycans are introduced) in U.S. Patent No. 9920118 was measured to have purity of 75.8%.

**Example 7: Evaluation of activity of long-acting GDF15 fusion proteins (dimers: FM10+Fc\_hole, FM11+Fc\_hole, and FM12+Fc\_hole)**

Using the FM1+Fc\_hole, the FM2+Fc\_hole, and the FM3+Fc\_hole, in each of which N-linked glycans were introduced at various positions in GDF15, as controls, the FM10+Fc\_hole, the FM11+Fc\_hole, and the FM12+Fc\_hole were evaluated, in terms of GDF15 activity, in the same manner as in Example 2. The results are shown in Table 7.

[Table 7]

| Designation of substance<br>(SEQ ID NO) | Changes in sequence of GDF15 in long-acting<br>GDF15 fusion protein | E <sub>max</sub> (%) | EC <sub>50</sub> (nM) |
|-----------------------------------------|---------------------------------------------------------------------|----------------------|-----------------------|
| FM1+Fc_hole<br>(SEQ ID NOs: 50 and 43)  | ΔN3, WS insertion, G4N, D5S, H6T                                    | 100.0                | 1.7                   |
| FM2+Fc_hole<br>(SEQ ID NOs: 51 and 43)  | ΔN3, G4N, D5S, H6T                                                  | 100.0                | 3.9                   |
| FM3+Fc_hole<br>(SEQ ID NOs: 52 and 43)  | ΔN2, R21N                                                           | 100.0                | 3.3                   |
| FM10+Fc_hole<br>(SEQ ID NOs: 58 and 43) | ΔN3, WS insertion, G4N, D5S, H6T, S64R                              | 267.0                | 2.3                   |
| FM11+Fc_hole<br>(SEQ ID NOs: 59 and 43) | ΔN3, G4N, D5S, H6T, S64R                                            | 269.5                | 2.9                   |
| FM12+Fc_hole<br>(SEQ ID NOs: 68 and 43) | ΔN2, R21N, S64R                                                     | 221.4                | 5.9                   |

As a result, as shown in Table 7, it was identified that the FM10+Fc\_hole, the FM11+Fc\_hole, and the FM12+Fc\_hole had improved GDF15 activity (E<sub>max</sub>) as compared with the FM1+Fc\_hole, the FM2+Fc\_hole, and the FM3+Fc\_hole (FIGS. 5 to 7).

**Example 8: Measurement of binding affinity of long-acting GDF15 fusion proteins (dimers: FM10+Fc\_hole and FM11+Fc\_hole)**

Binding affinity of the FM10+Fc\_hole or the FM11+Fc\_hole for the GDF15 receptors, GFRAL and RET, were compared and evaluated in the same manner as in Example 5. As a result, as illustrated in FIG. 6, remarkably superior affinity for the GDF15 receptors was measured in the FM10+Fc\_hole and the FM11+Fc\_hole as compared with the FWT+Fc\_hole as a control (FIG. 8).

**Example 9: Production of long-acting GDF15 fusion proteins (dimers: FM6+Fc\_hole, FM7+ Fc\_hole, and FM8+ Fc\_hole)**

Based on the results of Examples 1 to 8, long-acting GDF15 fusion proteins, in which the amino acids at positions 21 and/or 64 were substituted and N-linked glycans were introduced at various positions in GDF15, were additionally designed. In this regard, variants having increased correctly-assembled fusion protein dimer purity, which was obtained in a case where the variants were produced and subjected to first-step purification in the same manner as in Example 1, as compared with a dimer of the fusion protein FWT+Fc\_hole, are shown in Table 8.

[Table 8]

| Designation of substance<br>(SEQ ID NO) | Changes in sequence of GDF15 in long-acting<br>GDF15 fusion protein | Purity after first-step<br>purification<br>(Intact %) |
|-----------------------------------------|---------------------------------------------------------------------|-------------------------------------------------------|
| FWT+Fc_hole<br>(SEQ ID NOs: 49 and 43)  | $\Delta$ N2                                                         | 50.9                                                  |
| FM6+Fc_hole<br>(SEQ ID NOs: 55 and 43)  | $\Delta$ N3, WS insertion, G4N, D5S, H6T, S64K                      | 66.4                                                  |
| FM7+Fc_hole<br>(SEQ ID NOs: 56 and 43)  | $\Delta$ N3, G4N, D5S, H6T, S64K                                    | N/A                                                   |
| FM8+Fc_hole<br>(SEQ ID NOs: 67 and 43)  | $\Delta$ N2, R21N, S64K                                             | N/A                                                   |

**Example 10: Optimization of fusion carrier and linker for long-acting GDF15 fusion proteins**

In order to conduct optimization studies of a fusion carrier and a linker for the two variants (FM9+Fc\_hole and FM11+Fc\_hole) showing excellent activity and purity improvement after purification, long-acting GDF15 fusion proteins, in which

fusion carriers (SEQ ID NOs: 46 and 47) and various linkers (SEQ ID NOs: 92, 93, 94, 95, 96, and 97) were introduced into respective GDF15 sequences to minimize an effector function, were additionally designed and are shown in Table 9.

[Table 9]

| Designation of substance<br>(SEQ ID NO)    | Changes in sequence of<br>GDF15                     | Fusion carrier                                               | Linker sequence                             |
|--------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------|---------------------------------------------|
| FM9-1+Fc_hole<br>(SEQ ID NOs: 98 and 47)   | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>3</sub><br>(SEQ ID NO: 92)     |
| FM9-2+Fc_hole<br>(SEQ ID NOs: 99 and 47)   | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>5</sub><br>(SEQ ID NO: 93)     |
| FM9-3+Fc_hole<br>(SEQ ID NOs: 100 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>7</sub><br>(SEQ ID NO: 94)     |
| FM9-4+Fc_hole<br>(SEQ ID NOs: 101 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(E4EA) <sub>6</sub><br>(SEQ ID NO: 95)    |
| FM9-5+Fc_hole<br>(SEQ ID NOs: 102 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GSGGSS(PT) <sub>10</sub><br>(SEQ ID NO: 96) |
| FM9-6+Fc_hole<br>(SEQ ID NOs: 103 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(E4AAK) <sub>5</sub><br>(SEQ ID NO: 97)   |
| FM11-1+Fc_hole<br>(SEQ ID NOs: 104 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>3</sub><br>(SEQ ID NO: 92)     |
| FM11-2+Fc_hole<br>(SEQ ID NOs: 105 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>5</sub><br>(SEQ ID NO: 93)     |
| FM11-3+Fc_hole<br>(SEQ ID NOs: 106 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(G4S) <sub>7</sub><br>(SEQ ID NO: 94)     |
| FM11-4+Fc_hole<br>(SEQ ID NOs: 107 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(E4EA) <sub>6</sub><br>(SEQ ID NO: 95)    |
| FM11-5+Fc_hole<br>(SEQ ID NOs: 108 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GSGGSS(PT) <sub>10</sub><br>(SEQ ID NO: 96) |
| FM11-6+Fc_hole<br>(SEQ ID NOs: 109 and 47) | $\Delta$ N3, G4N, D5S, H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob (SEQ ID NO: 46)<br>IgG1 Fc_hole (SEQ ID NO: 47) | GS(E4AAK) <sub>5</sub><br>(SEQ ID NO: 97)   |

#### 5 Example 10.1: Expression and purification of optimized long-acting GDF15 fusion proteins (dimers)

The optimized long-acting GDF15 fusion proteins as shown in Table 9 were produced and subjected to first-step purification in the same manner as in Example 1.

To obtain a high-purity long-acting GDF15 fusion protein, a pool obtained by completing the first-step purification was subjected to second-step ion exchange (IEX) purification using anion exchange (AEX) resin and cation exchange (CEX) resin.

Specifically, for the anion exchange (AEX), the pool that had undergone the first step was loaded onto POROS HQ 50  $\mu$ m Strong Anion Exchange Resin (Thermo Fisher Scientific) equilibrated with 1 $\times$  PBS (pH 7.4), to induce binding. After completion of the binding between the first polypeptide and the second polypeptide, the POROS HQ 50  $\mu$ m Strong Anion Exchange Resin was washed with 1 $\times$  PBS (pH 7.4), and then elution was performed by concentration gradient using 50 mM Tris-HCl (pH 8.0) solution with 1 M sodium chloride, to obtain a final substance. Fractions meeting a criterion for purity of 95% or higher were pooled using size exclusion chromatography analysis.

In addition, for the cation exchange (CEX), the pool that had undergone the first step was subjected to pH adjustment depending on isoelectric points, and then loaded onto POROS XS Strong Cation Exchange Resin (Thermo Fisher Scientific) equilibrated with 20 mM sodium phosphate (pH 6.5) solution, to induce binding. After completion of the binding between the first polypeptide and the second polypeptide, the POROS XS Strong Cation Exchange Resin was washed with 20 mM sodium phosphate (pH 6.5) solution, and then elution was performed by concentration gradient using 20 mM sodium phosphate (pH 6.5) solution with 1 M sodium chloride, to obtain a final substance. Fractions meeting a criterion for purity of 95% or higher were pooled using size exclusion chromatography analysis.

#### **Example 10.2: Evaluation of activity of optimized long-acting GDF15 fusion proteins (dimers)**

The two variants (FM9+Fc\_hole and FM11+Fc\_hole) showing excellent activity and purity improvement after purification were compared and evaluated in terms of activity depending on linker type and length. Activity of the respective long-acting GDF15 fusion proteins was evaluated in the same manner as in Example 2, and the results are shown in Table 10. Here, the long-acting GDF15 fusion proteins

were compared, in terms of activity depending on GDF15 sequence, and linker type and length, based on *in vitro* GDF15 activity ( $E_{\max}$  of 100%) of the FM9-6+Fc\_hole.

[Table 10]

| Designation of substance<br>(SEQ ID NO)    | Changes in<br>sequence of<br>GDF15                     | Fusion carrier                                                         | Linker sequence                             | $E_{\max}$<br>(%) | $EC_{50}$<br>(nM) |
|--------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------|-------------------|-------------------|
| FM9-1+Fc_hole<br>(SEQ ID NOs: 98 and 47)   | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>3</sub> (SEQ<br>ID NO: 92)     | 97.6              | 9.0               |
| FM9-2+Fc_hole<br>(SEQ ID NOs: 99 and 47)   | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>5</sub> (SEQ<br>ID NO: 93)     | 110.8             | 9.5               |
| FM9-3+Fc_hole<br>(SEQ ID NOs: 100 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>7</sub> (SEQ<br>ID NO: 94)     | 95.6              | 9.3               |
| FM9-4+Fc_hole<br>(SEQ ID NOs: 101 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(EEEA) <sub>6</sub> (SEQ<br>ID NO: 95)    | 127.6             | 23.6              |
| FM9-5+Fc_hole<br>(SEQ ID NOs: 102 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GSGGSS(PT) <sub>10</sub><br>(SEQ ID NO: 96) | 100.0             | 5.3               |
| FM9-6+Fc_hole<br>(SEQ ID NOs: 103 and 47)  | $\Delta$ N2, S64R<br>(SEQ ID NO: 28)                   | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(EAAAK) <sub>5</sub><br>(SEQ ID NO: 97)   | 100.0             | 6.3               |
| FM11-1+Fc_hole<br>(SEQ ID NOs: 104 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>3</sub> (SEQ<br>ID NO: 92)     | 65.6              | 9.7               |
| FM11-2+Fc_hole<br>(SEQ ID NOs: 105 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>5</sub> (SEQ<br>ID NO: 93)     | 79.4              | 7.7               |
| FM11-3+Fc_hole<br>(SEQ ID NOs: 106 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole<br>(SEQ ID NO: 47) | GS(G4S) <sub>7</sub> (SEQ<br>ID NO: 94)     | 81.0              | 7.8               |
| FM11-4+Fc_hole<br>(SEQ ID NOs: 107 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc hole                    | GS(EEEA) <sub>6</sub> (SEQ<br>ID NO: 95)    | 104.8             | 45.4              |

|                                            |                                                        |                                                                        |                                             |      |     |
|--------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------|------|-----|
|                                            |                                                        | (SEQ ID NO: 47)                                                        |                                             |      |     |
| FM11-5+Fc_hole<br>(SEQ ID NOs: 108 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc_hole<br>(SEQ ID NO: 47) | GSGGSS(PT) <sub>10</sub><br>(SEQ ID NO: 96) | 68.2 | 5.1 |
| FM11-6+Fc_hole<br>(SEQ ID NOs: 109 and 47) | $\Delta$ N3, G4N, D5S,<br>H6T, S64R<br>(SEQ ID NO: 30) | IgG1 Fc_knob<br>(SEQ ID NO: 46)<br><br>IgG1 Fc_hole<br>(SEQ ID NO: 47) | GS(EAAAK) <sub>5</sub><br>(SEQ ID NO: 97)   | 80.3 | 6.8 |

As a result, as shown in Table 10, it was identified that the respective long-acting GDF15 fusion proteins exhibited similar activity except those in which the linker GS(EEEA)<sub>6</sub> (SEQ ID NO: 95) was used, and the long-acting GDF15 fusion proteins (FM9-4+Fc\_hole and FM11-4+Fc\_hole), in which linker GS(EEEA)<sub>6</sub> (SEQ ID NO: 95) was used, exhibited relatively low EC<sub>50</sub> value and high E<sub>max</sub> value (FIGS. 9 and 10).

### Example 10.3: Pharmacokinetic evaluation of optimized long-acting GDF15 fusion proteins (dimers)

On the day of drug treatment, six-week-old male C57BL/6 mice purchased from Orient BIO (Korea) were divided into groups (n=3 per blood collection time point) so that each group had a similar average value of body weight, and then the FM9-4+Fc\_hole, the FM9-6+Fc\_hole, the FM11-4+Fc\_hole, and the FM11-6+Fc\_hole were respectively administered subcutaneously once at a dose of 1 mg/kg. Blood samples were respectively collected 4, 24, 48, 72, 96, 120, 168, and 240 hours after the administration. A concentration of each long-acting GDF15 fusion protein (dimer) in mouse blood was measured using an immunoassay method. Based on the measured concentration values, pharmacokinetic parameter results were calculated for the respective long-acting GDF15 fusion proteins (dimers) and are shown in Table 11 below.

[Table 11]

| Designation of substance<br>(SEQ ID NO) | C <sub>max</sub><br>(ng/mL) | T <sub>max</sub><br>(hr) | CL/F<br>(mL/hr/kg) | Vd/F<br>(mL/kg) | AUC <sub>last</sub><br>(ng·hr/mL) | T <sub>1/2,app</sub><br>(hr) |
|-----------------------------------------|-----------------------------|--------------------------|--------------------|-----------------|-----------------------------------|------------------------------|
|-----------------------------------------|-----------------------------|--------------------------|--------------------|-----------------|-----------------------------------|------------------------------|

|                                            |         |    |      |        |           |       |
|--------------------------------------------|---------|----|------|--------|-----------|-------|
| FM9-4+Fc_hole<br>(SEQ ID NOs: 101 and 47)  | 8421.37 | 24 | 1.30 | 69.31  | 750497.02 | 36.84 |
| FM9-6+Fc_hole<br>(SEQ ID NOs: 103 and 47)  | 7581.92 | 24 | 0.91 | 111.02 | 939308.72 | 84.28 |
| FM11-4+Fc_hole<br>(SEQ ID NOs: 107 and 47) | 7200.02 | 24 | 1.41 | 82.63  | 690213.08 | 40.61 |
| FM11-6+Fc_hole<br>(SEQ ID NOs: 109 and 47) | 1547.77 | 24 | 8.43 | 314.10 | 116433.94 | 25.84 |

**Example 10.4: Evaluation of anti-obesity effect of optimized long-acting GDF15 fusion proteins (dimers), depending on different linker types, in diet-induced obese (DIO) mice by repeated administration**

Diet-induced obese (DIO) mice which have been induced by feeding a high-fat diet in mice, and are characterized by obesity, hyperglycemia, and insulin resistance. The DIO mice (Taconic, USA) which had been fed a high fat diet (60 kcal % fat, Research Diets, Cat# D12492, USA) in C57BL/6N mice for 8 weeks were purchased from Raon Bio (Animal Inc., Republic of Korea). After the arrival, these animals were additionally fed by the high-fat diet (60% fat) for 5 weeks, and then used in this study.

On the day before the dosing start, the animals were divided into groups (n=6 per group) based on mean body weight of individual mice, and then FM9-4+Fc\_hole, FM9-6+Fc\_hole, FM11-4+Fc\_hole, and FM11-6+Fc\_hole were administered subcutaneously at 2-day interval (Q2D) for a total of 4 weeks at a dose of 10 nmol/kg, respectively. As reference articles, B13a/B13b (US Patent No. 9920118) at 10 nmol/kg and semaglutide at 30 nmol/kg were administered subcutaneously at 2-day interval (Q2D) for a total of 4 weeks. For vehicle treatment, Dulbecco's phosphate buffered saline (DPBS; Gibco, USA) was administered subcutaneously at 2-day interval (Q2D). Body weight was measured every two days from the first day of drug treatment to Day 28, and the results were shown in Table 12 below.

[Table 12]

| Group                                      | Dose<br>(nmol/kg) | Change of body weight (%) vs. Day 0 |                    |
|--------------------------------------------|-------------------|-------------------------------------|--------------------|
|                                            |                   | Maximal efficacy                    | Efficacy on Day 27 |
| Vehicle                                    | -                 | -                                   | 4.44               |
| FM9-4+Fc_hole<br>(SEQ ID NOs: 101 and 47)  | 10                | -20.67 (on Day 27)                  | -20.67             |
| FM9-6+Fc_hole<br>(SEQ ID NOs: 103 and 47)  | 10                | -19.93 (on Day 27)                  | -19.93             |
| FM11-4+Fc_hole<br>(SEQ ID NOs: 107 and 47) | 10                | -22.11 (on Day 27)                  | -22.11             |
| FM11-6+Fc_hole<br>(SEQ ID NOs: 109 and 47) | 10                | -11.63 (on Day 22)                  | -9.93              |
| B13a/B13b                                  | 10                | -6.18 (on Day 8)                    | 0.60               |
| Semaglutide                                | 30                | -19.20 (on Day 22)                  | -16.41             |

As a result, it was confirmed that all test articles with different linker types (FM9-4+Fc\_hole, FM9-6+Fc\_hole, FM11-4+Fc\_hole, and FM11-6+Fc\_hole) demonstrated a marked body weight loss effect, compared to B13a/B13b of 10 nmol/kg, as a reference drug. In addition, three test articles, FM9-4+Fc\_hole, FM9-6+Fc\_hole, and FM11-4+Fc\_hole, showed a body weight reduction effect similar to semaglutide, 30 nmol/kg-treated group (FIG. 11).

#### **Example 10.5: Evaluation of anti-obesity effect of optimized long-acting GDF15 fusion proteins (dimers) in diet-induced obese mice by single administration**

Male C57BL/6N mice at 6-week-old were purchased from Orient Bio (via Hallym Lab. Animal Inc., Republic of Korea). After the arrival, C57BL/6N mice were induced DIO by feeding with a high-fat diet (60kcal% fat, Research Diets, Cat# D12492, USA) for a total of 13 weeks. On the day before the dosing start, the animals were divided into groups (n=6 per group) based on mean body weight of

individual mice, and then FM9-6+Fc\_hole of 1, 3, 10, and 30 nmol/kg was administered subcutaneously once. As a reference article, semaglutide of 30 nmol/kg was administered subcutaneously once. For vehicle treatment, Dulbecco's phosphate buffered saline (DPBS; Gibco, USA) was administered subcutaneously. A body weight was measured daily from the day of drug treatment to Day 42, and the results are shown in Table 13 below.

[Table 13]

| Group         | Dose (nmol/kg) | Change of body weight (%) vs. Day 0 |                    |
|---------------|----------------|-------------------------------------|--------------------|
|               |                | Maximal efficacy                    | Efficacy on Day 38 |
| Vehicle       | -              | -                                   | 10.02              |
| FM9-6+Fc_hole | 1              | -6.54 (on Day 10)                   | 3.10               |
| FM9-6+Fc_hole | 3              | -9.74 (on Day 15)                   | 3.23               |
| FM9-6+Fc_hole | 10             | -13.08 (on Day 18)                  | 0.63               |
| FM9-6+Fc_hole | 30             | -14.39 (on Day 18)                  | -5.51              |
| Semaglutide   | 30             | -8.38 (on Day 2)                    | 7.33               |

As a result, in terms of body weight loss effect by single administration, the semaglutide, 30 nmol/kg treated group, as a reference article, demonstrated a pharmacologic effect lasting for 2 days, whereas the single administration of FM9-6+Fc\_hole of 1, 3, 10, and 30 nmol/kg was confirmed that anti-obesity effect lasted for 10 days, 15 days, 18 days, and 18 days, respectively for each doses (FIG. 12).

#### **Example 10.6: Evaluation of anti-obesity effect of optimized long-acting GDF15 fusion proteins (dimers) in ob/ob mice by repeated administration**

ob/ob mice are genetically deficient in leptin gene and are characterized by hyperglycemia, insulin resistance, hyperorexia, and obesity. Male ob/ob mice at 5-week-old (Jackson Laboratory, USA) were purchased from Raon Bio (Animal Inc., Republic of Korea). The mice were acclimatized for 4 weeks with normal chow diet (Teklad Certified Irradiated Global 18% Protein Rodent Diet, 2918C, Harlan Co., USA) and drug treatment was initiated at 9-week-old. On the day before the dosing start, the animals were divided into groups (n=6 per group) based on mean body

weight and random blood glucose via tail vein of individual mice. Then, the FM9-6+Fc\_hole of 0.1, 1, and 3 nmol/kg, and semaglutide of 10 nmol/kg were administered subcutaneously at 3-day interval (Q3D) a total of 10 times, and body weight and food intake were measured every day or every 3 days during experimental period (Day 1–  
 5 Day 29), respectively. For vehicle treatment, Dulbecco's phosphate buffered saline (DPBS; Gibco, USA) was administered.

[Table 14]

| Group         | Dose<br>(nmol/kg) | Change of body weight (%) vs. ob/ob control |                    |
|---------------|-------------------|---------------------------------------------|--------------------|
|               |                   | Maximal efficacy                            | Efficacy on Day 29 |
| Vehicle       | -                 | -                                           | -                  |
| FM9-6+Fc_hole | 0.1               | -10.58 (on Day 28)                          | -9.98              |
| FM9-6+Fc_hole | 1                 | -21.49 (on Day 29)                          | -21.49             |
| FM9-6+Fc_hole | 3                 | -19.99 (on Day 29)                          | -19.99             |
| Semaglutide   | 10                | -10.04 (on Day 25)                          | -6.88              |

As a result, it was confirmed that FM9-6+Fc\_hole manifested body weight loss effect in a dose-dependent manner. FM9-6+Fc\_hole, 0.1 nmol/kg treated group  
 10 showed significant reduction in body weight similar to semaglutide, 10 nmol/kg treated group. FM9-6+Fc\_hole of 1 nmol/kg or more demonstrated the maximal efficacy in ob/ob mice (FIG. 13).

## Claims

### [Claim 1]

A GDF15 variant represented by Formula (I):

N-terminal extension domain - core domain (I)

(in Formula (I),

the N-terminal extension domain is a polypeptide consisting of any one amino acid sequence of SEQ ID NOs: 3 to 5; and

the core domain is a polypeptide represented by SEQ ID NO: 20, or a polypeptide derived from SEQ ID NO: 20 in which any one amino acid selected from the group consisting of amino acids at positions 15, 50, 58, 97, and combinations thereof in the amino acid sequence of SEQ ID NO: 20 is substituted with another amino acid;

wherein arginine (R), which is the amino acid at position 15, is substituted with alanine (A), aspartic acid (D), asparagine (N), cysteine (C), glutamic acid (E), glutamine (Q), glycine (G), histidine (H), isoleucine (I), leucine (L), lysine (K), methionine (M), phenylalanine (F), proline (P), serine (S), threonine (T), tryptophan (W), tyrosine (Y), or valine (V),

asparagine (N), which is the amino acid at position 50, is substituted with alanine, arginine (R), aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine,

serine (S), which is the amino acid at position 58, is substituted with alanine, arginine, aspartic acid, asparagine, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tryptophan, tyrosine, or valine, and

aspartic acid (D), which is the amino acid at position 97, is substituted with alanine, arginine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine).

[Claim 2]

The GDF15 variant of claim 1, wherein the core domain includes any one variation selected from the group consisting of the following variations (1) to (6):

(1) a variation in which arginine (R), which is the amino acid at position 15 in the amino acid sequence of SEQ ID NO: 20, is substituted with asparagine (N);

(2) a variation in which asparagine (N), which is the amino acid at position 50 in the amino acid sequence of SEQ ID NO: 20, is substituted with leucine (L);

(3) a variation in which serine (S), which is the amino acid at position 58 in the amino acid sequence of SEQ ID NO: 20, is substituted with lysine (K), arginine (R), asparagine (N), aspartic acid (D), glutamic acid (E), cysteine (C), or leucine (L);

(4) a variation in which aspartic acid (D), which is the amino acid at position 97 in the amino acid sequence of SEQ ID NO: 20, is substituted with leucine (L);

(5) a variation in which asparagine (N), which is the amino acid at position 50 in the amino acid sequence of SEQ ID NO: 20, and aspartic acid (D), which is the amino acid at position 97 in the amino acid sequence of SEQ ID NO: 20, are each substituted with cysteine (C) or serine (S); and

(6) a variation in which arginine (R), which is the amino acid at position 15 in the amino acid sequence of SEQ ID NO: 20, is substituted with asparagine (N), and serine (S), which is the amino acid at position 58 in the amino acid sequence of SEQ ID NO: 20, is substituted with lysine (K) or arginine (R).

## [Claim 3]

The GDF15 variant of claim 2, wherein the core domain consists of any one amino acid sequence selected from SEQ ID NOs: 6 to 19.

## [Claim 4]

The GDF15 variant of claim 1, wherein the GDF15 variant includes the N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 3 and the core domain consisting of an amino acid sequence represented by SEQ ID NO: 8, 9, or 20.

## [Claim 5]

The GDF15 variant of claim 1, wherein the GDF15 variant includes the N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 4 and the core domain consisting of an amino acid sequence represented by SEQ ID NO: 8, 9, or 20.

## [Claim 6]

The GDF15 variant of claim 1, wherein the GDF15 variant includes the N-terminal extension domain consisting of an amino acid sequence represented by SEQ ID NO: 5 and the core domain consisting of any one amino acid sequence selected from SEQ ID NO: 6 to 19.

## [Claim 7]

The GDF15 variant of claim 1, wherein the GDF15 variant consists of any one amino acid sequence selected from SEQ ID NOs: 21 to 39.

## [Claim 8]

A long-acting GDF15 fusion protein, in which the GDF15 variant of any one of claims 1 to 7 is bound to human IgG Fc or a variant thereof.

## [Claim 9]

The long-acting GDF15 fusion protein of claim 8, wherein the IgG Fc or a variant thereof includes:

a first polypeptide including an IgG1 Fc sequence, the IgG Fc sequence including a CH3 sequence that includes at least one engineered protuberance; and

a second polypeptide including an IgG1 Fc sequence, the IgG Fc sequence including a CH3 sequence that includes at least one engineered cavity,

in which the first polypeptide dimerizes with the second polypeptide via positioning of the protuberance of the first polypeptide into the cavity of the second polypeptide.

## [Claim 10]

The long-acting GDF15 fusion protein of claim 8, wherein the binding is such that the C-terminus of the first polypeptide or the C-terminus of the second polypeptide, in the IgG Fc or a variant thereof, is bound to the N-terminus of the GDF15 variant.

## [Claim 11]

The long-acting GDF15 fusion protein of claim 8, wherein the binding between the GDF15 variant and the IgG Fc or a variant thereof is made through a

linker

[Claim 12]

The long-acting GDF15 fusion protein of claim 11, wherein the linker is a peptide that consists of 10 to 50 amino acid residues, including glycine, serine, alanine, and glutamic acid residues.

[Claim 13]

The long-acting GDF15 fusion protein of claim 12, wherein the linker is

|                                       |      |    |     |         |
|---------------------------------------|------|----|-----|---------|
| GGGGSGGGGSGGGGSGGGGSGGGGS             | (SEQ | ID | NO: | 48),    |
| GSGGGGSGGGGSGGGGS                     | (SEQ | ID | NO: | 92),    |
| GSGGGGSGGGGSGGGGSGGGGSGGGGS           | (SEQ | ID | NO: | 93),    |
| GSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS | (SEQ | ID | NO: | 94),    |
| GSEEEAEEEEAEEEEAEEEEAEEEEA            | (SEQ | ID | NO: | 95),    |
| GSGGSSPTPTPTPTPTPTPTPTPTPT            | (SEQ | ID | NO: | 96), or |
| GSEAAAKEAAAKEAAAKEAAAKEAAAK           | (SEQ | ID | NO: | 97).    |

[Claim 14]

The long-acting GDF15 fusion protein of claim 9, wherein the first polypeptide consists of any one amino acid sequence selected from SEQ ID NOs: 42, 44, and 46.

[Claim 15]

The long-acting GDF15 fusion protein of claim 9, wherein the second polypeptide consists of any one amino acid sequence selected from SEQ ID NOs: 43, 45, and 47.

[Claim 16]

The long-acting GDF15 fusion protein of claim 8, wherein the GDF15 variant includes at least one N-linked glycan.

[Claim 17]

The long-acting GDF15 fusion protein of claim 8, wherein the long-acting GDF15 fusion protein includes i) a GDF15 variant consisting of any one amino acid sequence selected from SEQ ID NOs: 21 to 39, ii) a first polypeptide consisting of any one amino acid sequence selected from SEQ ID NOs: 42, 44, and 46, and iii) a second polypeptide consisting of any one amino acid sequence selected from SEQ ID NOs: 43, 45, and 47.

[Claim 18]

A fusion protein dimer, comprising:

two of the long-acting GDF15 fusion protein of claim 8.

[Claim 19]

An isolated nucleic acid molecule, encoding the GDF15 variant of any one of claims 1 to 7 or the long-acting GDF15 fusion protein of any one of claims 8 to 17.

[Claim 20]

An expression vector, comprising:

the nucleic acid molecule of claim 19.

## [Claim 21]

A host cell, comprising:  
the expression vector of claim 20.

## [Claim 22]

A pharmaceutical composition for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome, comprising as an active ingredient:

the GDF15 variant of any one of claims 1 to 7, the long-acting GDF15 fusion protein of any one of claims 8 to 17, or the fusion protein dimer of claim 18.

## [Claim 23]

A use of the GDF15 variant of any one of claims 1 to 7, the long-acting GDF15 fusion protein of any one of claims 8 to 17, or the fusion protein dimer of claim 18, for prevention or treatment of diabetes, obesity, dyslipidemia, or metabolic syndrome.

## [Claim 24]

A use of the GDF15 variant of any one of claims 1 to 7, the long-acting GDF15 fusion protein of any one of claims 8 to 17, or the fusion protein dimer of claim 18, for manufacture of a medicament for preventing or treating diabetes, obesity, dyslipidemia, or metabolic syndrome.

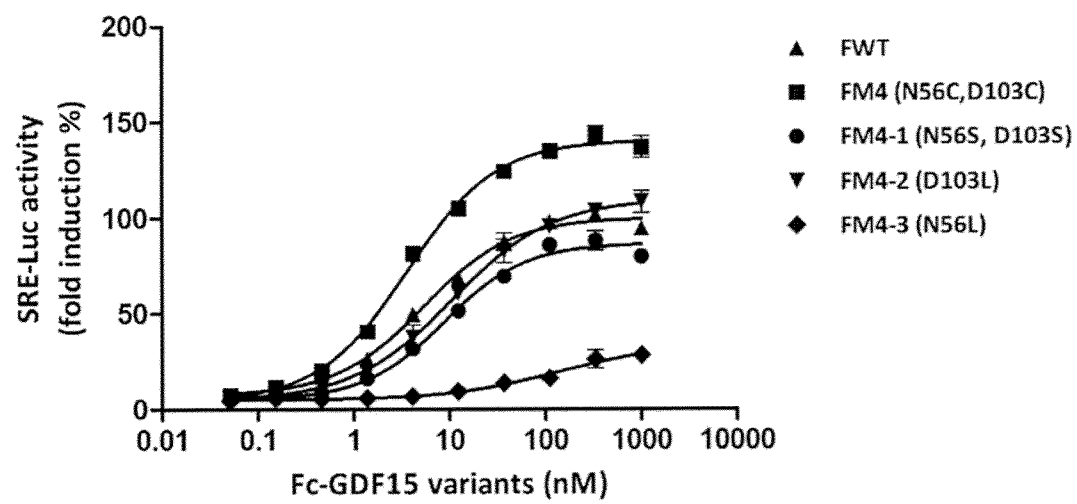
## [Claim 25]

A method for treating or preventing diabetes, obesity, dyslipidemia, or

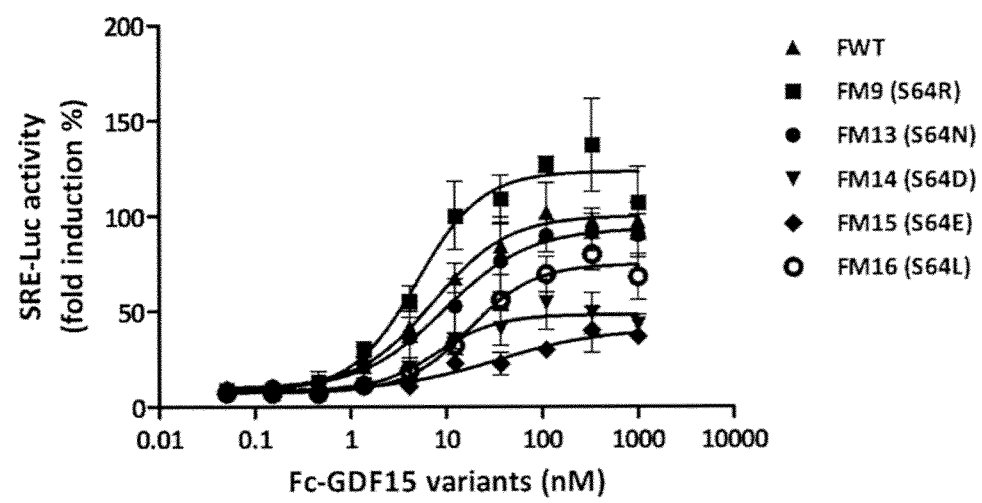
metabolic syndrome, comprising:

a step of administering, to an individual, the GDF15 variant of any one of claims 1 to 7, the long-acting GDF15 fusion protein of any one of claims 8 to 17, or the fusion protein dimer of claim 18.

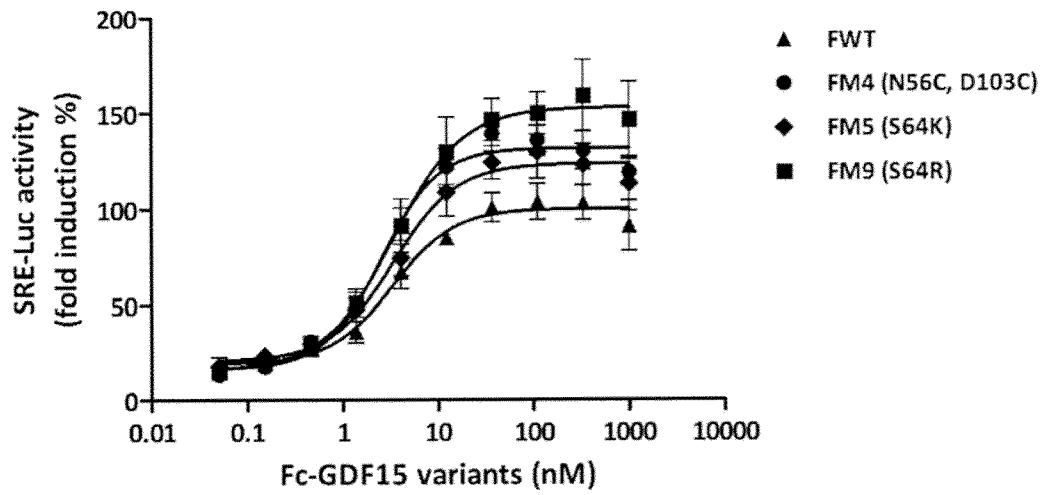
[FIG. 1]



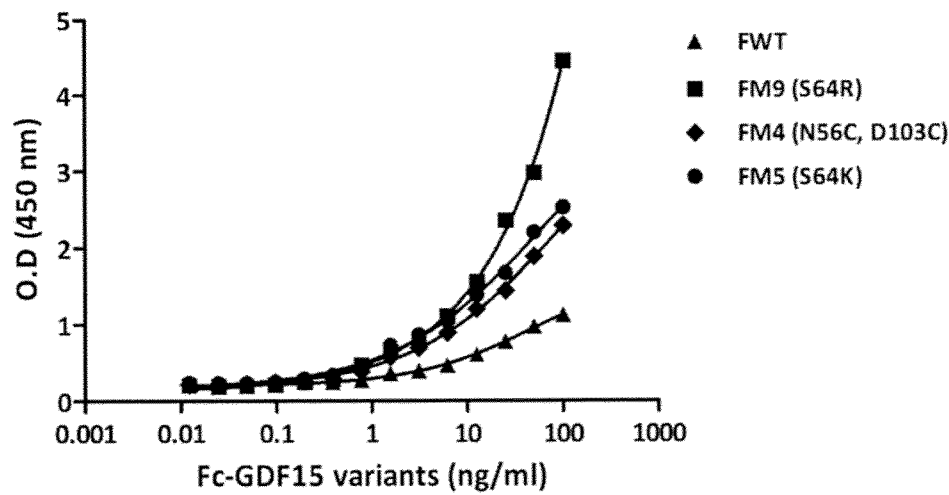
[FIG. 2]



[FIG. 3]

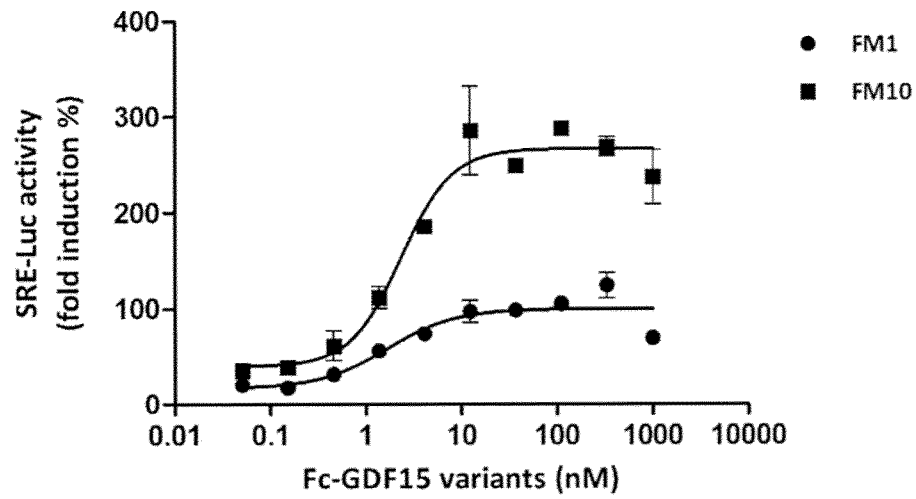


[FIG. 4]

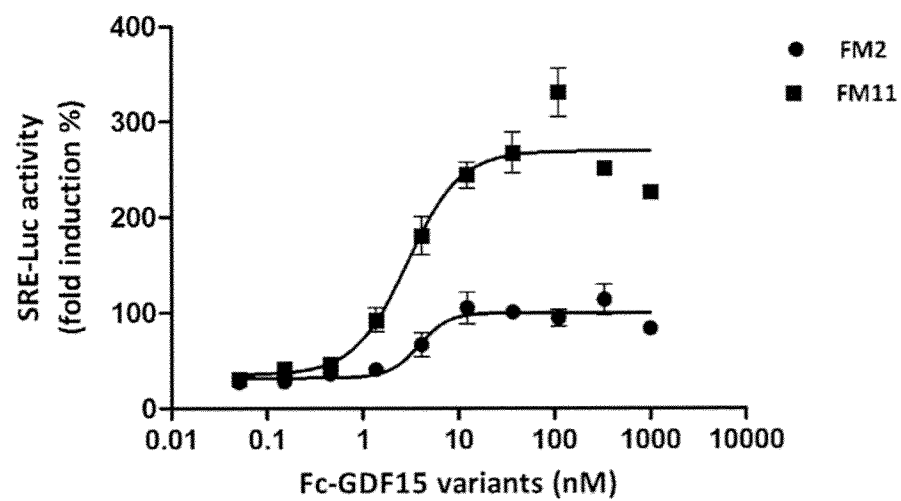


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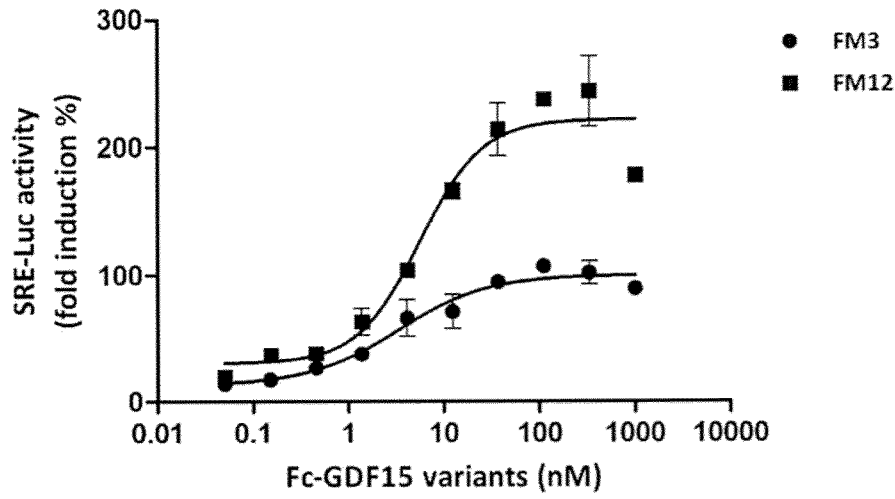
[FIG. 5]



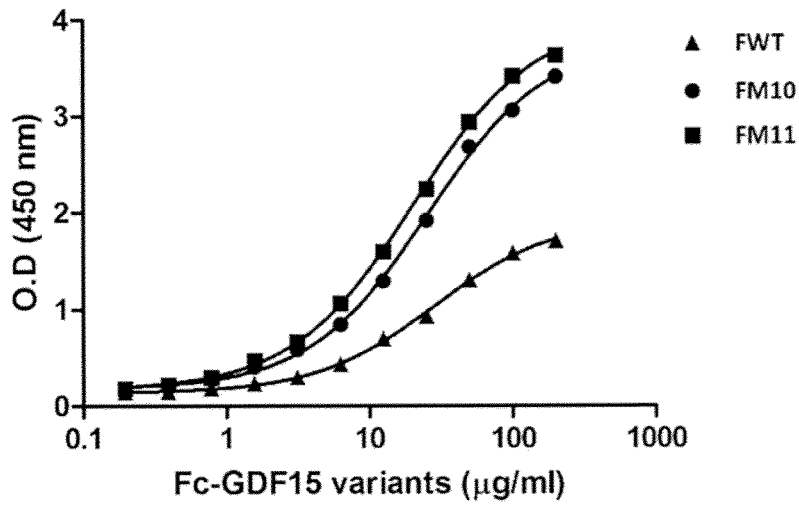
[FIG. 6]



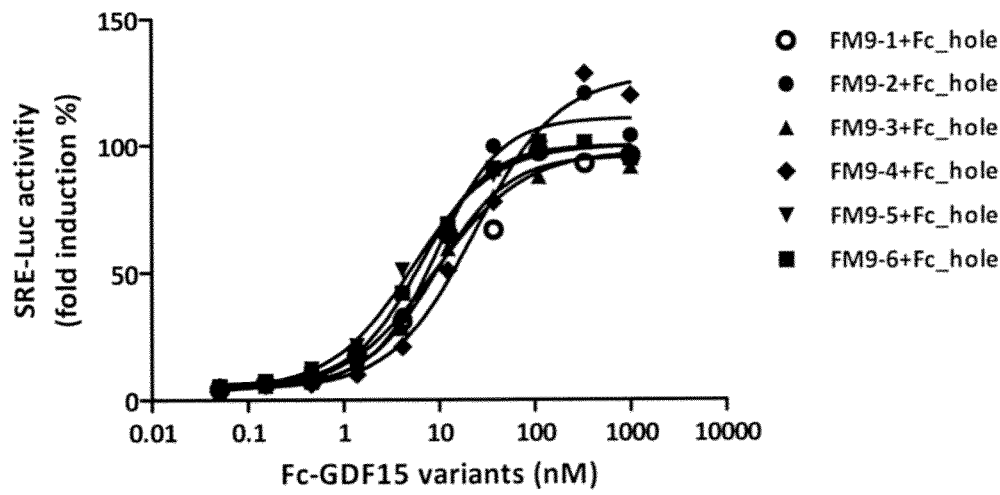
[FIG. 7]



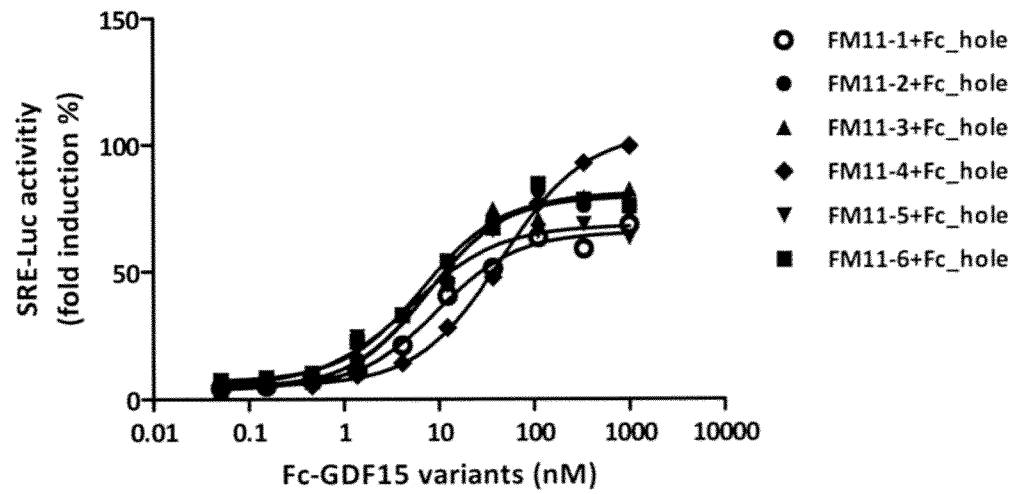
[FIG. 8]



[FIG. 9]

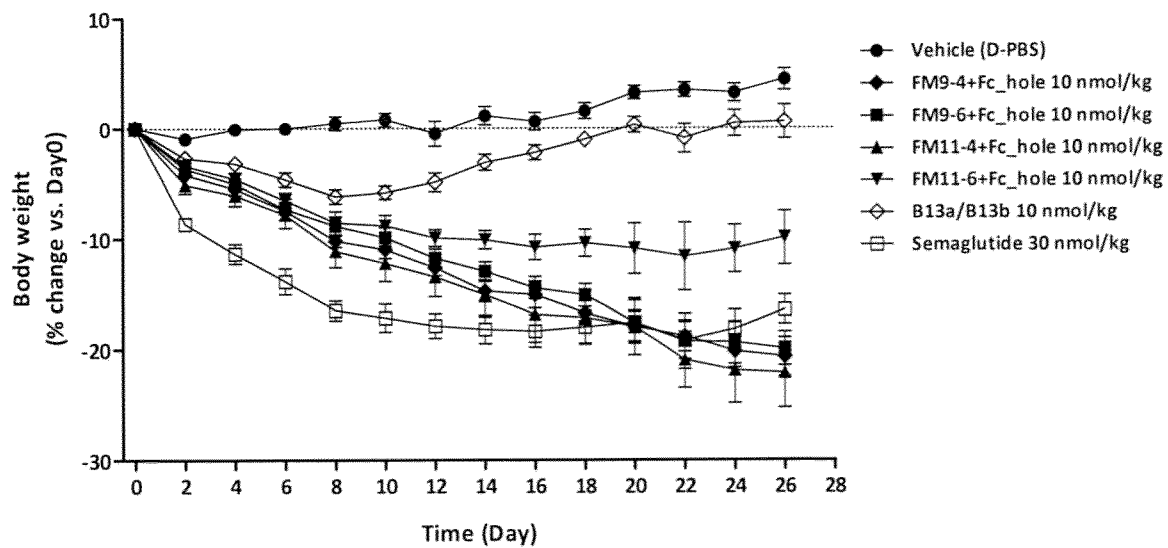


[FIG. 10]

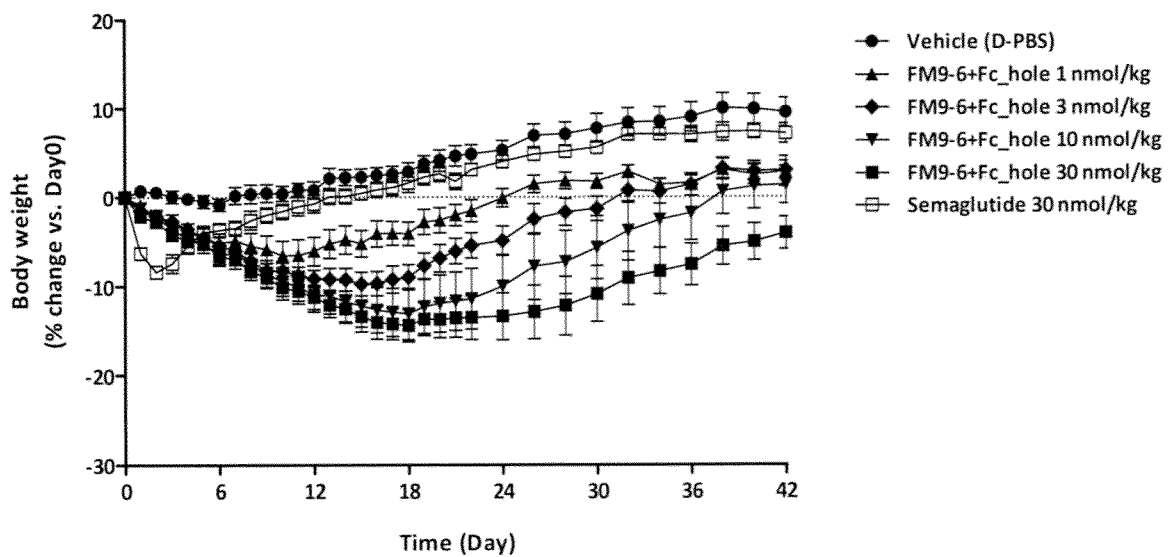


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[FIG. 11]

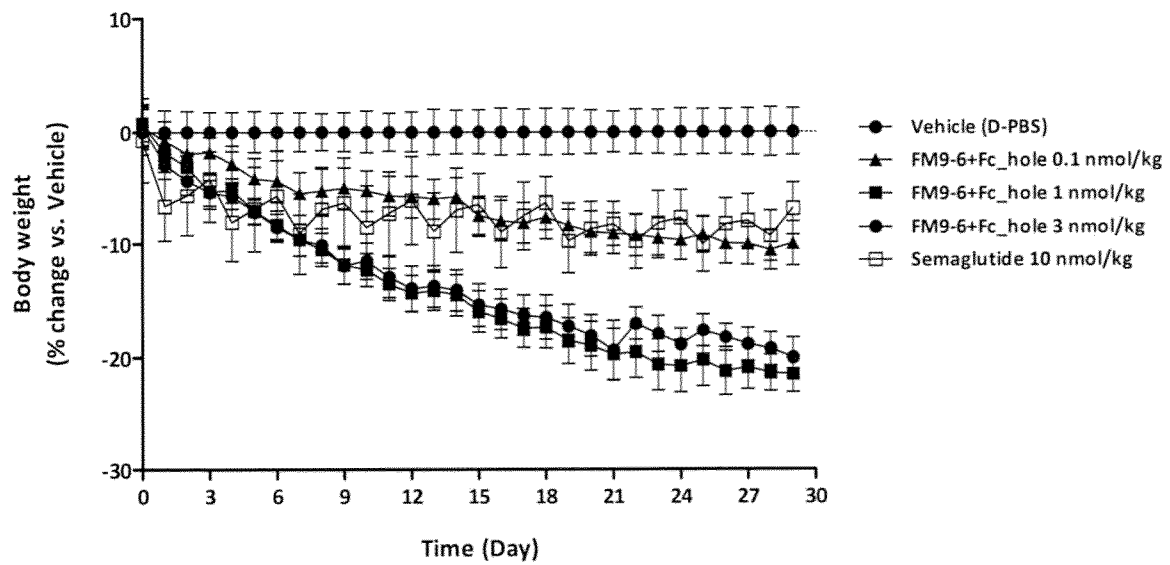


[FIG. 12]



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[FIG. 13]



PCC008069YUH.txt

&lt;110&gt; YUHAN CORPORATION

<120> LONG-ACTING GDF15 FUSION PROTEINS AND PHARMACEUTICAL COMPOSITION  
COMPRISING SAME

&lt;130&gt; PCC008069YUH

&lt;150&gt; KR 10-2019-0153680

&lt;151&gt; 2019-11-26

&lt;160&gt; 109

&lt;170&gt; KoPatentIn 3.0

&lt;210&gt; 1

&lt;211&gt; 112

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1

Ala Arg Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
1 5 10 15Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
20 25 30Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
35 40 45Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
50 55 60Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
65 70 75 80Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
85 90 95Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105 110

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&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;223&gt; Core Domain (R21X, N56X, S64X, D103X)

&lt;400&gt; 2

Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Xaa Ala  
1 5 10 15Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala

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35

40

45

Ala Xaa Met His Ala Gln Ile Lys Thr Xaa Leu His Arg Leu Lys Pro  
 50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95

Xaa Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

&lt;210&gt; 3

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; N-terminal extension domain I

&lt;400&gt; 3

Trp Ser Asn Ser Thr  
 1 5

&lt;210&gt; 4

&lt;211&gt; 3

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; N-terminal extension domain II

&lt;400&gt; 4

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 1

&lt;210&gt; 5

&lt;211&gt; 4

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; N-terminal extension domain III

&lt;400&gt; 5

Asn Gly Asp His  
 1

&lt;210&gt; 6

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;220&gt;

&lt;223&gt; Core Domain(R21N)

&lt;400&gt; 6

Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Asn Ala  
 1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
 50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

&lt;210&gt; 7

&lt;211&gt; 106

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Core Domain(N56L)

&lt;400&gt; 7

Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala  
 1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45

Ala Leu Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
 50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

&lt;210&gt; 8

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 <223> Core Domain(S64K)

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 20 25 30  
 Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45  
 Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95  
 Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

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 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

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 <223> Core Domain(S64R)

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 1 5 10 15  
 Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30  
 Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45  
 Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95  
 Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

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 <212> PRT  
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 1 5 10 15  
 Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30  
 Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45  
 Ala Asn Met His Ala Gln Ile Lys Thr Asn Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95  
 Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

<210> 11  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Core Domain(S64D)

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 1 5 10 15  
 Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30  
 Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45  
 Ala Asn Met His Ala Gln Ile Lys Thr Asp Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

<210> 12  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Core Domain(S64E)

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 Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala  
 1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Glu Leu His Arg Leu Lys Pro  
 50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

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 Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala  
 1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Cys Leu His Arg Leu Lys Pro  
 50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80

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Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
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   1                  5                  10                  15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
           20                  25                  30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
           35                  40                  45

Ala Asn Met His Ala Gln Ile Lys Thr Leu Leu His Arg Leu Lys Pro  
           50                  55                  60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
           65                  70                  75                  80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
                   85                  90                  95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           100                  105

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 <213> Artificial Sequence

<220>  
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   1                  5                  10                  15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
           20                  25                  30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
           35                  40                  45

Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
           50                  55                  60

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Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
85 90 95

Leu Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105

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20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
35 40 45

Ala Cys Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
85 90 95

Cys Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105

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<211> 106  
<212> PRT  
<213> Artificial Sequence

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<223> Core Domain(N56S, D103S)

<400> 17  
Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala  
1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
35 40 45

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Ala Ser Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95  
 Ser Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

<210> 18  
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 <223> Core Domain(R21N, S64R)

<400> 18  
 Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Asn Ala  
 1 5 10 15  
 Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30  
 Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
 35 40 45  
 Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His Arg Leu Lys Pro  
 50 55 60  
 Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
 65 70 75 80  
 Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
 85 90 95  
 Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

<210> 19  
 <211> 106  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Core Domain(R21N, S64K)

<400> 19  
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 1 5 10 15  
 Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
 20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu His Arg Leu Lys Pro  
50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105

<210> 20  
<211> 106  
<212> PRT  
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<223> Core Domain(human GDF15 7-112aa)

<400> 20  
Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala  
1 5 10 15

Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu  
20 25 30

Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala  
35 40 45

Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg Leu Lys Pro  
50 55 60

Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met  
65 70 75 80

Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp  
85 90 95

Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105

<210> 21  
<211> 111  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> GDF15 variant (delta N3, WS insertion, G4N, D5S, H6T/ FM1)

<400> 21  
Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
1 5 10 15

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
 20 25 30

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
 35 40 45

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu  
 50 55 60

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
 65 70 75 80

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
 85 90 95

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

<210> 22  
 <211> 109  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N3, G4N, D5S, H6T / FM2)

<400> 22  
 Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr  
 1 5 10 15

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser  
 20 25 30

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln  
 35 40 45

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His Arg  
 50 55 60

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr  
 65 70 75 80

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln  
 85 90 95

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105

<210> 23  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2, R21N / FM3)

<400> 23  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15  
 Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30  
 Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45  
 Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His  
 50 55 60  
 Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95  
 Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

<210> 24  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2, N56L / FM4-3)

<400> 24  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15  
 Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30  
 Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45  
 Gln Phe Arg Ala Ala Leu Met His Ala Gln Ile Lys Thr Ser Leu His  
 50 55 60  
 Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95  
 Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

<210> 25  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>

<223> GDF15 variant (delta N2, S64K / FM5)

<400> 25

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
1 5 10 15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
20 25 30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
35 40 45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu His  
50 55 60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
85 90 95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105 110

<210> 26

<211> 111

<212> PRT

<213> Artificial Sequence

<220>

<223> GDF15 variant (delta N3, WS insertion, G4N, D5S, H6T, S64K / FM6)

<400> 26

Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
1 5 10 15

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
20 25 30

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
35 40 45

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu  
50 55 60

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
65 70 75 80

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
85 90 95

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105 110

<210> 27

<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> GDF15 variant (delta N3, G4N, D5S, H6T, S64K / FM7)

<400> 27

Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr  
1 5 10 15

Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser  
20 25 30

Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln  
35 40 45

Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu His Arg  
50 55 60

Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr  
65 70 75 80

Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln  
85 90 95

Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105

<210> 28

<211> 110

<212> PRT

<213> Artificial Sequence

<220>

<223> GDF15 variant (delta N2, S64R / FM9)

<400> 28

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
1 5 10 15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
20 25 30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
35 40 45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His  
50 55 60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
85 90 95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
100 105 110

<210> 29  
 <211> 111  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N3, WS insertion, G4N, D5S, H6T, S64R/ FM10)

<400> 29  
 Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
 1 5 10 15  
 His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
 20 25 30  
 Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
 35 40 45  
 Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu  
 50 55 60  
 His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
 65 70 75 80  
 Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
 85 90 95  
 Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

<210> 30  
 <211> 109  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N3, G4N, D5S, H6T, S64R/ FM11)

<400> 30  
 Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr  
 1 5 10 15  
 Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser  
 20 25 30  
 Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln  
 35 40 45  
 Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His Arg  
 50 55 60  
 Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr  
 65 70 75 80  
 Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln  
 85 90 95  
 Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile

100

105

<210> 31  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2, S64N/ FM13)

<400> 31  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15  
 Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30  
 Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45  
 Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Asn Leu His  
 50 55 60  
 Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95  
 Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

<210> 32  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2,S64D/ FM14)

<400> 32  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15  
 Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30  
 Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45  
 Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Asp Leu His  
 50 55 60  
 Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu

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85                      90                      95  
 Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           100                      105                      110

<210> 33  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2,S64E/ FM15)

<400> 33  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
   1                      5                      10                      15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
           20                      25                      30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
           35                      40                      45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Glu Leu His  
           50                      55                      60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
           65                      70                      75                      80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
           85                      90                      95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           100                      105                      110

<210> 34  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2,S64L / FM16)

<400> 34  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
   1                      5                      10                      15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
           20                      25                      30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
           35                      40                      45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Leu Leu His  
           50                      55                      60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser

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65                      70                      75                      80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
                     85                      90                      95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                     100                      105                      110

<210> 35  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2, D103L / FM4-2)

<400> 35  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
   1                      5                      10                      15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
                     20                      25                      30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
                     35                      40                      45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His  
                     50                      55                      60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
                     65                      70                      75                      80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
                     85                      90                      95

Gln Thr Tyr Asp Leu Leu Leu Ala Lys Asp Cys His Cys Ile  
                     100                      105                      110

<210> 36  
 <211> 110  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> GDF15 variant (delta N2, N56C, D103C / FM4)

<400> 36  
 Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
   1                      5                      10                      15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
                     20                      25                      30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
                     35                      40                      45

Gln Phe Arg Ala Ala Cys Met His Ala Gln Ile Lys Thr Ser Leu His

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50

55

60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95

Gln Thr Tyr Asp Cys Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

&lt;210&gt; 37

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; GDF15 variant (delta N2, N56S, D103S/ FM4-1)

&lt;400&gt; 37

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45

Gln Phe Arg Ala Ala Ser Met His Ala Gln Ile Lys Thr Ser Leu His  
 50 55 60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95

Gln Thr Tyr Asp Ser Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

&lt;210&gt; 38

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; GDF15 variant (delta N2, R21N, S64K / FM8)

&lt;400&gt; 38

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15

Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser

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35

40

45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu His  
 50 55 60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

&lt;210&gt; 39

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; GDF15 variant (delta N2, R21N, S64R / FM12)

&lt;400&gt; 39

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15

Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu  
 20 25 30

Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
 35 40 45

Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His  
 50 55 60

Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
 65 70 75 80

Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
 85 90 95

Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 100 105 110

&lt;210&gt; 40

&lt;211&gt; 110

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; GDF15 (delta N2)

&lt;400&gt; 40

Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His  
 1 5 10 15

Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu

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20                      25                      30  
 Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser  
       35                      40                      45  
 Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu His  
       50                      55                      60  
 Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser  
       65                      70                      75                      80  
 Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu  
           85                      90                      95  
 Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           100                      105                      110

<210> 41  
 <211> 227  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Human IgG1 Fc

<400> 41  
 Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly  
       1                      5                      10                      15  
 Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met  
           20                      25                      30  
 Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His  
           35                      40                      45  
 Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val  
           50                      55                      60  
 His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr  
           65                      70                      75                      80  
 Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly  
           85                      90                      95  
 Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile  
           100                      105                      110  
 Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val  
           115                      120                      125  
 Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser  
           130                      135                      140  
 Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu  
           145                      150                      155                      160  
 Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro  
           165                      170                      175

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Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val  
 180 185 190

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met  
 195 200 205

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser  
 210 215 220

Pro Gly Lys  
 225

<210> 42  
 <211> 217  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(A-1)

<400> 42  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

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Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 210 215

<210> 43  
 <211> 217  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366S, L368A,  
 Y407V)-(A-2)

<400> 43  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 210 215

<210> 44  
 <211> 217

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<212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A, N297A)(T366W)-(B-1)

<400> 44  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 210 215

<210> 45  
 <211> 217  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A, N297A)(T366S, L368A, Y407V)-(B-2)

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<400> 45  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 210 215

<210> 46  
 <211> 217  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A, N297A)(T366W)-(C-1)

<400> 46  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr

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35

40

45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys  
 210 215

<210> 47  
 <211> 217  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A, N297A)(T366S, L368A,  
 Y407V)-(C-2)

<400> 47  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

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Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                   85                  90                  95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           100                  105                  110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
           115                  120                  125

Thr Lys Asn Gln Val Ser Leu Ser Cys Ala Val Lys Gly Phe Tyr Pro  
           130                  135                  140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
           145                  150                  155                  160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                   165                  170                  175

Val Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           180                  185                  190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
           195                  200                  205

Lys Ser Leu Ser Leu Ser Pro Gly Lys  
           210                  215

<210> 48  
 <211> 25  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-(G4S)5

<400> 48  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
   1                  5                  10                  15

Gly Gly Gly Ser Gly Gly Gly Gly Ser  
           20                  25

<210> 49  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A,  
       L235A)(T366W)-(G4S)5-GDF15(delta N2) - FWT

<400> 49  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
   1                  5                  10                  15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

PCC008069YUH.txt

20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
     35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
     50                      55                      60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
     65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
             85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
             100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
             115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
             130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
             165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
             180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
             195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
             210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
     225                      230                      235                      240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
             245                      250                      255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
             260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
             275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
             290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
     305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
             325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
             340                      345                      350

PCC008069YUH.txt

<210> 50  
 <211> 353  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N3, WS insertion, G4N, D5S, H6T)-FM1

<400> 50  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys

PCC008069YUH.txt

245                      250                      255  
 Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
     260                      265                      270  
 Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
     275                      280                      285  
 Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
     290                      295                      300  
 Ser Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
 305                      310                      315                      320  
 Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
     325                      330                      335  
 Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
     340                      345                      350

Ile

<210> 51  
 <211> 351  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N3, G4N, D5S, H6T)-FM2

<400> 51  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
     1                      5                      10                      15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
     20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
     35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
     50                      55                      60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
     65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
     130                      135                      140

PCC008069YUH.txt

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
 245 250 255

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
 260 265 270

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
 275 280 285

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser Leu  
 290 295 300

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
 305 310 315 320

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
 325 330 335

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 52

<211> 352

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, R21N)-FM3

<400> 52

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

PCC008069YUH.txt

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 53

PCC008069YUH.txt

<211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, N56L)-FM4-3

<400> 53  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

PCC008069YUH.txt

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Leu Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 54  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, S64K)-FM5

<400> 54  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

PCC008069YUH.txt

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 55  
 <211> 353  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N3, WS insertion, G4N, D5S, H6T, S64K)-FM6

<400> 55  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

PCC008069YUH.txt

65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
                     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
                     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
                     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
                     210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
                     225                      230                      235                      240  
 Gly Ser Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys  
                     245                      250                      255  
 Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
                     260                      265                      270  
 Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
                     275                      280                      285  
 Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
                     290                      295                      300  
 Lys Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
                     305                      310                      315                      320  
 Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
                     325                      330                      335  
 Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
                     340                      345                      350

Ile

<210> 56  
 <211> 351  
 <212> PRT  
 <213> Artificial Sequence

PCC008069YUH.txt

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
variant (delta N3, G4N, D5S, H6T, S64K)-FM7

&lt;400&gt; 56

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
225 230 235 240

Gly Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
245 250 255

His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
260 265 270

Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
275 280 285

PCC008069YUH.txt

Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys Leu  
 290 295 300

His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
 305 310 315 320

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
 325 330 335

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 57

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, S64R)-FM9

&lt;400&gt; 57

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln

PCC008069YUH.txt

195

200

205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 58

&lt;211&gt; 353

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N3, WS insertion, G4N, D5S, H6T, S64R)-FM10

&lt;400&gt; 58

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

PCC008069YUH.txt

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Trp Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys  
 245 250 255

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
 260 265 270

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
 275 280 285

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
 290 295 300

Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
 305 310 315 320

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
 325 330 335

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
 340 345 350

Ile

<210> 59  
 <211> 351  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N3, G4N, D5S, H6T, S64R)-FM11

PCC008069YUH.txt

<400> 59  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu  
 245 250 255  
 His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val  
 260 265 270  
 Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro  
 275 280 285  
 Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu  
 290 295 300  
 His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala  
 305 310 315 320

PCC008069YUH.txt

Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser  
 325 330 335

Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 60  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, S64N/ FM13)

<400> 60  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

PCC008069YUH.txt

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Asn  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 61  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2,S64D)-FM14

<400> 61  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

PCC008069YUH.txt

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Asp  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 62  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2,S64E)-FM15

<400> 62  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

PCC008069YUH.txt

20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
     35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
     50                      55                      60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
     65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
     210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
     225                      230                      235                      240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
     245                      250                      255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
     260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
     275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Glu  
     290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
     305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
     325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
     340                      345                      350

PCC008069YUH.txt

<210> 63  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2,S64L)-FM16

<400> 63  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg

PCC008069YUH.txt

245                      250                      255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
           260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
           275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Leu  
           290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
           325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           340                      345                      350

<210> 64  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, D103L)-FM4-2

<400> 64  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
   1                      5                      10                      15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
           35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
           50                      55                      60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
           115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
           130                      135                      140

PCC008069YUH.txt

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Leu Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 65  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, N56C, D103C)-FM4

<400> 65  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

PCC008069YUH.txt

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Cys Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Cys Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

PCC008069YUH.txt

<210> 66  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, N56S, D103S)-FM4-1

<400> 66  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

PCC008069YUH.txt

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Ser Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Ser Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 67  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, R21N, S64K)-FM8

<400> 67  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu

PCC008069YUH.txt

165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
           195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly  
           210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
           225                      230                      235                      240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
           245                      250                      255  
 Leu His Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
           260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
           275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Lys  
           290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
           305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
           325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
           340                      345                      350

<210> 68  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, R21N, S64R)-FM12

<400> 68  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
           1                      5                      10                      15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
           35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
           50                      55                      60

PCC008069YUH.txt

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Asn Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 69  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

PCC008069YUH.txt

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
variant (delta N2, W32F)

&lt;400&gt; 69

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
210 215 220Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
225 230 235 240Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
245 250 255Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Phe  
260 265 270Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
275 280 285

PCC008069YUH.txt

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 70

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, W32H)

&lt;400&gt; 70

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

PCC008069YUH.txt

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp His  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 71  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, W32Y)

<400> 71  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys

PCC008069YUH.txt

85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
     210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
     225                      230                      235                      240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
     245                      250                      255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Tyr  
     260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
     275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
     290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
     305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
     325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
     340                      345                      350

<210> 72  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q51H)

PCC008069YUH.txt

&lt;400&gt; 72

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser His Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro

PCC008069YUH.txt

305                    310                    315                    320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
                          325                    330                    335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                          340                    345                    350

<210> 73  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q51L)

<400> 73  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
   1                  5                  10                  15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
                   20                  25                  30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
                   35                  40                  45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                   50                  55                  60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
                   65                  70                  75                  80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                   85                  90                  95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
                   100                  105                  110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
                   115                  120                  125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
                   130                  135                  140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                   145                  150                  155                  160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                   165                  170                  175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                   180                  185                  190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                   195                  200                  205

PCC008069YUH.txt

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Leu Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 74  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q51E)

<400> 74  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

PCC008069YUH.txt

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Glu Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 75  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q51N)

<400> 75  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys

PCC008069YUH.txt

1            5            10            15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
           20            25            30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
           35            40            45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
           50            55            60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
           65            70            75            80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
           85            90            95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
           100            105            110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
           115            120            125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
           130            135            140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
           145            150            155            160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
           165            170            175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
           180            185            190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
           195            200            205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
           210            215            220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
           225            230            235            240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
           245            250            255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
           260            265            270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
           275            280            285  
 Pro Ser Asn Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
           290            295            300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
           305            310            315            320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
           325            330            335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 76  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q90H)

<400> 76  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly

225                    230                    235                    240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
                          245                    250                    255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
                          260                    265                    270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
                          275                    280                    285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
                          290                    295                    300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305                    310                    315                    320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile His Lys Thr Asp Thr Gly Val  
                          325                    330                    335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                          340                    345                    350

<210> 77  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q90E)

<400> 77  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
   1                    5                    10                    15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
                          20                    25                    30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
                          35                    40                    45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
                          50                    55                    60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
                          65                    70                    75                    80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                          85                    90                    95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
                          100                    105                    110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
                          115                    120                    125

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Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Glu Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 78

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q90K)

&lt;400&gt; 78

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Lys Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 79  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, D93E)

<400> 79  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Glu Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 80  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, D93L)

<400> 80  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn

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145                    150                    155                    160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                          165                    170                    175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                          180                    185                    190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                          195                    200                    205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
                          210                    215                    220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
                          225                    230                    235                    240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
                          245                    250                    255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
                          260                    265                    270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
                          275                    280                    285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
                          290                    295                    300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
                          305                    310                    315                    320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Leu Thr Gly Val  
                          325                    330                    335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                          340                    345                    350

<210> 81  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, D93N)

<400> 81  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
   1                  5                  10                  15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
                   20                  25                  30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
                   35                  40                  45

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Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asn Thr Gly Val  
325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
340 345 350

<210> 82

PCC008069YUH.txt

<211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, D93Q)

<400> 82  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

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Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Gln Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 83  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Q60L)

<400> 83  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

PCC008069YUH.txt

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Leu Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 84  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2,Q60N)

<400> 84  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His

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65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
                     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
                     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
                     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
                     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
                     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
                     210                      215                      220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
                     225                      230                      235                      240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
                     245                      250                      255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
                     260                      265                      270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
                     275                      280                      285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Asn Ile Lys Thr Ser  
                     290                      295                      300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
                     305                      310                      315                      320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
                     325                      330                      335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                     340                      345                      350

<210> 85  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

PCC008069YUH.txt

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
variant (delta N2, S64Q)

&lt;400&gt; 85

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Gln

PCC008069YUH.txt

290

295

300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 86

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, T92S)

&lt;400&gt; 86

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

PCC008069YUH.txt

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Ser Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 87

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, T92E)

&lt;400&gt; 87

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

PCC008069YUH.txt

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Glu Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 88  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, S97N)

PCC008069YUH.txt

```

<400> 88
Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
 1           5           10          15
Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
      20           25           30
Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
      35           40           45
Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
      50           55           60
Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
      65           70           75           80
Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
      85           90           95
Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
      100          105          110
Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met
      115          120          125
Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro
      130          135          140
Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
      145          150          155          160
Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
      165          170          175
Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
      180          185          190
Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
      195          200          205
Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly
      210          215          220
Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
      225          230          235          240
Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg
      245          250          255
Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp
      260          265          270
Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys
      275          280          285
Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser
      290          295          300
Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro
      305          310          315          320

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Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Asn Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 89  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, S97Q)

<400> 89  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly

PCC008069YUH.txt

210

215

220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Gln Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

&lt;210&gt; 90

&lt;211&gt; 352

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2,Y101F)

&lt;400&gt; 90

Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

PCC008069YUH.txt

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240

Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Phe Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 91  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(E233A, L235A)(T366W)-(G4S)5-GDF15  
 variant (delta N2, Y101Q)

<400> 91  
 Ala Pro Ala Leu Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Gly Gly Ser Gly Gly  
 210 215 220  
 Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly  
 225 230 235 240  
 Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Ser  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

PCC008069YUH.txt

Ser Leu Gln Thr Gln Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 92  
 <211> 17  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GS(G4S)3

<400> 92  
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 1 5 10 15

Ser

<210> 93  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GS(G4S)5

<400> 93  
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Ser  
 20 25

<210> 94  
 <211> 37  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GS(G4S)7

<400> 94  
 Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly  
 1 5 10 15

Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser  
 20 25 30

Gly Gly Gly Gly Ser  
 35

<210> 95

PCC008069YUH.txt

<211> 26  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GS(EEEA)6

<400> 95  
 Gly Ser Glu Glu Glu Ala Glu Glu Glu Ala Glu Glu Ala Glu Glu  
 1 5 10 15  
 Glu Ala Glu Glu Glu Ala Glu Glu Glu Ala  
 20 25

<210> 96  
 <211> 26  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GSGGSS(PT)10

<400> 96  
 Gly Ser Gly Gly Ser Ser Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr  
 1 5 10 15  
 Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr  
 20 25

<210> 97  
 <211> 27  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> linker-GS(EAAAK)5

<400> 97  
 Gly Ser Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala  
 1 5 10 15  
 Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys  
 20 25

<210> 98  
 <211> 344  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(G4S)3-GDF15 variant (delta N2, S64R / FM9-1)

<400> 98

PCC008069YUH.txt

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Ser  
 210 215 220  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Gly Asp His Cys Pro  
 225 230 235 240  
 Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu  
 245 250 255  
 Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln  
 260 265 270  
 Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn  
 275 280 285  
 Met His Ala Gln Ile Lys Thr Arg Leu His Arg Leu Lys Pro Asp Thr  
 290 295 300  
 Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu  
 305 310 315 320  
 Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu

PCC008069YUH.txt

325

330

335

Leu Ala Lys Asp Cys His Cys Ile  
340

&lt;210&gt; 99

&lt;211&gt; 354

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(L234A, L235A,  
N297A)(T366W)-GS(G4S)5-GDF15 variant (delta N2, S64R / FM9-2)

&lt;400&gt; 99

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Ser  
210 215 220

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
225 230 235 240

Gly Gly Gly Ser Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys  
245 250 255

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala  
260 265 270

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly  
275 280 285

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys  
290 295 300

Thr Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys  
305 310 315 320

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr  
325 330 335

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His  
340 345 350

Cys Ile

<210> 100  
<211> 364  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Hinge deleted human IgG1-Fc(L234A, L235A,  
N297A)(T366W)-GS(G4S)7-GDF15 variant (delta N2, S64R / FM9-3)

<400> 100  
Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Ser  
210 215 220

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
225 230 235 240

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Gly  
245 250 255

Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val  
260 265 270

Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro  
275 280 285

Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe  
290 295 300

Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His Arg Leu  
305 310 315 320

Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn  
325 330 335

Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr  
340 345 350

Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
355 360

<210> 101

<211> 353

<212> PRT

<213> Artificial Sequence

<220>

<223> Hinge deleted human IgG1-Fc(L234A, L235A,  
N297A)(T366W)-GS(E4E4)6-GDF15 variant (delta N2, S64R / FM9-4)

<400> 101

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

PCC008069YUH.txt

20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
     35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
     50                      55                      60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
     65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Glu Glu Glu Ala Glu  
     210                      215                      220  
 Glu Glu Ala Glu Glu Glu Ala Glu Glu Glu Ala Glu Glu Glu Ala Glu  
     225                      230                      235                      240  
 Glu Glu Ala Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys  
     245                      250                      255  
 Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
     260                      265                      270  
 Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
     275                      280                      285  
 Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
     290                      295                      300  
 Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
     305                      310                      315                      320  
 Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
     325                      330                      335  
 Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
     340                      345                      350

PCC008069YUH.txt

Ile

<210> 102  
 <211> 353  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GSGGSS(PT)10-GDF15 variant (delta N2, S64R / FM9-5)

<400> 102  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Ser Ser Pro  
 210 215 220  
 Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro  
 225 230 235 240

PCC008069YUH.txt

Thr Pro Thr Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys Cys  
 245 250 255

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
 260 265 270

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
 275 280 285

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
 290 295 300

Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
 305 310 315 320

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
 325 330 335

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
 340 345 350

Ile

<210> 103  
 <211> 354  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(EAAAK)5-GDF15 variant (delta N2, S64R / FM9-6)

<400> 103  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro

130

135

140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Glu Ala Ala Ala Lys  
 210 215 220

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu  
 225 230 235 240

Ala Ala Ala Lys Asn Gly Asp His Cys Pro Leu Gly Pro Gly Arg Cys  
 245 250 255

Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala  
 260 265 270

Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly  
 275 280 285

Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys  
 290 295 300

Thr Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys  
 305 310 315 320

Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr  
 325 330 335

Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His  
 340 345 350

Cys Ile

&lt;210&gt; 104

&lt;211&gt; 343

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(G4S)3-GDF15 variant (delta N3, G4N, D5S, H6T,  
 S64R/ FM11-1)

&lt;400&gt; 104

Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val

20                      25                      30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
     35                      40                      45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
     50                      55                      60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
     65                      70                      75                      80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
     85                      90                      95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
     100                      105                      110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
     115                      120                      125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
     130                      135                      140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
     145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Gly Ser  
     210                      215                      220  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Ser Thr Cys Pro Leu  
     225                      230                      235                      240  
 Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg Ala Ser Leu Glu  
     245                      250                      255  
 Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg Glu Val Gln Val  
     260                      265                      270  
 Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg Ala Ala Asn Met  
     275                      280                      285  
 His Ala Gln Ile Lys Thr Arg Leu His Arg Leu Lys Pro Asp Thr Val  
     290                      295                      300  
 Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro Met Val Leu Ile  
     305                      310                      315                      320  
 Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu  
     325                      330                      335  
 Ala Lys Asp Cys His Cys Ile  
     340

<210> 105  
 <211> 353  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(G4S)5-GDF15 variant (delta N3, G4N, D5S, H6T,  
 S64R/ FM11-2)

<400> 105  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Gly Ser  
 210 215 220  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 225 230 235 240  
 Gly Gly Gly Ser Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys  
 245 250 255

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
260 265 270

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
275 280 285

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
290 295 300

Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
305 310 315 320

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
325 330 335

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
340 345 350

Ile

<210> 106  
<211> 363  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Hinge deleted human IgG1-Fc(L234A, L235A,  
N297A)(T366W)-GS(G4S)7-GDF15 variant (delta N3, G4N, D5S, H6T,  
S64R/ FM11-3)

<400> 106  
Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
130 135 140

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145                      150                      155                      160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                     165                      170                      175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                     180                      185                      190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                     195                      200                      205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Gly Gly Ser  
                     210                      215                      220  
 Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly  
 225                      230                      235                      240  
 Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asn Ser  
                     245                      250                      255  
 Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg Leu His Thr Val Arg  
                     260                      265                      270  
 Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp Val Leu Ser Pro Arg  
                     275                      280                      285  
 Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys Pro Ser Gln Phe Arg  
                     290                      295                      300  
 Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg Leu His Arg Leu Lys  
 305                      310                      315                      320  
 Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro Ala Ser Tyr Asn Pro  
                     325                      330                      335  
 Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val Ser Leu Gln Thr Tyr  
                     340                      345                      350  
 Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
                     355                      360

<210> 107  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(EEEA)6-GDF15 variant (delta N3, G4N, D5S, H6T,  
 S64R/ FM11-4)

<400> 107  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1                      5                      10                      15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
                     20                      25                      30

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Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Glu Glu Glu Ala Glu  
 210 215 220  
 Glu Glu Ala Glu Glu Glu Ala Glu Glu Glu Ala Glu Glu Glu Ala Glu  
 225 230 235 240  
 Glu Glu Ala Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg  
 245 250 255  
 Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270  
 Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285  
 Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg  
 290 295 300  
 Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320  
 Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335  
 Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

PCC008069YUH.txt

<210> 108  
 <211> 352  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A, N297A)(T366W)-GSGGSS(PT)10-GDF15 variant (delta N3, G4N, D5S, H6T, S64R/ FM11-5)

<400> 108  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15  
 Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30  
 Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45  
 Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60  
 Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80  
 Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95  
 Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110  
 Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125  
 Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140  
 Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145 150 155 160  
 Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
 165 170 175  
 Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
 180 185 190  
 Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
 195 200 205  
 Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Gly Gly Ser Ser Pro  
 210 215 220  
 Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro Thr Pro  
 225 230 235 240  
 Thr Pro Thr Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys Arg

PCC008069YUH.txt

245 250 255

Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp Trp  
 260 265 270

Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala Cys  
 275 280 285

Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr Arg  
 290 295 300

Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val Pro  
 305 310 315 320

Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly Val  
 325 330 335

Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys Ile  
 340 345 350

<210> 109  
 <211> 353  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Hinge deleted human IgG1-Fc(L234A, L235A,  
 N297A)(T366W)-GS(EAAAK)5-GDF15 variant (delta N3, G4N, D5S, H6T,  
 S64R/ FM11-6)

<400> 109  
 Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys  
 1 5 10 15

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
 20 25 30

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
 35 40 45

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
 50 55 60

Gln Tyr Ala Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
 65 70 75 80

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
 85 90 95

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
 100 105 110

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met  
 115 120 125

Thr Lys Asn Gln Val Ser Leu Trp Cys Leu Val Lys Gly Phe Tyr Pro  
 130 135 140

PCC008069YUH.txt

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
 145                      150                      155                      160

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
                     165                      170                      175

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
                     180                      185                      190

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
                     195                      200                      205

Lys Ser Leu Ser Leu Ser Pro Gly Lys Gly Ser Glu Ala Ala Ala Lys  
                     210                      215                      220

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu  
 225                      230                      235                      240

Ala Ala Ala Lys Asn Ser Thr Cys Pro Leu Gly Pro Gly Arg Cys Cys  
                     245                      250                      255

Arg Leu His Thr Val Arg Ala Ser Leu Glu Asp Leu Gly Trp Ala Asp  
                     260                      265                      270

Trp Val Leu Ser Pro Arg Glu Val Gln Val Thr Met Cys Ile Gly Ala  
                     275                      280                      285

Cys Pro Ser Gln Phe Arg Ala Ala Asn Met His Ala Gln Ile Lys Thr  
                     290                      295                      300

Arg Leu His Arg Leu Lys Pro Asp Thr Val Pro Ala Pro Cys Cys Val  
 305                      310                      315                      320

Pro Ala Ser Tyr Asn Pro Met Val Leu Ile Gln Lys Thr Asp Thr Gly  
                     325                      330                      335

Val Ser Leu Gln Thr Tyr Asp Asp Leu Leu Ala Lys Asp Cys His Cys  
                     340                      345                      350

Ile