

CLAIMS

What is claimed is:

1. A complex comprising a first heterodimer and a second heterodimer, each of the first heterodimer and second heterodimer comprising:
 - (i) a first polypeptide comprising from the N-terminus to the C-terminus:
 - a human IgG1 Fc comprising a hinge region and a CH3 sequence comprising a substitution selected from the group consisting of Q347W/Y, T366W/Y, and T394W/Y, according to EU numbering,
 - a linker, and
 - an N-glycosylated GDF15 mutein comprising the amino acid sequence of SEQ ID NO: 129, and
 - (ii) a second polypeptide comprising a human IgG1 Fc comprising a hinge region and a CH3 sequence comprising a substitution selected from the group consisting of T366S, L368A, T394S, F405T/V/A, and Y407T/V/A, according to EU numbering.
2. The complex of claim 1, wherein the linker comprises the sequence $(G_4S)_n$, wherein $n=2-10$.
3. The complex of claim 2, wherein the linker comprises the sequence $(G_4S)_3$.
4. The complex of claim 2, wherein the linker comprises the sequence $(G_4S)_5$.
5. The complex of claim 1, wherein the first polypeptide comprises the substitution T366W/Y and the second polypeptide comprises the substitution Y407T/V/A; wherein the first polypeptide comprises the substitution T366Y and the second polypeptide comprises the substitution Y407T; or wherein the first polypeptide comprises the substitution T366W and the second polypeptide comprises the substitution Y407A.

6. The complex of claim 1, wherein the N-glycosylated GDF15 mutein comprises the amino acid sequence of SEQ ID NO: 128.
7. The complex of claim 1, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 3 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 4.
8. The complex of claim 1, wherein the first polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 5 and the second polypeptide comprises the amino acid sequence set forth in SEQ ID NO: 6.
9. A complex comprising a first heterodimer and a second heterodimer, each of the first heterodimer and second heterodimer comprising:
 - a first polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5;
 - and
 - a second polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 6,wherein the first polypeptide is N-glycosylated, and
wherein the first polypeptide is dimerized with the second polypeptide via one or two disulphide bonds formed between hinge regions present in Ig Fc sequences in the first and second polypeptides.
10. A pharmaceutical composition comprising the complex of any one of claims 1-9 and a pharmaceutically acceptable diluent, carrier or excipient.
11. The pharmaceutical composition of claim 10 for use in treating obesity or hyperglycemia in a mammalian subject.
12. The pharmaceutical composition for use according to claim 11, wherein the subject is human and wherein the treating results in reduction in body weight of the subject.

13. The pharmaceutical composition for use according to claim 11, wherein the subject is a human and the treating results in a reduction in blood glucose in the subject.
14. The pharmaceutical composition for use according to claim 11, wherein the subject is human and has diabetes mellitus.
15. The pharmaceutical composition for use according to claim 11, wherein the subject is human and is obese.