GIVEQCCTSX$_1$CSLX$_2$QLENYCX$_3$X$_4$

wherein X$_1$ is T or I; X$_2$ is D, Y, Q or E; X$_3$ is G, N, S or A; and X$_4$ is any naturally occurring amino acid, or is absent, provided that if X$_3$ is N, then X$_4$ must be an amino acid other than G or N (SEQ ID NO:2);

b) a second peptide linker; and

c) a human IgG Fc region;

wherein the C-terminal residue of the insulin receptor agonist is directly fused to the N-terminal residue of the second peptide linker, and the C-terminal residue of the second peptide linker is directly fused to the N-terminal residue of the human IgG Fc region; and

wherein the second peptide linker is a peptide having between 10 and 25 amino acids, wherein at least 50% of said amino acids are G residues.

In a second aspect of the present disclosure, there is provided a fusion protein having the amino acid sequence of SEQ ID NO:12.

In a third aspect of the present disclosure, there is provided a homodimer of two fusion proteins of the first or second aspects.

In a fourth aspect of the present disclosure, there is provided a pharmaceutical composition comprising either a fusion protein of the first or second aspects, or a homodimer of the third aspect, and at least one excipient.

In a fifth aspect of the present disclosure, there is provided a pharmaceutical composition comprising a homodimer of the third aspect and dulaglutide.

In a sixth aspect of the present disclosure, there is provided a fusion protein of the first or second aspects for use in therapy.

In a seventh aspect of the present disclosure, there is provided a use of the fusion protein of the first or second aspects in the manufacture of a medicament for the treatment of diabetes mellitus.

In an eighth aspect of the present disclosure, there is provided the fusion protein of the first or second aspects for use in simultaneous, separate or sequential combination with an additional active ingredient.

In a ninth aspect of the present disclosure, there is provided the fusion protein of the first or second aspects for use in simultaneous, separate or sequential combination with dulaglutide.

WE CLAIM:

1. A fusion protein comprising:

a) an insulin receptor agonist having the general formula Z_1-Z_2-Z_3, wherein:

i) Z_1 is an insulin B-chain analog, comprising the amino acid sequence:

$X_1X_2X_3$QHLCGSHLVEALX_4LVCGERGFX_5Y$X_6X_7X_8X_9$

wherein X_1 is F, Q or A; X_2 is V or G; X_3 is N, K, D, G, Q, A or E; X_4 is E, Y, Q, or H; X_5 is H or F; X_6 is G, T, S, H, V or is absent; X_7 is G, E, P, K, D, S, H or is absent; X_8 is G, E, K, P, Q, D, H or is absent; X_9 is G, T, S, E, K, A or is absent, provided that the insulin B-chain analog includes at least one modification from the amino acid sequence of the B-chain of a molecule of human insulin at X_4, X_5, X_6, X_7, X_8, or X_9 (SEQ ID NO:1);

ii) Z_2 is a first peptide linker comprising 5 to 10 amino acids, wherein at least 5 of said amino acids are G residues; and

iii) Z_3 is an insulin A-chain analog comprising the amino acid sequence:

GIVEQCCTSX_1CSLX_2QLENYCX_3X_4

wherein X_1 is T or I; X_2 is D, Y, Q or E; X_3 is G, N, S or A; and X_4 is any naturally occurring amino acid, or is absent, provided that if X_3 is N, then X_4 must be an amino acid other than G or N (SEQ ID NO:2);

b) a second peptide linker; and

c) a human IgG Fc region;

wherein the C-terminal residue of the insulin receptor agonist is directly fused to the N-terminal residue of the second peptide linker, and the C-terminal residue of the second peptide linker is directly fused to the N-terminal residue of the human IgG Fc region; and wherein the second peptide linker is a peptide having between 10 and 25 amino acids, wherein at least 50% of said amino acids are G residues.

2. The fusion protein of claim 1, wherein:

the insulin B-chain analog includes at least one modification from the amino acid sequence of the human insulin B-chain at X_4 or X_5 of SEQ ID NO:1; and

and the insulin A-chain analog includes at least one modification from the amino acid sequence of the human insulin A-chain at X_1 or X_2 of SEQ ID NO:2.

3. The fusion protein of either of claims 1 or 2, wherein:
the insulin B-chain analog comprises the sequence of SEQ ID NO:1, wherein: X_1 is F; X_2 is V; X_3 is N or D; X_4 is E; X_5 is H; and
the insulin A-chain analog comprises the sequence of SEQ ID NO:2, wherein: X_1 is I or T; X_2 is D; X_3 is G; and X_4 is absent.
4. The fusion protein of any of claims 1-3, wherein the insulin B-chain analog comprises the sequence of SEQ ID NO:1, wherein X_6-X_9 are each G.
5. The fusion protein of any of claims 1-4, wherein the first peptide linker comprises the following amino acid sequence:
X_1GX_2GGGG
wherein X_1 is G or is absent; and X_2 is G, S or is absent (SEQ ID NO:3).
6. The fusion protein of claim 5, wherein X_1 and X_2 of SEQ ID NO:3 are G and S, respectively.
7. The fusion protein of any of claims 1-6, wherein the insulin receptor agonist has the following amino acid sequence:
FVNQHLCGSHLVEALELVCGERGFHYGGGGGGSGGGGGIVEQCCTSTCSLDQLENYCG
(SEQ ID NO:5).
8. The fusion protein of any of claims 1-7, wherein the second peptide linker comprises a peptide having the sequence $[GGGGX]_n$
wherein X is Q, E or S; and wherein $_n$ is 2-5.
9. The fusion protein of any of claims 1-8, wherein the second peptide linker comprises the following amino acid sequence:
$GGGGX_1GGGGX_2GGGGX_3GGGGX_4X_5X_6$
X_1 is Q or E
X_2 is Q or E
X_3 is Q or E
X_4 is G, E, Q or is absent
X_5 is G or absent; and
X_6 is G or is absent

(SEQ ID NO:6).

10. The fusion protein of any of claims 1-9, wherein the second peptide linker has the following amino acid sequence:
GGGGQGGGGQGGGGQGGGGG (SEQ ID NO:7).

11. The fusion protein of any of claims 1-10, wherein the human IgG Fc region is an Fc region from an IgG1, IgG2 or IgG4.
12. The fusion protein of any of claims 1-11, wherein the human IgG Fc region comprises an amino acid sequence selected from the group consisting of SEQ ID NO:8, SEQ ID NO:9 and SEQ ID NO:10.
13. A fusion protein having the amino acid sequence of SEQ ID NO:12.
14. A homodimer of two fusion proteins of any of claims 1-13.
15. A pharmaceutical composition comprising either a fusion protein of any of claims 1-13 or a homodimer of claim 14, and at least one excipient.
16. The pharmaceutical composition of claim 15, wherein the composition further comprises one or more buffering agents, one or more surfactants, and one or more isotonicity agents.
17. The pharmaceutical composition of claim 15, further comprising citrate, citric acid, polysorbate 80, and mannitol.
18. The pharmaceutical composition of any of claims 15-17 wherein the pH ranges from 5.5 to 8.0.
19. The pharmaceutical composition of any of claims 15-18 wherein the pH ranges from 6.0 to 6.75.
20. The pharmaceutical composition of any of claims 15-19, further comprising an additional active ingredient.
21. The pharmaceutical composition of claim 20, wherein the additional active ingredient is an incretin-based therapy.
22. The pharmaceutical composition of claim 21, wherein the incretin-based therapy is a GLP-1R agonist.
23. The pharmaceutical composition of claim 22 wherein the GLP-1R agonist is dulaglutide.
24. A pharmaceutical composition comprising a homodimer of claim 14 and dulaglutide.

25. The fusion protein of any of claims 1-13 for use in therapy.
26. Use of the fusion protein of any of claims 1-13 in the manufacture of a medicament for the treatment of diabetes mellitus.
27. The fusion protein of any of claims 1-13 for use in simultaneous, separate or sequential combination with an additional active ingredient.
28. The fusion protein of any of claims 1-13 for use in simultaneous, separate or sequential combination with dulaglutide.
29. The homodimer of claim 14 for use in simultaneous, separate or sequential combination with dulaglutide.
30. A polynucleotide encoding the fusion protein of any of claims 1-13.