[CLAIMS]

[Claim 1]

A pharmaceutical composition for the prevention or treatment of diabetes mellitus, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a substitution in one amino acid at the position 14 of the A chain of native insulin is substituted with glutamic acid, and

wherein the insulinotropic peptide is imidazo-acetyl exendin-4.

[Claim 2]

A pharmaceutical composition for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in diabetic patients, comprising:

a long-acting insulin analogue conjugate in which an insulin analogue is linked to a biocompatible material capable of prolonging duration of activity of the insulin analogue via a linker or a covalent bond; and

a long-acting insulinotropic peptide conjugate in which an insulinotropic peptide is linked to a biocompatible material capable of prolonging duration of activity of the insulinotropic peptide via a linker or a covalent bond,

wherein the insulin analogue is characterized in having a substitution in one amino acid at the position 14 of the A chain of native insulin is substituted with glutamic acid, and

wherein the insulinotropic peptide is imidazo-acetyl exendin-4.

[Claim 3]

The composition according to claim 1 or 2, wherein the insulin analogue comprises the amino acid sequence of SEQ ID No. 34.

[Claim 4]

The composition according to claim 1 or 2, wherein the long-acting insulin analogue conjugate is characterized that an insulin analogue in which an amino acid at position 14 of A chain of insulin is substituted with glutamic acid, is linked to an immunoglobulin Fc region via a non-peptidyl polymer as a linker, and the long-acting insulinotropic peptide conjugate is characterized that an imidazo-acetyl exendin-4 as insulinotropic peptide is linked to an immunoglobulin Fc region via a non-peptidyl polymer as a linker.

[Claim 5]

The composition according to claim 1 or 2, wherein the biocompatible material is selected from the group consisting of polyethylene glycol, fatty acid, cholesterol, albumin and fragments thereof, albumin-binding materials, a polymer of repeating units of a particular amino acid sequence, antibodies, antibody fragments, FcRn binding material, in vivo connective tissues or derivatives thereof, nucleotides, fibronectin, transferrin, saccharides, and polymers.

[Claim 6]

The composition according to claim 5, wherein the insulin analogue or the insulinotropic peptide is linked to the biocompatible material via a linker selected from the group consisting of polyethylene glycol, fatty acids, saccharides, polymers, low-molecular weight compounds, nucleotides, and combinations thereof.

[Claim 7]

The composition according to claim 1 or 2, wherein the insulin analogue or the insulinotropic peptide is linked to the biocompatible material via a linker, and the biocompatible material is an FcRn binding material, wherein the linker is a peptide linker or a non-peptidyl linker selected from the group consisting of polyethylene glycol, polypropylene glycol, ethylene glycol-propylene glycol copolymer, polyoxyethylated polyol, polyvinyl alcohol, polysaccharide, dextran, polyvinyl ethyl ether, a biodegradable polymer, a lipid polymer, chitin, hyaluronic acid, and combinations thereof.

[Claim 8]

The composition according to claim 7, wherein the FcRn binding material includes an immunoglobulin Fc region.

[Claim 9]

The composition according to claim 7, wherein each end of the non-peptidyl linker respectively binds to the biocompatible material and an amine or thiol group of the insulin analogue or the insulinotropic peptide.

[Claim 10]

The composition according to claim 8, wherein the immunoglobulin Fc region is aglycosylated.

[Claim 11]

The composition according to claim 8, wherein the immunoglobulin Fc region is composed of one to four domains selected from the group consisting of CH1, CH2, CH3, and CH4 domains.

[Claim 12]

The composition according to claim 8, wherein the immunoglobulin Fc region further includes a hinge region.

[Claim 13]

The composition according to claim 8, wherein the immunoglobulin Fc region is an Fc region derived from IgG, IgA, IgD, IgE, or IgM.

[Claim 14]

The composition according to claim 8, wherein the immunoglobulin Fc region is hybrid of domains of different origins selected from the group consisting of IgG, IgA, IgD, IgE, and IgM.

[Claim 15]

The composition according to claim 8, wherein the immunoglobulin Fc region is a dimer or a multimer composed of single-chain immunoglobulins consisting of domains of the same origin.

[Claim 16]

The composition according to claim 1 or 2, further comprising a pharmaceutically acceptable carrier.

[Claim 17]

The composition according to claim 1 or 2, wherein the long-acting insulin conjugate and the long-acting insulinotropic peptide conjugate are to be administered simultaneously, sequentially, or reversely.

[Claim 18]

The composition according to claim 2, wherein the composition inhibits the progression of diabetes.

[Claim 19]

The composition according to claim 2, wherein the composition improves diabetic prognosis of subject suffering from diabetes mellitus.

[Claim 20]

Use of the composition of claim 1 in the manufacture of a medicament for the treatment of diabetes mellitus.

[Claim 21]

Use of the composition of claim 2 in the manufacture of a medicament for reducing one or more pancreatic beta cell side-effects selected from the group consisting of lipotoxicity, glucotoxicity, abnormality in the function of pancreatic beta cells and reduction in the pancreatic beta cell mass in a diabetic subject suffering from diabetes mellitus.