enhanced half-life would allow for less frequent dosing of patients being administered the protein. Such proteins are described herein.

SUMMARY OF THE INVENTION

An isolated polypeptide comprising an amino acid sequence of SEQ ID NO: 4 and further comprising: (a) at least one amino acid substitution at position 180; and (b) at least one amino acid substitution selected from the group consisting of: (i) a substitution at position 171; and (ii) a substitution at position 98; and (c) combinations thereof is disclosed.

In one embodiment the isolated polypeptide comprises a substitution at position 98 and a substitution at position 180 and wherein: (a) the substitution at position 98 is selected from the group consisting of an arginine, cysteine, glutamic acid, glutamine, lysine, and threonine; and (b) the substitution at position 180 is selected from the group consisting of glycine, proline, serine or glutamic acid; and (c) combinations thereof. In one embodiment the residue at position 98 is arginine and the residue at position 180 is glutamic acid. Also provided is a fusion polypeptide comprising the isolated polypeptide fused to a heterologous amino acid sequence. In one embodiment the heterologous amino acid sequence is an Fc domain or fragment thereof, and can comprise the amino acid sequence of SEQ ID NO:11. In another embodiment the polypeptide is fused to the Fc domain via a linker and in yet another embodiment the linker comprises GGGGSGGGGSGGGGS (SEQ ID NO:31). In one specific embodiment the polypeptide comprises SEQ ID NO:47. Also disclosed is a multimer comprising two or more of the fusion polypeptides. A pharmaceutical composition comprising the isolated polypeptide and a pharmaceutically acceptable formulation agent, such as a hydrogel, is also disclosed. In one other aspect, the present invention refers to the use of a pharmaceutical composition as defined in claim 12 in the manufacture of a medicament for treating a metabolic disorder, wherein the use comprises administration to a human patient in need thereof the medicament. In another example~~aspect~~, a method of treating a metabolic disorder is disclosed~~provided~~ and in one embodiment comprises administering to a human patient in need thereof a pharmaceutical composition provided herein. In one embodiment the metabolic disorder is diabetes and in another the metabolic disorder is obesity. Nucleic acids encoding the isolated polypeptide are also provided and in one embodiment the nucleic acid comprises SEQ ID NO:46. The nucleic acid can be present in a vector, which can itself be present in a host cell. In still another embodiment the polypeptide comprises: (a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; (b) a carboxyl-terminal truncation of no

more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or (c) an amino-terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal. In still other embodiments the polypeptide is covalently linked to one or more polymers, such as PEG.

In another embodiment the isolated polypeptide comprises a substitution at position 171 and a substitution at position 180 and wherein: (a) the substitution at position 180 is selected from the group consisting of glycine, proline, serine and glutamic acid; (b) the substitution at position 171 is selected from the group consisting of an alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, serine, threonine, tryptophan, and tyrosine; and (c) combinations thereof. In one embodiment the residue at position 171 is glycine and the residue at position 180 is glutamic acid. Also provided is a fusion polypeptide comprising the isolated polypeptide fused to a heterologous amino acid sequence. In one embodiment the heterologous amino acid sequence is an Fc domain or fragment thereof, and can comprise the amino acid sequence of SEQ ID NO:11. In another embodiment the polypeptide is fused to the Fc domain via a linker and in yet another embodiment the linker comprises GGGGSGGGGSGGGGS (SEQ ID NO:31). In one specific embodiment the polypeptide comprises SEQ ID NO:47. Also disclosed is a multimer comprising two or more of the fusion polypeptides. A pharmaceutical composition comprising the isolated polypeptide and a pharmaceutically acceptable formulation agent, such as a hydrogel, is also disclosed. In one other aspect, the present invention refers to the use of a pharmaceutical composition as defined in claim 32 in the manufacture of a medicament for treating a metabolic disorder, wherein the use comprises administration to a human patient in need thereof the medicament. In another example~~aspect~~, a method of treating a metabolic disorder is disclosed~~provided~~ and in one embodiment comprises administering to a human patient in need thereof a pharmaceutical composition provided herein. In one embodiment the metabolic disorder is diabetes and in another the metabolic disorder is obesity. Nucleic acids encoding the isolated polypeptide are also provided and in one embodiment the nucleic acid comprises SEQ ID NO:46. The nucleic acid can be present in a vector, which can itself be present in a host cell. In still another embodiment the polypeptide comprises: (a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; (b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; or (c) an amino-

terminal truncation of no more than 8 amino acid residues and a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal. In still other embodiments the polypeptide is covalently linked to one or more polymers, such as PEG.

In yet another embodiment the polypeptide comprises a substitution at position 98, a substitution at position 171 and a substitution at position 180 of SEQ ID NO:4 and wherein: (a) the substitution at position 171 is selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, lysine, serine, threonine, tryptophan, or tyrosine; (b) the substitution at position 98 is selected from the group consisting of arginine, cysteine, glutamic acid, glutamine, lysine, or threonine; and (c) the substitution at position 180 is selected from the group consisting of glycine, proline, serine or glutamic acid; and combinations thereof. In a further embodiment the residue at position 98 is arginine, the residue at position 171 is glycine and the residue at position 180 is a glutamic acid. Also provided is a fusion polypeptide comprising the isolated polypeptide fused to a heterologous amino acid sequence. In one embodiment the heterologous amino acid sequence is an Fc domain or fragment thereof, and can comprise the amino acid sequence of SEQ ID NO:11. In another embodiment the polypeptide is fused to the Fc domain via a linker and in yet another embodiment the linker comprises GGGGSGGGGSGGGGS (SEQ ID NO:31). In one specific embodiment the polypeptide comprises SEQ ID NO:47. Also disclosed is a multimer comprising two or more of the fusion polypeptides. In another aspect, the present invention refers to a polypeptide comprising: (a) the polypeptide of SEQ ID NO:4, wherein (i) the leucine at position 98 is substituted with an arginine; (ii) the proline at position 171 is substituted with glycine; and (iii) the alanine at position 180 is substituted with glutamic acid; (b) a linker sequence comprising SEQ ID NO:31; and (c) an Fc domain comprising SEQ ID NO:11. In another aspect, the present invention refers to a polypeptide comprising the sequence of SEQ ID NO:47. In another aspect, the present invention refers to a polypeptide encoded by the nucleic acid sequence of SEQ ID NO:46. A pharmaceutical composition comprising the isolated polypeptide and a pharmaceutically acceptable formulation agent, such as a hydrogel, is also disclosed. In another aspect, the present invention refers to the use of a pharmaceutical composition as defined in claim 56 or 57 in the manufacture of a medicament for treating a metabolic disorder, wherein the use comprises administration to a human patient in need thereof the medicament. In another exampleaspect, a method of treating a metabolic disorder is disclosedprovided and in one embodiment comprises administering to a human patient in need thereof a pharmaceutical composition provided herein. In one embodiment the metabolic disorder is diabetes and in another the metabolic disorder is obesity. Nucleic acids encoding the isolated polypeptide are also provided and in one embodiment the nucleic acid comprises SEQ ID NO:46. The nucleic acid can be present in a vector, which can itself be present in a host cell. In still another embodiment the polypeptide comprises: (a) an amino-terminal truncation of no more than 8 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a mammal; (b) a carboxyl-terminal truncation of no more than 12 amino acid residues, wherein the polypeptide is capable of lowering blood glucose in a