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

SUMMARY

In one aspect, the present disclosure refers to a use of a polypeptide comprising an amino acid sequence of SEQ ID NO: 4 and further comprising: (a) a substitution of a glycine residue for the proline residue at position 171; and (b) at least one amino acid substitution selected from the group consisting of: (i) a substitution of a glutamic acid residue for the alanine residue at position 180; and (ii) a substitution of a arginine residue for the leucine residue at position 98; and (iii) combinations thereof, in the manufacture of a medicament for treating Nonalcoholic steatohepatitis (NASH) in a human subject in need thereof.

In another aspect, the present disclosure refers to a use of a fusion polypeptide comprising: (a) a 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 the manufacture of a medicament for treating Nonalcoholic steatohepatitis (NASH) in a human subject in need thereof.

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 example 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 example 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 example 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 example the polypeptide is fused to the Fc domain via

CLAIMS

1. Use of a polypeptide comprising an amino acid sequence of SEQ ID NO: 4 and further comprising:

(a) a substitution of a glycine residue for the proline residue at position 171; and

(b) at least one amino acid substitution selected from the group consisting of:

(i) a substitution of a glutamic acid residue for the alanine residue at position 180; and

(ii) a substitution of a arginine residue for the leucine residue at position 98; and

(iii) combinations thereof,

in the manufacture of a medicament for treating Nonalcoholic steatohepatitis (NASH) in a human subject in need thereof.

2. The use of claim 1, wherein the residue at position 98 is arginine, the residue at position 171 is glycine, and the residue at position 180 is glutamic acid.

3. The use of claim 1, wherein the polypeptide comprises 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.

4. The use of any one of claims 1-3, wherein the polypeptide is fused to a heterologous amino acid sequence.

5. The use of claim 4, wherein the heterologous amino acid sequence is an Fc domain or fragment thereof.

6. The use of claim 5, wherein the Fc domain comprises the amino acid sequence of SEQ ID NO: 11.

7. The use of claim 5 or claim 6, wherein the polypeptide is fused to the Fc domain via a linker.

8. The use of claim 7, wherein the linker comprises GGGGSGGGGSGGGGS (SEQ ID NO:31).

9. The use of any one of claims 1-8, wherein the polypeptide comprises SEQ ID NO:47.

10. The use of any one of claims 1-8, wherein the polypeptide is encoded by the nucleic acid sequence of SEQ ID NO:46.

11. The use of any one of claims 1-10, wherein the polypeptide is covalently linked to one or more polymers.

12. The use of claim 11, wherein the polymer is PEG.

13. Use of a fusion polypeptide comprising:

(a) a 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 the manufacture of a medicament for treating Nonalcoholic steatohepatitis (NASH) in a human subject in need thereof.