METHODS OF TREATMENT OF NASH USING MUTANT FGF-21 PEPTIDE CONJUGATES

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Patent Application Serial No. 63/373,352, filed August 24, 2022, U.S. Provisional Patent Application Serial No. 63/373,694, filed August 26, 2022, U.S. Provisional Patent Application Serial No. 63/382,058, filed November 2, 2022, U.S. Provisional Patent Application Serial No. 63/482,078, filed January 30, 2023, U.S. Provisional Patent Application Serial No. 63/494,011, filed April 4, 2023, and U.S. Provisional Patent Application Serial No. 63/510,041, filed June 23, 2023, the disclosure of each of which is incorporated herein by reference in their entireties.

SEQUENCE LISTING

The instant application contains a Sequence Listing which includes the file entitled 180234-011706.xml, 40,011 bytes in size, which was created August 20, 2023, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

Therapeutic regimens and uses of mutant Fibroblast Growth Factor-21 (FGF-21) peptide conjugates comprising a polyethylene glycol (PEG) moiety attached to a mutant FGF-21 peptide via a glycosyl moiety thereof are provided.

BACKGROUND OF THE INVENTION

FGF-21 is an endocrine hormone that is naturally found as a monomeric non-glycosylated protein. Together with FGF-19 and FGF-23, FGF-21 belongs to the endocrine-acting sub-family while the remaining of the 18 mammalian FGF ligands are grouped into five paracrine-acting sub-families.

SUMMARY OF THE INVENTION

In one aspect, provided herein is use of a pharmaceutical composition comprising from 16.2 mg to 48.4 mg of a mutant Fibroblast Growth Factor-21 (FGF-21) peptide conjugate and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof, wherein the mutant FGF-21 peptide conjugate comprises: i) a mutant FGF-21 peptide comprising the amino acid sequence

of SEQ ID NO: 2, ii) a glycosyl moiety, and iii) a 20 kDa polyethylene glycol (PEG), wherein the mutant FGF-21 peptide is attached to the glycosyl moiety by a covalent bond between a threonine at amino acid position 173 of SEQ ID NO: 2 and a first site of the glycosyl moiety and wherein the glycosyl moiety is attached to the 20 kDa PEG by a covalent bond between a second site of the glycosyl moiety and the 20 kDa PEG, wherein the medicament is to be administered once every two weeks to the subject in need thereof and results in at least one of: a reduction of liver fat, an improvement in liver fibrosis score, NASH resolution, ≥2 point improvement of NAFLD Activity score, improvement of VCTE score, improvement of FAST score, improvement of FIB-4 score, a reduction of liver size as assessed by Magnetic resonance imaging – Proton density fat fraction, a reduction of levels of one or more biomarkers comprising Pro-C3, alanine transaminase (ALT), Enhanced Liver Fibrosis (ELF) panel, CK-18, inflammation marker high-sensitivity C-reactive protein (hs-CRP), Hemoglobin A1c (HbA1c), Triglycerides, LDL-c, non-HDL-c, and an increase of the levels of HDL-c and/or adiponectin.

In another aspect, provided herein is Use of a pharmaceutical composition comprising from 36 to 55 mg of a mutant Fibroblast Growth Factor-21 (FGF-21) peptide conjugate and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof, wherein the mutant FGF-21 peptide conjugate comprises: i) a mutant FGF-21 peptide comprising the amino acid sequence of SEQ ID NO: 2, ii) a glycosyl moiety, and iii) a 20 kDa polyethylene glycol (PEG), wherein the mutant FGF-21 peptide is attached to the glycosyl moiety by a covalent bond between a threonine at amino acid position 173 of SEQ ID NO: 2 and a first site of the glycosyl moiety and wherein the glycosyl moiety is attached to the 20 kDa PEG by a covalent bond between a second site of the glycosyl moiety and the 20 kDa PEG, wherein the medicament is to be administered to the subject in need thereof and results in at least one of: a reduction of liver fat, an improvement in liver fibrosis score, NASH resolution, ≥2 point improvement of NAFLD Activity score, improvement of VCTE score, improvement of FAST score, improvement of FIB-4 score, a reduction of liver size as assessed by Magnetic resonance imaging – Proton density fat fraction, a reduction of levels of one or more biomarkers comprising Pro-C3, alanine transaminase (ALT), Enhanced Liver Fibrosis (ELF) panel, CK-18, inflammation marker high-sensitivity C-reactive protein (hs-CRP), Hemoglobin A1c (HbA1c), Triglycerides, LDL-c, non-HDL-c, and an increase of the levels of HDL-c and/or

adiponectin.

In another aspect, provided herein is use of a pharmaceutical composition comprising from 13.5 mg to 33 mg of a mutant Fibroblast Growth Factor-21 (FGF-21) peptide conjugate and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof, wherein the mutant FGF-21 peptide conjugate comprises: i) a mutant FGF-21 peptide comprising the amino acid sequence of SEQ ID NO: 2, ii) a glycosyl moiety, and iii) a 20 kDa polyethylene glycol (PEG), wherein the mutant FGF-21 peptide is attached to the glycosyl moiety by a covalent bond between a threonine at amino acid position 173 of SEQ ID NO: 2 and a first site of the glycosyl moiety and wherein the glycosyl moiety is attached to the 20 kDa PEG by a covalent bond between a second site of the glycosyl moiety and the 20 kDa PEG, wherein the medicament is to be administered once a week to the subject in need thereof and results in at least one of: a reduction of liver fat, an improvement of liver fibrosis score, resolution of NASH, ≥2 point improvement of NAFLD Activity score, improvement of VCTE score, improvement of FAST score, improvement of FIB-4 score, a reduction of liver size as assessed by Magnetic resonance imaging – Proton density fat fraction, a reduction of levels of one or more biomarkers comprising Pro-C3, alanine transaminase (ALT), Enhanced LiverFibrosis (ELF) panel, CK-18, inflammation marker high-sensitivity C-reactive protein (hs-CRP), Hemoglobin A1c (HbA1c), non-HDL-c, LDL-c, and Triglycerides, and an increase of the levels of HDL-c and/or adiponectin.

Provided herein are methods of treating nonalcoholic steatohepatitis (NASH) in a subject in need thereof. In some embodiments, the methods comprise administering once a week to the subject in need thereof a pharmaceutical composition comprising from about 15 mg to about 30 mg of a mutant Fibroblast Growth Factor-21 (FGF-21) peptide conjugate and a pharmaceutically